National Clinical Guideline Centre

MI - secondary prevention

Secondary prevention in primary and secondary care for patients following a myocardial infarction

Partial update of NICE CG48

Appendices

November 2013

November 2020: NICE's original guidance on Myocardial infarction - secondary prevention was published in 2007. It was updated in 2013. See the NICE website for the guideline recommendations and for the 2020 Acute coronary syndromes update. This document preserves evidence reviews and committee discussions from the 2013 guideline.

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Contents

Appendices

Appendix A: Scope

FINAL

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SCOPE

1 Guideline title

Myocardial infarction: secondary prevention in primary and secondary care for patients following a myocardial infarction

1.1 Short title

MI: secondary prevention

2 The remit

This is a partial update of 'MI: secondary prevention', NICE clinical guideline 48 (2007). See section 4.3.1 for details of which sections will be updated. We will also carry out an editorial review of all recommendations to ensure that they comply with NICE's duties under equalities legislation.

This update is being undertaken as part of the guideline review cycle.

3 Clinical need for the guideline

3.1 Epidemiology

a) Myocardial infarction (MI) remains a common condition, despite recent falls in incidence. For men aged between 30 and 74 the incidence is about 174 per 100,000 per year in England and for women it is about 60 per 100,000. Across the United Kingdom there are a total of 124,000 MIs annually.

b) It is estimated that 1 million men and about 500,000 women living in the UK in 2010 have had an MI.

c) MI is a complication of coronary heart disease (CHD). CHD is a preventable and treatable disease. The death rate from CHD has

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been falling since the early 1970s and for people aged below 75, rates have fallen by 44% between 1990 and 2010. In spite of these improvements, the UK death rate from CHD is relatively high when compared with that in western European countries. The age standardised death rate for men is 132 per 100,000 and 61 per 100,000 for women.

d) CHD death rates in the UK vary with age, gender, socioeconomic status and ethnicity, for example:

- in people younger than 75, death rates in men are nearly three times higher than in women
- death rates in affluent areas in the UK are half of those in deprived areas
- people of South Asian origin have a death rate almost 50% higher than the general population.

3.2 *Current practice*

a) Secondary prevention measures for MI have helped to significantly reduce mortality from coronary artery disease.

b) In England, 99% of people discharged after an MI receive aspirin, 96% beta blockers, 97% statins, 94% angiotensin-converting enzyme (ACE) inhibitors and 95% clopidogrel or another thienopyridine inhibitor on discharge. In Wales, 98% receive aspirin, 95% beta blockers, 95% statins, 91% ACE inhibitors and 92% clopidogrel or another thienopyridine inhibitor. These data reflect excellent provision of current evidence-based care for pharmacological agents.

c) In 2010/11 over 80% of STEMI patients who were eligible for reperfusion as part of their acute treatment strategy received primary PCI compared to less than 20% in 2006/7. In light of this significant change in the acute management of MI, there is now

uncertainty about the appropriateness of existing secondary prevention pharmacological treatment recommendations.

d) Cardiac rehabilitation programmes are not widely accessed, despite being consistently shown to reduce mortality rates in people with CHD. Cardiac rehabilitation is a coordinated programme of physical, psychological and social interventions to enable the person with CHD to preserve or resume optimal functioning in society.

e) Uptake of cardiac rehabilitation varies across the UK, and differs across socioeconomic and demographic groups. In 2008/09 only 39% of people who had an MI were referred for cardiac rehabilitation. In 2008/2009, 24% of patients referred to cardiac rehabilitation did not attend.

4 The guideline

The guideline development process is described in detail on the NICE website (see section 6, 'Further information').

This scope defines what the guideline update will (and will not) examine, and what the guideline developers will consider.

The areas that will be addressed by the guideline update are described in the following sections.

4.1 Population

4.1.1 Groups that will be covered in the update

a) Adults (18 years and older).

b) People who have had an MI (type 1 according to the universal definition). This will include those not yet discharged from hospital, where relevant and those found to have had a proven MI in the past.

c) Specific consideration will be given to the needs of populations thought to have reduced adherence to cardiac rehabilitation programmes. These include people from South Asian communities, black and minority ethnic groups, low socioeconomic groups or rural communities; people with physical and learning disabilities; women; and people with anxiety and/or depression.

4.1.2 Groups that will not be covered

a) Children and young people (younger than 18).

b) Patients diagnosed as having a type 2, 3, 4a, 4b or 5 MI according to the universal definition of myocardial infarction.

4.2 Healthcare setting

a) Primary care and hospital settings, excluding early acute care and accident and emergency departments.

b) Care from healthcare professionals who have direct contact with people after the early acute phase of an MI. The guideline will also be relevant to people working in occupational health services and the voluntary sector, although specific recommendations on their practice will not be made.

4.3 Clinical management

4.3.1 Key clinical issues that will be covered

Areas from the original guideline that will be updated

a) Interventions to increase uptake and adherence to cardiac rehabilitation programmes.

b) Fish diet and omega-3-acid ethyl esters.

c) Pharmacological interventions, including:

- ACE inhibitors, including:
  - Dose titration

- Antiplatelet agents, including:
  - initiating agents after the acute phase
  - use in patients already prescribed oral anticoagulants.
  - duration of therapy
  - duration of therapy after stenting
- Vitamin K antagonists
- Beta blockers
- Angiotensin receptor blockers, including:

  - in patients with a proven past MI without heart failure and with preserved left ventricular function

Note that guideline recommendations will normally fall within licensed indications; exceptionally, and only if clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.

d) Mapping and review of recommendations in relation to more recent NICE guidance (see section 5.1.1)

Areas that were not part of the original guideline but will be included in the update

e) Factors affecting uptake and adherence to cardiac rehabilitation programmes, including both patient and healthcare-provider factors

4.3.2 Clinical issues that will not be covered

Areas from the original guideline that will not be updated

No new evidence has been identified to change the 2007 recommendations on:

a) Lifestyle, except fish diet and omega-3-acid ethyl esters.

b) Cardiac rehabilitation, excluding those areas in 4.3.1 a

c) Coronary revascularisation.

d) Hypertension.

e) Left ventricular dysfunction.

f) Communication of diagnosis and advice.

g) Potassium channel activators

h) Calcium channel blockers

i) Aldosterone antagonists

Areas that will be removed

j) Recommendations relating to lipid lowering pharmaceutical agents will be removed from the updated guideline. These will be covered by the upcoming update of 'Lipid modification', NICE clinical guideline 67 (2008) to which the update of this guideline will cross-refer.

Areas not covered by the original guideline or the update

k) Acute or retrospective diagnosis of MI.

l) Interventions specific to the early phase of acute MI. These are covered by the relevant acute management guidelines (Unstable angina and NSTEMI [NICE clinical guideline 94] and Myocardial infarction: acute management of STEMI [guideline in development]).

m) Assessment of cardiac status before coronary revascularisation.

4.4 Main outcomes

a) Mortality.

b) Myocardial reinfarction.

c) Revascularisation.

d) Rehospitalisation.

e) Stroke.

f) Adverse events, including bleeding complications.

g) Health-related quality of life.

h) Uptake and adherence to cardiac rehabilitation.

4.5 Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually be only from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in 'The guidelines manual' (see 'Further information').

4.6 Status

4.6.1 Scope

This is the final scope.

4.6.2 Timing

The development of the guideline recommendations will begin in March 2012.

5 Related NICE guidance

5.1 Published guidance

5.1.1 NICE guidance to be updated

This guideline will update and replace the following NICE guidance:

- MI: secondary prevention. NICE clinical guideline 48 (2007)

5.1.2 Related NICE guidance

- Patient experience in generic terms. NICE clinical guideline 138 (2012).
- Bivalirudin for the treatment of ST-segment-elevation myocardial infarction. NICE technology appraisal 230 (2011)
- Hyperglycaemia in acute coronary syndromes. NICE clinical guideline 130 (2011)
- Ticagrelor for the treatment of acute coronary syndromes. NICE technology appraisal guidance 236 (2011)
- Hypertension. NICE clinical guideline 127 (2011)
- Stable angina. NICE clinical guideline 126 (2011)
- Anxiety. NICE clinical guideline 113 (2011)
- Prevention of cardiovascular disease at population level. NICE public health guidance 25 (2010)
- Chronic heart failure. NICE clinical guideline 108 (2010)
- Chest pain of recent onset. NICE clinical guideline 95 (2010)
- Unstable angina and NSTEMI. NICE clinical guideline 94 (2010)
- Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events. NICE technology appraisal 210 (2010)
- Depression with a chronic physical health problem. NICE clinical guideline 91 (2009)
- Depression in adults (update). NICE clinical guideline 90 (2009)
- Type 2 diabetes: newer agents. NICE clinical guideline 87 (2009)
- Medicines adherence. NICE clinical guideline 76 (2009)
- Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention. NICE technology appraisal guidance 182 (2009)
- Drug-eluting stents for the treatment of coronary artery disease. NICE technology appraisal guidance 152 (2008)
- Lipid modification. NICE clinical guideline 67 (2008)
- Smoking cessation services in primary care, pharmacies, local authorities and workplaces. NICE public health guidance 10 (2008)

- MI: secondary prevention. NICE clinical guideline 48 (2007)

5.1.2 Related NICE guidance

- Patient experience in generic terms. NICE clinical guideline 138 (2012).
- Bivalirudin for the treatment of ST-segment-elevation myocardial infarction. NICE technology appraisal 230 (2011)
- Hyperglycaemia in acute coronary syndromes. NICE clinical guideline 130 (2011)
- Ticagrelor for the treatment of acute coronary syndromes. NICE technology appraisal guidance 236 (2011)
- Hypertension. NICE clinical guideline 127 (2011)
- Stable angina. NICE clinical guideline 126 (2011)
- Anxiety. NICE clinical guideline 113 (2011)
- Prevention of cardiovascular disease at population level. NICE public health guidance 25 (2010)
- Chronic heart failure. NICE clinical guideline 108 (2010)
- Chest pain of recent onset. NICE clinical guideline 95 (2010)
- Unstable angina and NSTEMI. NICE clinical guideline 94 (2010)
- Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events. NICE technology appraisal 210 (2010)
- Depression with a chronic physical health problem. NICE clinical guideline 91 (2009)
- Depression in adults (update). NICE clinical guideline 90 (2009)
- Type 2 diabetes: newer agents. NICE clinical guideline 87 (2009)
- Medicines adherence. NICE clinical guideline 76 (2009)
- Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention. NICE technology appraisal guidance 182 (2009)
- Drug-eluting stents for the treatment of coronary artery disease. NICE technology appraisal guidance 152 (2008)
- Lipid modification. NICE clinical guideline 67 (2008)
- Smoking cessation services in primary care, pharmacies, local authorities and workplaces. NICE public health guidance 10 (2008)

- Varenicline for smoking cessation. NICE technology appraisal guidance 123 (2007)
- Behaviour change. NICE public health guidance 6 (2007)
- Brief interventions and referral for smoking cessation in primary care and other settings. NICE public health guidance 1 (2006)
- Obesity. NICE clinical guideline 43 (2006)
- Implantable cardioverter defibrillators (ICDs) for the treatment of arrhythmias. NICE technology appraisal guidance 95 (2006)
- Statins for the prevention of cardiovascular events in patients at increased risk of developing cardiovascular disease or those with established cardiovascular disease. NICE technology appraisal guidance 94 (2006)
- Dyspepsia. NICE clinical guideline 17 (2004)
- Type 1 diabetes. NICE clinical guideline 15 (2004)

5.1.3 Other related NICE products

- Cardiac rehabilitation service commissioning guide. NICE service commissioning guide (2008)

5.2 Guidance under development

NICE is currently developing the following related guidance (details available from the NICE website):

- Myocardial infarction: acute management of STEMI. NICE clinical guideline. Publication expected 2013.
- Acute heart failure. NICE clinical guideline. Publication date to be confirmed.
- Venous thromboembolism – rivaroxaban. NICE technology appraisal. Publication date to be confirmed.

6 Further information

Information on the guideline development process is provided in:

- 'How NICE clinical guidelines are developed: an overview for stakeholders the public and the NHS'

- 'The guidelines manual'.

These are available from the NICE website (www.nice.org.uk/GuidelinesManual). Information on the progress of the guideline will also be available from the NICE website (www.nice.org.uk).

Appendix B: Declarations of interest

B.1 Philip Adams

GDG meeting	Declaration of Interests	Action taken
On appointment	Nothing to declare.	None.
First GDG meeting [15.03.12]	No changes to declarations of interest.	None.
Second GDG meeting [25.04.12]	No change to declarations of interest.	None.
Third GDG meeting [12.06.12] & Fourth GDG meeting [13.06.12]	No change to declarations of interest.	None.
Fifth GDG meeting [10.07.12]	No change to declarations of interest.	None.
Sixth GDG meeting [18.09.12]	No change to declarations of interest.	None.
Seventh GDG meeting [01.11.12]	No change to declarations of interest.	None.
Eighth GDG meeting [12.12.12]	Did not attend.	None.
Ninth GDG meeting [06.02.13]	No change to declarations of interest.	None.
Tenth GDG meeting [14.03.13]	No change to declarations of interest.	None.
Eleventh GDG meeting [07.08.13]	No change to declarations of interest.	None.

B.2 Ivan Benett

GDG meeting	Declaration of Interests	Action taken
On appointment	Declared a personal specific pecuniary interest: • Attended advisory board for MSD on the use of ezetimibe (October 2011) and received an honorarium for attendance. • Presented at the Primary Care Cardiology conference, receiving an honoraria from Servier laboratories (September 2011). • Attended the American College of Cardiology conference in Chicago as a guest of Boehringer Ingelheim. Flight, accommodation and registration fee were paid for (March 2012).	None.
First GDG meeting [15.03.12]	No change to declarations of interest.	None.

GDG meeting	Declaration of Interests	Action taken
Second GDG meeting [25.04.12]	No change to declarations of interest.	None.
Third GDG meeting [12.06.12] & Fourth GDG meeting [13.06.12]	No change to declarations of interest.	Declare and withdraw from discussion and drafting of recommendations relating to antiplatelets in those with a pre-existing indication for oral anticoagulation.
Fifth GDG meeting [10.07.12]	Did not attend.	None.
Sixth GDG meeting [18.09.12]	Did not attend.	None.
Seventh GDG meeting [01.11.12]	Declared a personal specific non-pecuniary interest: due to chair a meeting on 1.12.12 on a new DVT pathway for rivaroxaban, sponsored by Bayer, for which no honorarium will be received.	Declare and participate.
Eighth GDG meeting [12.12.12]	Did not attend.	None.
Ninth GDG meeting [06.02.13]	No change to declarations of interest.	None.
Tenth GDG meeting [14.03.13]	No change to declarations of interest.	None.
Eleventh GDG meeting [07.08.13]	Did not attend.	None.

B.3 Kathryn Carver

GDG meeting	Declaration of Interests	Action taken
On appointment	Declared a non-personal specific pecuniary interest: Is treasurer of the British Association of Cardiovascular Prevention and Rehabilitation (BACPR), an affiliate group of the British Cardiovascular Society. The BACPR received support from the healthcare industry for its national conference, amounting to £20,000 - £30,000 per year from a range of companies, the exact amounts and companies varies from year to year. Declared a personal non-pecuniary interest: Is a member of the BACPR Council, currently holding position of treasurer.	None.
First GDG meeting [15.03.12]	No change to declarations of interest.	None.
Second GDG meeting [25.04.12]	No change to declarations of interest.	None.

GDG meeting	Declaration of Interests	Action taken
Third GDG meeting [12.06.12] & Fourth GDG meeting [13.06.12]	No change to declarations of interest.	None.
Fifth GDG meeting [10.07.12]	No change to declarations of interest.	None.
Sixth GDG meeting [18.09.12]	No change to declarations of interest.	Declare and participate.
Seventh GDG meeting [01.11.12]	No change to declarations of interest.	None.
Eighth GDG meeting [12.12.12]	No change to declarations of interest.	None.
Ninth GDG meeting [06.02.13]	No change to declarations of interest.	None.
Tenth GDG meeting [14.03.12]	No change to declarations of interest.	None.
Eleventh GDG meeting [TBC]	No change to declarations of interest.	None.

B.4 William Cunningham

GDG meeting	Declaration of Interests	Action taken
On appointment	Nothing to declare.	None.
First GDG meeting [15.03.12]	No change to declarations of interest.	None.
Second GDG meeting [25.04.12]	No change to declarations of interest.	None.
Third GDG meeting [12.06.12] & Fourth GDG meeting [13.06.12]	No change to declarations of interest.	None.
Fifth GDG meeting [10.07.12]	No change to declarations of interest.	None.
Sixth GDG meeting [18.09.12]	No change to declarations of interest.	None.
Seventh GDG meeting [01.11.12]	No change to declarations of interest.	None.
Eighth GDG meeting [12.12.12]	No change to declarations of interest.	None.
Ninth GDG meeting [06.02.13]	No change to declarations of interest.	None.
Tenth GDG meeting [14.03.13]	No change to declarations of interest.	None.
Eleventh GDG meeting [07.08.13]	No change to declarations of interest.	None.

B.5 Jennifer Jones

GDG meeting	Declaration of Interests	Action taken
On appointment	Declared a personal non-pecuniary interest: Is current President of the British Association for Cardiovascular Prevention and Rehabilitation. The association's mission is 'promoting excellence in cardiovascular disease prevention and rehabilitation', which is aligned to the aims of this NICE guidance and not a conflict as such but based on the descriptors provided is being declared.	Declare and participate.
First GDG meeting [15.03.12]	Declared a non-personal pecuniary interest: Is the President of the BACPR which has recently published new Standards and Core Components. BACPR are part of a Taskforce for the REACCT project by Roche. BACPR have received £600 to attend a meeting (Dec 2011) and contribute to a toolkit being produced which is essentially a patient pathway for ACS and innovation in practice to reduce variation in care. Roche are also main sponsors at the BACPR conference 2012 in Edinburgh.	Declare and participate.
Second GDG meeting [25.04.12]	No change to declarations of interest.	None.
Third GDG meeting [12.06.12] & Fourth GDG meeting [13.06.12]	Did not attend.	None.
Fifth GDG meeting [10.07.12]	No change to declarations of interest.	None.
Sixth GDG meeting [18.09.12]	No change to declarations of interest.	None.
Seventh GDG meeting [01.11.12]	No change to declarations of interest.	None.
Eighth GDG meeting [12.12.12]	No change to declarations of interest.	None.
Ninth GDG meeting [06.02.13]	Did not attend.	None.
Tenth GDG meeting [14.03.13]	No change to declarations of interest.	None.
Eleventh GDG meeting [07.08.13]	No change to declarations of interest.	None.

B.6 Caroline Levie

GDG meeting	Declaration of Interests	Action taken
On appointment	Declared a personal pecuniary interest: BHF adopted nurse. BHF supported education and training for BHF adopted nurses. The process is:- study leave is applied for and paid for by the nurse and then if the study is agreed by the BHF they then reimburse the nurse the conference fee. Declared a personal non-pecuniary interest: Participated in a study on Hospital marketing services for CSD health research (Dec 2011). CSD health research did not recommend/influence which drugs to prescribe.	Declare and participate.
First GDG meeting [15.03.12]	No change to declarations of interest.	None.
Second GDG meeting [25.04.12]	No change to declarations of interest.	None.
Third GDG meeting [12.06.12] & Fourth GDG meeting [13.06.12]	No change to declarations of interest.	None.
Fifth GDG meeting [10.07.12]	No change to declarations of interest.	None.
Sixth GDG meeting [18.09.12]	No change to declarations of interest.	None.
Seventh GDG meeting [01.11.12]	No change to declarations of interest.	None.
Eighth GDG meeting [12.12.12]	No change to declarations of interest.	None.
Ninth GDG meeting [06.02.13]	No change to declarations of interest.	None.
Tenth GDG meeting [14.03.13]	No change to declarations of interest.	None.
Eleventh GDG meeting [07.08.13]	No change to declarations of interest.	None.

B.7 Joseph Mills (until July 2012)

GDG meeting	Declaration of Interests	Action taken
On appointment	Declared a personal specific pecuniary interest: • Attended an advisory board for Abbott on omega-3-acid-ethyl esters for which an honorarium was received (December 2011).	None.

GDG meeting	Declaration of Interests	Action taken
	Declared a personal non-pecuniary interest: Is a council member of the British Association of Cardiovascular Prevention and Rehabilitation.	
First GDG meeting [15.03.12]	Did not attend.	None.
Second GDG meeting [25.04.12]	Declared a personal specific pecuniary interest: • Attended an advisory board for Boehringer Ingelheim on dabigatran for the management of atrial fibrilliation (January 2012), for which an honorarium was received. • Attended an advisory board for Astra Zeneca on ticagrelor (February 2012), for which an honorarium was received. • Attended an advisory board for Lilly on prasugrel (November 2011), for which an honorarium was received • Involved in an education programme for general practitioners on the management of stable angina, in line with the NICE guideline on stable angina, funded by Mennarini.	Declare and withdraw from discussions of evidence and drafting of recommendations relating to: • Omega-3-acid-ethyl esters
Third GDG meeting [12.06.12] & Fourth GDG [13.06.12]	No changes to declarations of interest.	Declare and withdraw from discussions of evidence and drafting of recommendations relating to : • Antiplatelet therapy in those with a pre-existing indication for anticoagulation. • Late initiation of antiplatelet therapy • Duration of clopidogrel therapy
Fifth GDG meeting [10.07.12]	Did not attend.	None.

NB. Joseph Mills left the GDG after GDG meeting 5.

B.8 Jerry Murphy

GDG meeting	Declaration of Interests	Action taken
On appointment	Declared a personal specific pecuniary interest: • Attended an advisory board for MSD on the use of ezetemibe (October 2011).	None.
First GDG meeting	Did not attend.	None.

GDG meeting	Declaration of Interests	Action taken
[15.03.12]		
Second GDG meeting [25.04.12]	No changes to declarations of interest.	None.
Third GDG meeting [12.06.12] & Fourth GDG meeting [13.06.12]	No changes to declarations of interest.	None.
Fifth GDG meeting [10.07.12]	Did not attend.	None.
Sixth GDG meeting [18.09.12]	Did not attend.	None.
Seventh GDG meeting [01.11.12]	No changes to declarations of interest.	Declared but did not withdraw from discussions of evidence and drafting of recommendations relating to ACE inhibitors and ARBs as declarations expired October 2012.
Eighth GDG meeting [12.12.12]	Declared a personal specific pecuniary interest: • Presented on the use of rivaroxaban (10th October & 7th November 2012), for which an honorarium was received from Bayer.	Declare and withdraw from future discussions of evidence and drafting of recommendations relating to: • Antiplatelets in those with a pre-existing indication for anticoagulation.
Ninth GDG meeting [06.02.13]	Did not attend.	None.
Tenth GDG meeting [14.03.13]	No changes to declarations of interest.	None.
Eleventh GDG meeting [07.08.13]	Did not attend.	None.

B.9 Sanjay Ramdany

GDG meeting	Declaration of Interests	Action taken
On appointment	No declarations of interest.	None.
First GDG meeting [15.03.12]	No change to declarations of interest.	None.
Second GDG meeting [25.04.12]	Did not attend.	None.
Third GDG meeting [12.06.12] & Fourth GDG meeting [13.06.12]	No change to declarations of interest.	None.
Fifth GDG meeting [10.07.12]	No change to declarations of interest.	None.
Sixth GDG meeting [18.09.12]	No change to declarations of interest.	None.
Seventh GDG meeting [01.11.12]	Did not attend.	None.

GDG meeting	Declaration of Interests	Action taken
Eighth GDG meeting [12.12.12]	No change to declarations of interest.	None.
Ninth GDG meeting [06.02.13]	No change to declarations of interest.	None.
Tenth GDG meeting [14.03.12]	No change to declarations of interest.	None.
Eleventh GDG meeting [07.08.13]	Did not attend.	None.

B.10 Linda Speck

GDG meeting	Declaration of Interests	Action taken
On appointment	Declared a personal non-specific non-pecuniary interest: Is an elected council member for the British Association for Cardiovascular Prevention and Rehabilitation (BACPR).	Declare and participate.
First GDG meeting [15.03.12]	No change to declarations of interest.	None.
Second GDG meeting [25.04.12]	No change to declarations of interest.	None.
Third GDG meeting [12.06.12] & Fourth GDG meeting [13.06.12]	Did not attend.	None.
Fifth GDG meeting [10.07.12]	No change to declarations of interest.	None.
Sixth GDG meeting [18.09.12]	No change to declarations of interest.	None.
Seventh GDG meeting [01.11.12]	Did not attend.	None.
Eighth GDG meeting [12.12.12]	No change to declarations of interest.	None.
Ninth GDG meeting [06.02.13]	No change to declarations of interest.	None.
Tenth GDG meeting [14.03.13]	No change to declarations of interest.	None.
Eleventh GDG meeting [07.08.13]	Did not attend.	None.

B.11 John Walsh

GDG meeting	Declaration of Interests	Action taken
On appointment	Nothing to declare.	None.
First GDG meeting [15.03.12]	No change to declarations of interest.	None.

GDG meeting	Declaration of Interests	Action taken
Second GDG meeting [25.04.12]	No change to declarations of interest.	None.
Third GDG meeting [12.06.12] & Fourth GDG meeting [13.06.12]	No change to declarations of interest.	None.
Fifth GDG meeting [10.07.12]	No change to declarations of interest.	None.
Sixth GDG meeting [18.09.12]	No change to declarations of interest.	None.
Seventh GDG meeting [01.11.12]	Did not attend.	None.
Eighth GDG meeting [12.12.12]	No change to declarations of interest.	None.
Ninth GDG meeting [06.02.13]	No change to declarations of interest.	None.
Tenth GDG meeting [14.03.13]	No change to declarations of interest.	None.
Eleventh GDG meeting [07.08.13]	Did not attend.	None.

B.12 Maria Wray

GDG meeting	Declaration of Interests	Action taken
On appointment	Nothing to declare.	None.
First GDG meeting [15.03.12]	No change to declarations of interest.	None.
Second GDG meeting [25.04.12]	No change to declarations of interest.	None.
Third GDG meeting [12.06.12] & Fourth GDG meeting [13.06.12]	Did not attend.	None.
Fifth GDG meeting [10.07.12]	No change to declarations of interest.	None.
Sixth GDG meeting [18.09.12]	No change to declarations of interest.	None.
Seventh GDG meeting [01.11.12]	No change to declarations of interest.	None.
Eighth GDG meeting [12.12.12]	No change to declarations of interest.	None.
Ninth GDG meeting [06.02.13]	Did not attend.	None.
Tenth GDG meeting [14.03.13]	Did not attend.	None.
Eleventh GDG meeting [07.08.13]	Did not attend.	None.

B.13 Paul Wright

GDG meeting	Declaration of Interests	Action taken
On appointment	Nothing to declare.	None.
First GDG meeting [15.03.12]	No change to declarations of interest.	None.
Second GDG meeting [25.04.12]	No change to declarations of interest.	None.
Third GDG meeting [12.06.12] & Fourth GDG meeting [13.06.12]	No change to declarations of interest.	None.
Fifth GDG meeting [10.07.12]	No change to declarations of interest.	None.
Sixth GDG meeting [18.09.12]	No change to declarations of interest.	None.
Seventh GDG meeting [01.11.12]	No change to declarations of interest.	None.
Eighth GDG meeting [12.12.12]	No change to declarations of interest.	None.
Ninth GDG meeting [06.02.13]	No change to declarations of interest.	None.
Tenth GDG meeting [14.03.13]	No change to declarations of interest.	None.
Eleventh GDG meeting [07.08.13]	No change to declarations of interest.	None.

B.14 Robert Wright (from September 2012)

GDG meeting	Declaration of Interests	Action taken
On appointment	Nothing to declare.	None.
Fifth GDG meeting [10.07.12]	No change to declarations of interest.	None.
Sixth GDG meeting [18.09.12]	Did not attend.	None.
Seventh GDG meeting [01.11.12]	No change to declarations of interest.	None.
Eighth GDG meeting [12.12.12]	No change to declarations of interest.	None.
Ninth GDG meeting [06.02.13]	No change to declarations of interest.	None.
Tenth GDG meeting [14.03.13]	No change to declarations of interest.	None.
Eleventh GDG meeting [07.08.13]	No change to declarations of interest.	None.

B.15 Jo Farrington (co-opted expert)

GDG meeting	Declaration of Interests	Action taken
On appointment	Declared a personal non-pecuinary interest: Is a member of the British Dietetic Association and its UK Heart Health & Thoracic Specialist interest group.	Declare and participate.
First GDG meeting [15.03.12]	No change to declarations of interest.	None.
Second GDG meeting [25.04.12]	No change to declarations of interest.	None.
Sixth GDG meeting [18.09.12]	No change to declarations of interest.	None.
Tenth GDG meeting [14.03.13]	No changes to declarations of interest.	None.

B.16 NCGC members

GDG meeting	Declaration of Interests	Action taken
First GDG meeting [15.03.12]	Nothing to declare	None
Second GDG meeting [25.04.12]	No change to declarations of interest.	None
Third GDG meeting [12.06.12] & Fourth GDG meeting [13.06.12]	No change to declarations of interest.	None
Fifth GDG meeting [10.07.12]	No change to declarations of interest.	None
Sixth GDG meeting [18.09.12]	No change to declarations of interest.	None
Seventh GDG meeting [01.11.12]	No change to declarations of interest.	None
Eighth GDG meeting [12.12.12]	No change to declarations of interest.	None
Ninth GDG meeting [06.02.13]	No change to declarations of interest.	None
Tenth GDG meeting [14.03.13]	No change to declarations of interest.	None
Eleventh GDG meeting [07.08.13]	No change to declarations of interest.	None.

Appendix C: Review protocols

C.1 Clinical evidence reviews

C.1.1 Lifestyle

C.1.1.1 Omega-3 fatty acids

Review question	What is the clinical and cost effectiveness of omega-3-fatty acids in all people with myocardial infarction?
Objectives	To assess the clinical and cost effectiveness of pharmaceutical or foods supplemented with omega-3 fatty acids-for the secondary prevention of myocardial infarction.
Strata	Food supplementation (e.g. fortified margarine) vs. capsule form of omega-3-fatty acids.
Population	**Population:** Adult individuals or groups who have had an MI (type 1 universal definition) (>75% post MI is considered a direct population) Including: • Patients following the acute early phase, providing the patient is stable. • STEMI patients • NSTEMI patients • In older ACS studies, a large proportion of unstable angina patients would now be classified in the direct population as NSTEMI (based on changes in ECG and enzyme levels). • If insufficient high quality data, extend this to include all patients with a history of CHD (stable angina, unstable angina, or revascularisation) and <75% post MI patients (indirect population).
Criteria	**Duration** Minimum of 6 months/26 weeks or180 days for advice trials, follow-up must have been at least six months following advice, for trials where food supplements are provided then the provision must have continued for at least six months. **Included:** • Randomised controlled trials. If RCTs are unavailable cohort studies will be included. **Excluded:** • Patients diagnosed as having a type 2, 3, 4a, 4b or 5 MI as per the universal definition of myocardial infarction. • Papers with a study design that included a lifestyle intervention, unless the effect of diet or supplementation could be separated out from the other interventions • Patients with heart failure • Patient with implanted cardiac defibrillators. **Interventions** • Omega-3-acid ethyl esters (EPA±DHA±AHA) provided in capsule or margarine form (± vitamins, concomitant medication). • Comparisons • Placebo (± vitamins, concomitant medication) • Dietary advice **Study design** • Randomised controlled trials (RCTs) and if RCTs are unavailable, cohort studies will be

Review question	What is the clinical and cost effectiveness of omega-3-fatty acids in all people with myocardial infarction?
	included. **Outcomes:** **CRITICAL** • Mortality (all cause, cardiac or sudden) • Quality of life (report all, inc EQ-5D (EuroQol), SF-36 (Short Form 36), SF6D (Short Form 6-Dimensions), SF-12 (Short Form 12-Dimensions), RAND-36 (Research and Development Medical Outcomes Study Short Form-36), HUI (Health Utilities Index), EQ-VAS (Euroqol visual analogue scale), 15D - 15 dimensions, QWB (Quality of Well Being), AQol (Assessment of Quality of Life)) **IMPORTANT** • Reinfarction • Revascularisation • Stroke **RELEVANT** • Readmission/Hospitalisation • Side effects/Adverse events **Settings:** • Primary care • Secondary care • Tertiary care • Community settings in which NHS care is delivered. **Population size and directness:** • No limitations on sample size. • Studies with indirect populations (<75% post MI) will be considered if no data is available or only low quality data is available on direct populations (>75% post MI). • Papers with more than 30% HF patients will be excluded.
Search	• The databases to be searched are Medline, Embase and the Cochrane Library. • Type of studies included: randomised controlled trials (RCTs) and if RCTs are unavailable, prospective cohort studies will be included. • Studies will be restricted to English language only. • June 2006 onwards. • Abstracts will be excluded unless there are no other studies available for a particular outcome or clinical question. • Phase I and II (non-randomised) and cross-over studies are excluded. • No trial duration maximum limit.
Review strategy	**Cochrane Reviews** Cochrane reviews will be quality assessed and presented. Any papers included in the Cochrane review that were not included in the original guideline and deemed to be important, will be ordered and considered for inclusion. **Data analysis** The outcomes will be presented and analysed using Hazard Ratios (HR) or Relative Risk (RR) where appropriate. Hazard ratios are presented in preference to RR for outcomes that are influenced by trial duration i.e. mortality, reinfarction, regardless of the number of papers

Review question	What is the clinical and cost effectiveness of omega-3-fatty acids in all people with myocardial infarction?
	available for each calculation. The exceptions to this are: 1) when the quality of the HR data is low or; 2) key papers that influence current medical practice are excluded from the analysis because they only provide RR data. In such instances RR data will also be presented. Hazard ratios will be calculated wherever possible. Relative risk will be used for adverse events. Default minimal important differences (MIDs) for hazard ratios and relative risks will be used: 0.75 and 1.25. Meta-analysis will be conducted wherever possible (i.e. where similar studies can be combined). **Data synthesis of RCT data and subgroups:** Meta-analysis where appropriate will be conducted. The following subgroups will be investigated regardless of whether or not there is heterogeneity. These subgroups were raised as an area to investigate by the stakeholders and the GDG may give separate recommendations on these groups. Food supplementation (e.g. margarine fortified with EPA+DHA±AHA) vs. capsule form of omega-3 fatty acids. **Heterogeneity / sub group analysis.** If there is heterogeneity sensitivity analysis will first be explored by eliminating any papers that have a high risk of bias. Once sensitivity analysis has been performed the impact of the following subgroups on heterogeneity will be examined: ○ Population (% of patients post MI <75% vs.>75%) ○ Timing of onset of treatment after MI (< 3 months vs.> 3 months) ○ Fish versus plant source of omega-3-acid ethyl esters. Fish sources include purified eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA), plant sources included linseed (flax), canola (rapeseed), mustard seed, candlenut or walnut oils or as a food and purified alpha-linolenic acid (AHA). If heterogeneity cannot be explained by the subgroups, then the results will be presented as random effects, rather than fixed effects.

C.1.1.2 Oily fish consumption

Review question	What is the clinical and cost effectiveness of an oily fish diet in all people with myocardial infarction?
Objectives	To assess the clinical and cost effectiveness of oily fish consumption, rich in omega-3 fatty acids, for the secondary prevention of myocardial infarction.
Criteria	**Population:** Adult individuals or groups who have had an MI (type 1 universal definition) (>75% post MI = direct population) **Including:** • Patients following the acute early phase, providing the patient is stable. • STEMI patients • NSTEMI patients • In older ACS studies, a large proportion of unstable angina patients would now be classified in the direct population as NSTEMI (based on changes in ECG and enzyme levels) • If insufficient high quality data, extend this to include all patients with a history of CHD (stable angina, unstable angina, or revascularisation) and <75% post MI patients (indirect population).

Review question	What is the clinical and cost effectiveness of an oily fish diet in all people with myocardial infarction?
	Duration • Minimum of 6 months/26 weeks or • 180 days for advice trials, follow-up must have been at least six months following advice. **Included:** • Randomised controlled trials. If RCTs are unavailable, cohort studies will be included. • Studies that compared dietary advice on oily fish rich in omega-3-acid ethyl esters with usual diet or no advice. **Excluded:** • Patients diagnosed as having a type 2, 3, 4a, 4b or 5 MI as per the universal definition of myocardial infarction. • Papers with a study design that included a lifestyle intervention, unless the effect of diet could be separated out from the other interventions. • Papers that included a Mediterranean diet, unless the effect of the fish diet can be separated out. • Study populations with more than 30% heart failure patients **Study design:** • Randomised controlled trials (RCTs) • If RCTs are unavailable, cohort studies will be included. **Intervention** • Oily fish **Control** • Usual diet • Other dietary advice **Outcomes:** **CRITICAL** • Mortality (all cause, cardiac or sudden) • Quality of life (report all, inc EQ-5D (EuroQol), SF-36 (Short Form 36), SF6D (Short Form 6-Dimensions), SF-12 (Short Form 12-Dimensions), RAND-36 (Research and Development Medical Outcomes Study Short Form-36), HUI (Health Utilities Index), EQ-VAS (Euroqol visual analogue scale), 15D - 15 dimensions, QWB (Quality of Well Being), AQol (Assessment of Quality of Life)) **IMPORTANT** • Re-infarction • Revascularisation • Stroke **RELEVANT** • Readmission/Hospitalisation • Side effects/Adverse events

Review question	What is the clinical and cost effectiveness of an oily fish diet in all people with myocardial infarction?
	Settings: • Primary care • Secondary care • Tertiary care • Community settings in which NHS care is delivered **Population size and directness:** • No limitations on sample size • Studies with indirect populations (<75% post MI) will be considered if no data is available or only low quality data is available in a direct population (<75%) MI . • Study populations with ≥30% heart failure patients will be excluded
Search strategy	• The databases to be searched are Medline, Embase and the Cochrane Library. • Type of studies included: randomised controlled trials (RCTs) and if RCTs are unavailable, cohort studies will be included. • Studies will be restricted to English language only. • June 2006 onwards. • Abstracts will be excluded unless there are no other studies available for a particular outcome or clinical question. • Phase I and II (non randomised) and cross-over studies are excluded. • No trial duration maximum limit.
Review strategy	**Cochrane Reviews** Cochrane reviews will be quality assessed and presented. Any papers included in the Cochrane, that were not reviewed in the original guideline and deemed to be important, will be ordered and considered for inclusion. **Data analysis** The outcomes will be presented and analysed using Hazard Ratios (HR) and or Relative Risk (RR) where appropriate. Hazard ratios are presented in preference to RR for outcomes that are influenced by trial duration i.e. mortality, reinfarction, regardless of the number of papers available for each calculation. Hazard ratios will be calculated wherever possible. Relative risk will be used for adverse events. Default minimal important differences (MIDs) for hazard ratios and relative risks will be used: 0.75 and 1.25. Meta-analysis will be conducted wherever possible (i.e. where similar studies can be combined). **Heterogeneity** If there is heterogeneity sensitivity analysis will first be explored by eliminating any papers that have a high risk of bias. Once sensitivity analysis has been performed the impact of the following subgroups on heterogeneity will be examined: o Population direct vs. indirect (<75% vs. >75% of post MI patients) o Onset of treatment <3 months vs. >3 months post MI. If heterogeneity cannot be explained the RR results will be presented as random effects, rather than fixed effects

C.2 Cardiac rehabilitation

C.2.1.1 Barriers to the uptake of and adherence to cardiac rehabilitation

Review question	Which factors are associated with a persons' uptake and adherence to a cardiac rehabilitation programme (CRP) after an MI?
Objectives	To assess the barriers and factors associated with participating in a cardiac rehabilitation programme.
Strata	Factors associated with patient's uptake and adherence to CRP Factors associated with healthcare professionals in promoting patient's uptake and adherence to CRP
Criteria	**Population:** • Adults (≥ 18 years) who have had an MI (type 1 universal definition). • Healthcare professionals • If insufficient high quality data, extend this to include all patients with a history of CHD (stable angina, unstable angina, or revascularisation) and <75% post MI patients. (indirect population) • For indirect populations, we will accept a maximum of 30% heart failure patients **Areas of focus** • Ethnicity (South Asian, black and minority groups) • Men vs. women • Socioeconomic background • Rural communities • People with anxiety and depression • People with physical and learning disabilities • Age <75 yrs vs. >75 yrs • English vs. non-English speaking • Working vs. non-working **Excluded:** • Patients diagnosed as having a type 2, 3, 4a, 4b or 5 MI as per the universal definition of myocardial infarction. • Heart failure patients **Outcomes:** • Factors associated with patient's uptake and adherence to CRP. • Factors associated with healthcare professionals in promoting patient's uptake and adherence to CRP **Settings:** • All areas of care. **Population size and directness:** • No minimum number of patients • Studies with indirect populations will be considered if limited data is available on our direct population
Search strategy	• The databases to be searched are CINAHL, Medline, Embase, the Cochrane Library and PsychINFO.

Review question	Which factors are associated with a persons' uptake and adherence to a cardiac rehabilitation programme (CRP) after an MI?
	• Type of studies included: qualitative studies (interviews, focus groups and questionnaires) and reviews. • Types of studies excluded: case studies • Studies will be restricted to English language only and UK based studies • June 2006 onwards. This date reflects a reasonable cut off from when healthcare professionals are aware they should refer patients' to cardiac rehabilitation programs. If they are not referring patients we need to know why. • Abstracts will be excluded unless there are no other studies available for a particular outcome or clinical question
Review strategy	**Part 1** This review will follow-on from the results extracted from the review on 'Interventions that increase adherence and uptake to cardiac rehabilitation programs'. This review captured reasons why patients didn't participate in the CRP in a quantitative manner. We will present these results as part one of this review. **Part 2** Systematic reviews on this topic will be preferentially used to identify factors associated with uptake and adherence to CRPs. If insufficient data is available, individual papers will be used to identify these factors. Thematic data analysis will be conducted to identify all relevant factors associated with uptake and adherence to CRP. We will tabulate the reasons why particular groups (previously identified by the GDG, CG48 and in the NICE scope as listed above) known to be poor adherers of cardiac rehabilitation programs do not participate in the CRP. Results will be presented in a table with the groups of interest listed across the top and the reasons vertically. Each time a paper identifies a reason for a group, we will record this in the table. Data will be extracted until the point of saturation, i.e. when all factors predicting uptake or adherence are detected and no new information is being found. From this point on, no more papers will be reviewed. UK only papers will be included initially. If insufficient information, papers from outside the UK will be included.

C.2.1.2 Interventions to increase uptake of and adherence to a cardiac rehabilitation programme

Review question	Which interventions designed to increase engagement in and/or adherence to cardiac rehabilitation programmes are effective and cost effective in people who have had an MI?
Objectives	To assess the clinical and cost effectiveness of interventions to uptake and adhere to a cardiac rehabilitation programme.
Strata	• Ethnicity (South Asian, black and minority groups)/ • Gender • Socioeconomic background • Rural communities • People with anxiety and depression

Review question	Which interventions designed to increase engagement in and/or adherence to cardiac rehabilitation programmes are effective and cost effective in people who have had an MI?
	• People with physical and learning disabilities • Age <75 years vs. >75 years • English vs. non-English speaking • Working vs. non-working • Timing of recruitment (role of cardiologist is a key factor) • Programmes targeting particular groups
Criteria	**Population:** • Adult individuals or groups who have had an MI (type 1 universal definition) (>75% post MI = direct population) • If insufficient high quality data, extend this to include all patients with a history of CHD (stable angina, unstable angina, or revascularisation) and <75% post MI patients. • Note: In older ACS studies, a large proportion of unstable angina patients would now be classified in the direct population as NSTEMI (based on changes in ECG and enzyme levels) **Intervention** • Any intervention with the aim of increasing patient uptake of, or adherence to, cardiac rehabilitation of any of its component parts. **Comparison** • No intervention or usual care. **Study design:** • Randomised controlled trials • Non randomised trials i.e. prospective cohort studies n=100 total (50/group) • Non-blinded, single + double-blinded trials **Outcomes:** **CRITICAL** • Adherence • Uptake **IMPORTANT** • Reasons for withdrawal • Quality of life • Adverse effects **Settings:** • Primary care • Secondary care • Tertiary care • Community settings in which NHS care is delivered **Population size and directness:** • Greater than 80 people in total • Studies with indirect populations will be considered if low quality data or no data is available. • Study populations with ≥30% heart failure patients will be excluded.
Search	• The databases to be searched are Medline, Embase and the Cochrane Library

Review question	Which interventions designed to increase engagement in and/or adherence to cardiac rehabilitation programmes are effective and cost effective in people who have had an MI?
	• Type of studies included: randomised controlled trials (RCTs), large prospective non-randomised trials. • Retrospective studies will be excluded. • Studies will be restricted to English language only • Abstracts will be excluded unless there are no other studies available for a particular outcome or clinical question • 2006 to now
Review strategy	**Cochrane Reviews** Cochrane reviews will be quality assessed and presented. Any papers included in the Cochrane, that were not reviewed in the original guideline and deemed to be important, will be ordered and considered for inclusion. **Health Technology Assessment** The health TA on this topic "Provision, update and cost of cardiac rehabilitation programs: improving services to under-represented groups" will be incorporated, where possible, in the review. **Data analysis** Meta-analysis will be conducted wherever possible (i.e. where similar studies can be combined). For data that cannot be meta-analysed the results will presented in a descriptive manner. In the case in which we have missing data, available case analysis will be performed unless the GDG has good reason to perform intention-to-treat with imputation. **Heterogeneity (sensitivity analysis and subgroups)** If heterogeneity is found it will first be explored by performing sensitivity analysis and eliminating papers that have a high risk of bias. If heterogeneity is still present, the influence of the following subgroups will then be examined: ○ Diagnosis (STEMI vs. NSTEMI) ○ Non-UK studies ○ Treatment i.e. PCI, CABG, medical ○ Comorbidity If heterogeneity cannot be explained the RR results will be presented as random effects, rather than fixed effects

C.3 Drug therapy

C.3.1.1 ACE inhibitors

Review question	What is the clinical and cost effectiveness of adding ACE inhibitors versus placebo to improve outcome in people after an MI and is there an optimal duration?
Objectives	To assess the clinical and cost effectiveness of using ACE inhibitors in people after an MI and identify whether there is an optimal duration of treatment.
Strata	In people after an MI who have: • LVSD or with heart failure • Without heart failure • Unselected LV function

	• Had a proven MI in the past (>1 year) (including those with LVSD, without heart failure and with unselected LV function)
Criteria	Adult individuals or groups who have had an MI (type 1 universal definition) (>75% post MI = direct population) **Including:** • Patients following the acute early phase (<72 hrs), providing the patient is stable. • Patients following the sub-acute phase (>72 hrs up to 12m) • Patients who have had an MI in the past (>1 yr) • STEMI patients • NSTEMI patients • In older ACS studies, a large proportion of unstable angina patients would now be classified in the direct population as NSTEMI (based on changes in ECG and enzyme levels) • If insufficient high quality data, extend this to include all patients with a history of CHD (stable angina, unstable angina, or revascularisation) and <75% post MI patients. (indirect population) • For indirect populations, we will accept a maximum of 30% heart failure patients **Intervention** • Captopril • Cilazapril • Enalapril • Fosinopril • Imidapril • Lisinopril • Moexipril • Perindopril • Quinapril • Ramipril • Trandolapril **Comparison** • Placebo **Study design** • Randomised controlled trials (RCTs) **Outcomes** **CRITICAL** • Mortality (all cause, cardiac or sudden) • Quality of life (report all, inc EQ-5D (EuroQol), SF-36 (Short Form 36), SF6D (Short Form 6-Dimensions), SF-12 (Short Form 12-Dimensions), RAND-36 (Research and Development Medical Outcomes Study Short Form-36), HUI (Health Utilities Index), EQ-VAS (Euroqol visual analogue scale), 15D - 15 dimensions, QWB (Quality of Well Being), AQol (Assessment of Quality of Life)) **IMPORTANT** • Re-infarction • Revascularisation • Stroke **RELEVANT**

	• Readmission/Hospitalisation • Side effects/Adverse events **Settings:** • Primary care • Secondary care • Tertiary care • Community settings in which NHS care is delivered
Search	• The databases to be searched are Medline, Embase and the Cochrane Library • Type of studies included: randomised controlled trials (RCTs) • Studies will be restricted to English language only • Abstracts will be excluded unless there are no other studies available for a particular outcome or clinical question • Phase I and II (non-randomised) and cross-over studies are excluded • Non-randomised controlled studies and open-label studies are excluded • 2006 to now • No trial duration limit.
Review strategy	**Cochrane Reviews** Cochrane reviews will be quality assessed and presented. Any papers included in the Cochrane, that were not reviewed in the original guideline and deemed to be important, will be ordered and considered for inclusion. **Data analysis** The outcomes will be presented and analysed using Hazard Ratios (HR) or Relative Risk (RR) where appropriate. Hazard ratios are presented in preference to RR for outcomes that are influenced by trial duration i.e. mortality, reinfarction, regardless of the number of papers available for each calculation. The exceptions to this are: 1) when the quality of the HR data is low or; 2) key papers that influence current medical practice are excluded from the analysis because they only provide RR data. In such instances RR data will also be presented. Relative risk will be used for adverse events. Default minimal important differences (MIDs) of 0.75 and 1.25 will be used for hazard ratios and relative risk. Meta-analysis will be conducted wherever possible (i.e. where similar studies can be combined). The numbers reported in the paper will be used, whether they be intention to treat (ITT), available case analysis (ACA) or per protocol analysis (PPA) **Heterogeneity (sensitivity analysis and subgroups)** If heterogeneity is found, it will first be explored by performing sensitivity analysis and eliminating papers that have a high risk of bias. If heterogeneity is still present, the influence of the following subgroups will then be examined: • Timing of initiating treatment: acute (≤72hrs post MI); sub-acute (>72 to ≤12m); in the past (>12m) • COPD: No COPD vs. COPD • type of treatment of MI (PCI or CABG or medical) • Diagnosis (STEMI vs. NSTEMI) • Age <75 yrs vs. >75 yrs

	• Diabetes • Ethnicity (Caucasian vs. non-Caucasian) • Kidney function If heterogeneity cannot be explained, the RR results will be presented as random effects rather than fixed effects.

C.3.1.2 Initiation of ACE inhibitors

Review question	**Is there an optimal time for ACE inhibitors to be initiated in people who have had a MI?**
Objectives	To estimate whether early initiation of ACE inhibitors or later initiation of ACE inhibitors is more clinically and cost-effective.
Criteria	**Population** Adult individuals or groups who have had an MI (type 1 universal definition) (>75% post MI = direct population) Including: • Patients following the acute early phase, providing the patient is stable. • STEMI patients • NSTEMI patients • In older ACS studies, a large proportion of unstable angina patients would now be classified in the direct population as NSTEMI (based on changes in ECG and enzyme levels) • If insufficient high quality data, extend this to include all patients with a history of CHD (stable angina, unstable angina, or revascularisation) and <75% post MI patients. (indirect population) For indirect populations, we will accept a maximum of 30% heart failure patients **Intervention** • Captopril • Cilazapril • Enalapril • Fosinopril • Imidapril • Lisinopril • Moexipril • Perindopril • Quinapril • Ramipril • Trandolapril • Direct study design: ACE inhibitor vs. same ACE inhibitor (for example, ACE inhibitor initiated day 3 vs. 7) • Indirect comparison: ACE inhibitor vs. placebo (comparing different papers that initiated treatment at different time points) **Duration** • Studies with all durations of follow-up will be included in the review. **Excluded:** People who: • Patients diagnosed as having a type 2,3, 4a, 4b, or 5 MI as per the universal definition of

Review question	Is there an optimal time for ACE inhibitors to be initiated in people who have had a MI?
	myocardial infarction. • Patients with heart failure if more than 25% of total population • Patient with implanted cardiac defibrillators **Comparison** • See above **Outcomes:** **CRITICAL** • Mortality (all cause, cardiac or sudden) • Quality of life (report all, inc EQ-5D (EuroQol), SF-36 (Short Form 36), SF6D (Short Form 6-Dimensions), SF-12 (Short Form 12-Dimensions), RAND-36 (Research and Development Medical Outcomes Study Short Form-36), HUI (Health Utilities Index), EQ-VAS (Euroqol visual analogue scale), 15D - 15 dimensions, QWB (Quality of Well Being), AQol (Assessment of Quality of Life)) **IMPORTANT** • Re-infarction • Revascularisation • Stroke **RELEVANT** • Readmission/Hospitalisation • Side effects/Adverse events **Settings:** • Primary care • Secondary care • Tertiary care • Community settings in which NHS care is delivered **Study design:** • Include: for direct study designs: cohort studies + randomised controlled trials • Include for: indirect studies designs: double blind randomised controlled trials • Exclude: trials that compare different ACE inhibitor to one another
Search	• The databases to be searched are Medline, Embase and the Cochrane Library • Type of studies included: randomised controlled trials (RCTs) and cohort studies • Studies will be restricted to English language only • Abstracts will be excluded unless there are no other studies available for a particular outcome or clinical question • Phase I and II (non randomised) and cross-over studies are excluded • Non-randomised controlled studies and open-label studies are excluded • New search • No trial duration limit.
Review strategy	**Cochrane Reviews** Cochrane reviews will be quality assessed and presented. Any papers included in the Cochrane, that were not reviewed in the original guideline and deemed to be important, will be ordered and considered for inclusion.

Review question	Is there an optimal time for ACE inhibitors to be initiated in people who have had a MI?
	Data analysis The outcomes will be presented and analysed using Hazard Ratios (HR) or Relative Risk (RR) where appropriate. Hazard ratios are presented in preference to RR for outcomes that are influenced by trial duration i.e. mortality, reinfarction, regardless of the number of papers available for each calculation. The exceptions to this are: 1) when the quality of the HR data is low or; 2) key papers that influence current medical practice are excluded from the analysis because they only provide RR data. In such instances RR data will also be presented. Relative risk will be used for adverse events. Default minimal important differences (MIDs) of 0.75 and 1.25 will be used for hazard ratios and relative risk. For decision making, MIDs for absolute changes in mortality and reinfarction is set at ±10% Meta-analysis will be conducted wherever possible (i.e. where similar studies can be combined). In the case in which we have missing data, available case analysis will be performed unless the GDG has good reason to perform intention-to-treat with imputation. **Heterogeneity (sensitivity analysis and subgroups)** If heterogeneity is found, it will first be explored by performing sensitivity analysis and eliminating papers that have a high risk of bias. If heterogeneity is still present, the influence of the following subgroups will then be examined: ○ type of treatment of MI (PCI or CABG or medical) ○ Diagnosis (STEMI vs. NSTEMI) ○ Age <75 years vs. >75 years ○ Diabetes ○ Ethnicity (Caucasian vs. non-Caucasian) ○ Kidney function If heterogeneity cannot be explained the RR results will be presented as random effects, rather than fixed effects.

C.3.1.3 Titration of ACE inhibitors

Review protocol	Is early dose titration of ACE inhibitors in hospital more clinically and cost effective than dose titration over an extended period of time in people who have had a MI?
Objectives	To produce a recommendation on the use of ACE inhibitors in people after a MI.
Strata	**Acute MI** • with left ventricular systolic dysfunction (LVSD) • normal left ventricular systolic function (normal LV function) • unselected patients
Criteria	**Population:** Adult individuals or groups who have had an MI (type 1 universal definition) (>75% post MI = direct population) **Including:**

Review protocol	Is early dose titration of ACE inhibitors in hospital more clinically and cost effective than dose titration over an extended period of time in people who have had a MI?
	• Patients following the acute early phase, providing the patient is stable. • STEMI patients • NSTEMI patients • In older ACS studies, a large proportion of unstable angina patients would now be classified in the direct population as NSTEMI (based on changes in ECG and enzyme levels) • If insufficient high quality data, extend this to include all patients with a history of CHD (stable angina, unstable angina, or revascularisation) and <75% post MI patients. (indirect population) • For indirect populations, we will accept a maximum of 30% heart failure patients. **Intervention /Comparison** ACE inhibitors vs. same ACE inhibitors (for example, titration to maximum dose over 3 days vs. 7 days, or other durations of titration that reflect current practice). **ACE inhibitors** • Captopril • Cilazapril • Enalapril • Fosinopril • Imidapril • Lisinopril • Moexipril • Perindopril • Quinapril • Ramipril • Trandolapril **Duration** • Studies with all durations of follow up after titration to maximum dose has been achieved will be included in the review. **Excluded:** • Patients diagnosed as having a type 2, 3, 4a, 4b or 5 MI as per the universal definition of myocardial infarction. • Studies that include more than 30% HF patients. • Patient with implanted cardiac defibrillators **Study design:** • Double blind randomised controlled trials **Outcomes:** **CRITICAL** • Mortality (all cause, cardiac or sudden) • Quality of life (report all, inc EQ-5D (EuroQol), SF-36 (Short Form 36), SF6D (Short Form 6-Dimensions), SF-12 (Short Form 12-Dimensions), RAND-36 (Research and Development Medical Outcomes Study Short Form-36), HUI (Health Utilities Index), EQ-VAS (Euroqol visual analogue scale), 15D - 15 dimensions, QWB (Quality of Well Being), AQol (Assessment of Quality of Life))

Review protocol	Is early dose titration of ACE inhibitors in hospital more clinically and cost effective than dose titration over an extended period of time in people who have had a MI?
	IMPORTANT • Re-infarction • Revascularisation • Stroke **RELEVANT** • Readmission/Hospitalisation • Side effects/Adverse events **Settings:** • Primary care • Secondary care • Tertiary care **Population size and directness:** • No limitations on sample size • Studies with indirect populations will be considered if low quality data or no data from direct populations are available.
Search strategy	• The databases to be searched are Medline, Embase and the Cochrane Library • Type of studies included: randomised controlled trials (RCTs) • Studies will be restricted to English language only • Abstracts will be excluded unless there are no other studies available for a particular outcome or clinical question • Phase I and II (non randomised) and cross-over studies are excluded • Non-randomised controlled studies and open-label studies are excluded • New search • No trial duration limit.
Review strategy	**Cochrane Reviews** Cochrane reviews will be quality assessed and presented. Any papers included in the Cochrane, that were not reviewed in the original guideline and deemed to be important, will be ordered and considered for inclusion. **Data analysis** The outcomes will be presented and analysed using Hazard Ratios (HR) or Relative Risk (RR) where appropriate. Hazard ratios are presented in preference to RR for outcomes that are influenced by trial duration i.e. mortality, reinfarction, regardless of the number of papers available for each calculation. The exceptions to this are: 1) when the quality of the HR data is low or; 2) key papers that influence current medical practice are excluded from the analysis because they only provide RR data. In such instances RR data will also be presented. Relative risk will be used for adverse events. Default minimal important differences (MIDs) of 0.75 and 1.25 will be used for hazard ratios and relative risk. Meta-analysis will be conducted wherever possible (i.e. where similar studies can be combined).

Review protocol	Is early dose titration of ACE inhibitors in hospital more clinically and cost effective than dose titration over an extended period of time in people who have had a MI?
	In the case in which we have missing data, available case analysis will be performed unless the GDG has good reason to perform intention-to-treat with imputation. **Heterogeneity (sensitivity analysis and subgroups)** If heterogeneity is found, it will first be explored by performing sensitivity analysis and eliminating papers that have a high risk of bias. If heterogeneity is still present, the influence of the following subgroups will then be examined: type of treatment of MI (PCI or CABG or medical) ○ Diagnosis (STEMI vs NSTEMI) ○ Age <75 yrs vs. >75 yrs ○ Diabetes ○ Ethnicity (Caucasian vs. non-Caucasian) ○ Kidney function If heterogeneity cannot be explained the RR results will be presented as random effects, rather than fixed effects

C.3.1.4 ACE inhibitors vs. ARBs

Review question	What is the clinical and cost effectiveness of adding ACE inhibitors versus ARBs or in combination versus ACE inhibitors to improve outcomes in people after an MI?
Objectives	To assess the clinical and cost effectiveness of ACE inhibitors versus ARBs, as well as in combination, in people who have had an MI, including those without heart failure or LVSD and who are intolerant to ACE inhibitors and have LVSD.
Strata	In people who have had an acute MI (0-72 hours) ○ people after a MI with left ventricular systolic dysfunction (LVSD) ○ unselected LV function people after a MI (mix of with and without LVSD) ○ without LVSD or heart failure In people who have had a sub-acute MI (>72 hours) ○ people after a MI with left ventricular systolic dysfunction (LVSD) ○ unselected LV function people after a MI (mix of with and without LVSD) ○ without LVSD or heart failure In people who have had an MI at some point in the past (>1year) ○ people after a MI with left ventricular systolic dysfunction (LVSD) ○ unselected LV function people after a MI (mix of with and without LVSD) ○ without LVSD or heart failure
Criteria	**Population:** Adults (≥ 18 years) who have had an MI (type 1 universal definition) The following groups are included: • Patients following the acute early phase, providing the patient is stable. • STEMI patients • NSTEMI patients • People after MI without LVSD or heart failure • People after MI with left ventricular systolic dysfunction (LVSD) • People with heart failure, left ventricular systolic dysfunction and have had an MI

Review question	What is the clinical and cost effectiveness of adding ACE inhibitors versus ARBs or in combination versus ACE inhibitors to improve outcomes in people after an MI?
	• If insufficient high quality data, extend this to include all patients with a history of CHD (stable angina, unstable angina, or revascularisation) and <75% post MI patients. • Note: In older ACS studies, a large proportion of unstable angina patients would now be classified in the direct population as NSTEMI (based on changes in ECG and enzyme levels) **Intervention /Comparison** • ACE inhibitors vs. ARBs • ACE inhibitors + ARB vs. ACE inhibitors • ARBs vs. placebo **ACE inhibitors** • Captopril • Cilazapril • Enalapril • Fosinopril • Imidapril • Lisinopril • Moexiprl • Perindopril • Quinapril • Ramipril • Trandolapril **ARBs** • Candesartan • Eprosartan • Irbesartan • Telmisartan • Valsartan • Losartan • Olmesartan **Duration** • Studies with all durations of follow up will be included in the review. **Exclusion:** People who • Patients diagnosed as having a type 2, 3, 4a, 4b or 5 MI as per the universal definition of myocardial infarction. • Patients with chronic heart failure (>75% of population) • Patient with implanted cardiac defibrillators **Study design:** • Randomised controlled trials (RCTs) • If RCTs are unavailable, prospective cohort studies will be included. • single, double or non-blinded

Review question	What is the clinical and cost effectiveness of adding ACE inhibitors versus ARBs or in combination versus ACE inhibitors to improve outcomes in people after an MI?
	Outcomes: **CRITICAL** • Mortality (all cause, cardiac or sudden) • Quality of life (report all, inc EQ-5D (EuroQol), SF-36 (Short Form 36), SF6D (Short Form 6-Dimensions), SF-12 (Short Form 12-Dimensions), RAND-36 (Research and Development Medical Outcomes Study Short Form-36), HUI (Health Utilities Index), EQ-VAS (Euroqol visual analogue scale), 15D - 15 dimensions, QWB (Quality of Well Being), AQol (Assessment of Quality of Life)) **IMPORTANT** • Re-infarction • Revascularisation • Stroke **RELEVANT** • Readmission/Hospitalisation • Side effects/Adverse events **Settings:** • Primary care • Secondary care • Tertiary care • Community settings in which NHS care is delivered **Population size and directness:** • No limitations on sample size • Studies with indirect populations (<75% post MI) will be considered if no data is available or only low quality data is available on direct population (>75% post MI). • Papers with more than 30% HF patients will be excluded.
Search	• The databases to be searched are Medline, Embase and the Cochrane Library • Type of studies included: randomised controlled trials (RCTs) and if RCTs are unavailable, prospective cohort studies will be included. • Studies will be restricted to English language only • Abstracts will be excluded unless there are no other studies available for a particular outcome or clinical question • Phase I and II (non-randomised) and cross-over studies are excluded • 2006 to now • No trial duration maximum limit.
Review strategy	**Cochrane Reviews** Cochrane reviews will be quality assessed and presented. Any papers included in the Cochrane, that were not reviewed in the original guideline and deemed to be important, will be ordered and considered for inclusion. **Data analysis** The outcomes will be presented and analysed using Hazard Ratios (HR) or Relative Risk (RR) where appropriate. Hazard ratios are presented in preference to RR for outcomes that are influenced by trial duration i.e. mortality, reinfarction, regardless of the number of papers

Review question	What is the clinical and cost effectiveness of adding ACE inhibitors versus ARBs or in combination versus ACE inhibitors to improve outcomes in people after an MI?
	available for each calculation. The exceptions to this are: 1) when the quality of the HR data is low or; 2) key papers that influence current medical practice are excluded from the analysis because they only provide RR data. In such instances RR data will also be presented. Relative risk will be used for adverse events. Default minimal important differences (MIDs) of 0.75 and 1.25 will be used for hazard ratios and relative risk. For decision making, MIDs for absolute changes in response to the intervention are decided upon in the GDG. Meta-analysis will be conducted wherever possible (i.e., where similar studies can be combined) In the case in which we have missing data, available case analysis will be performed unless the GDG has good reason to perform intention-to-treat with imputation. **Heterogeneity (sensitivity analysis and subgroups)** If heterogeneity is found, it will first be explored by performing sensitivity analysis and eliminating papers that have a high risk of bias. If heterogeneity is still present, the influence of the following subgroups will then be examined: ○ Type of treatment of MI (PCI or CABG or medical) ○ Diagnosis (STEMI vs NSTEMI) ○ Age <75 yrs vs. >75 yrs If heterogeneity cannot be explained the RR results will be presented as random effects, rather than fixed effects

C.3.1.5 Optimal duration of clopidogrel therapy

Review question	What is the optimal duration that clopidogrel should be continued in people after an MI?
Objectives	To produce a recommendation on optimal duration of clopidogrel and aspirin in STEMI and NSTEMI patients. Strata: • Duration of treatment 0 to 30d, 0 to 1yr OR 30d to 1yr, 0 to >1 yr • STEMI, NSTEMI • Type of treatment (PCI, CABG, medical treatment)
Population	**Population:** • Adult individuals or groups who have had an MI (type 1 universal definition) (>75% post MI = direct population) The following groups are included: • Patients following the acute early phase, providing the patient is stable. • STEMI patients • NSTEMI patients • In older ACS studies, a large proportion of unstable angina patients would now be classified in the direct population as NSTEMI (based on changes in ECG and enzyme levels) • If insufficient high quality data, extend this to include all patients with a history of CHD (stable angina, unstable angina, or revascularisation) and <75% post MI patients. (indirect population) **Intervention/comparison** • Different duration of dual therapy

Review question	What is the optimal duration that clopidogrel should be continued in people after an MI?
	• Dual antiplatelet: Aspirin + Clopidogrel vs Aspirin alone **Duration** • Studies with all durations of follow up will be included in the review. **Excluded:** • Patients diagnosed as having a type 2, 3, 4a, 4b or 5 MI as per the universal definition of myocardial infarction. • Patients with heart failure • Patient with implanted cardiac defibrillators **Study design:** • Single or double blind randomised controlled trials • Prospective cohort studies Date of search: 2006 onwards **Outcomes:** **CRITICAL** • Mortality (all cause, cardiac or sudden) • Quality of life (report all, inc EQ-5D (EuroQol), SF-36 (Short Form 36), SF6D (Short Form 6-Dimensions), SF-12 (Short Form 12-Dimensions), RAND-36 (Research and Development Medical Outcomes Study Short Form-36), HUI (Health Utilities Index), EQ-VAS (Euroqol visual analogue scale), 15D - 15 dimensions, QWB (Quality of Well Being), AQol (Assessment of Quality of Life)) **IMPORTANT** • Re-infarction • Revascularisation • Stroke **RELEVANT** • Readmission/Hospitalisation • Side effects/Adverse events **Settings:** • Primary care • Secondary care • Tertiary care • Community settings in which NHS care is delivered **Population size and directness:** • No limitations on sample size • Studies with indirect populations (<75% post MI) will be considered if no data is available or only low quality data is available on direct population (>75% post MI). • Papers with more than 30% HF patients will be excluded.
Search	• The databases to be searched are Medline, Embase and the Cochrane Library • Type of studies included: randomised controlled trials (RCTs) and large prospective cohort

Review question	What is the optimal duration that clopidogrel should be continued in people after an MI?
	studies. • Studies will be restricted to English language only. • Abstracts will be excluded unless there are no other studies available for a particular outcome or clinical question. • Phase I and II (non randomised) and cross-over studies are excluded. • Non-randomised controlled studies and open-label studies are excluded. • 2006 to now. • No trial duration maximum limit.
Review strategy	**Cochrane Reviews** Cochrane reviews will be quality assessed and presented. Any papers included in the Cochrane, that were not reviewed in the original guideline and deemed to be important, will be ordered and considered for inclusion. **Data analysis** The outcomes will be presented and analysed using Hazard Ratios (HR) or Relative Risk (RR) where appropriate. Hazard ratios are presented in preference to RR for outcomes that are influenced by trial duration i.e. mortality, reinfarction, regardless of the number of papers available for each calculation. The exceptions to this are: 1) when the quality of the HR data is low or; 2) key papers that influence current medical practice are excluded from the analysis because they only provide RR data. In such instances RR data will also be presented. Relative risk will be used for adverse events. Default minimal important differences (MIDs) for hazard ratios and relative risks will be used: 0.75 and 1.25. Meta-analysis will be conducted wherever possible (i.e. where similar studies can be combined). In the case in which we have missing data, available case analysis will be performed unless the GDG has good reason to perform intention-to-treat with imputation. Meta-analysis where appropriate will be conducted. **Heterogeneity (sensitivity analysis and subgroups)** If heterogeneity is found, it will first be explored by performing sensitivity analysis and eliminating papers that have a high risk of bias. If heterogeneity is still present, the influence of the following subgroups will then be examined: type of stent (DES vs BMS) If heterogeneity can not be explained by the subgroups, then the results will be presented as Random effects, rather than Fixed effects.

C.3.1.6 Late initiation of antiplatelet therapy

Review question	In people with an MI in the past who were not initiated on dual antiplatelet therapy (clopidogrel, prasugrel or ticagrelor in combination with aspirin), should this be initiated?
Objectives	To assess the clinical and cost effectiveness of dual antiplatelet therapy in patients with MI who were not treated acutely and to update the recommendations to incorporate new antiplatelets (prasugrel + ticagrelor).
Population	Adults (≥ 18 years) who have had an MI (type 1 universal definition) at some point in the past. The following groups are included: • STEMI patients • NSTEMI patients

Review question	In people with an MI in the past who were not initiated on dual antiplatelet therapy (clopidogrel, prasugrel or ticagrelor in combination with aspirin), should this be initiated?
	• If insufficient high quality data, extend this to include all patients with a history of CHD (stable angina, unstable angina, or revascularisation) and <75% post MI patients. • Note: In older ACS studies, a large proportion of unstable angina patients would now be classified in the direct population as NSTEMI (based on changes in ECG and enzyme levels)
Criteria	**Intervention** Dual antiplatelet therapy: • Aspirin + clopidogrel • Aspirin + prasugrel • Aspirin + ticagrelor **Comparison:** • Aspirin alone **Duration:** • Studies with all durations of follow up will be included in the review. **Excluded:** • Patients diagnosed as having a type 2, 3, 4a, 4b or 5 MI as per the universal definition of myocardial infarction. • Study populations with ≥30% heart failure patients • Patient with implanted cardiac defibrillators **Study design:** • Single or double blind randomised controlled trials • If RCTs are not available, prospective cohort studies will be included. **Outcomes** **CRITICAL** • Mortality (all cause, cardiac or sudden) • Quality of life (report all, inc EQ-5D (EuroQol), SF-36 (Short Form 36), SF6D (Short Form 6-Dimensions), SF-12 (Short Form 12-Dimensions), RAND-36 (Research and Development Medical Outcomes Study Short Form-36), HUI (Health Utilities Index), EQ-VAS (Euroqol visual analogue scale), 15D - 15 dimensions, QWB (Quality of Well Being), AQol (Assessment of Quality of Life)) **IMPORTANT** • Re-infarction • Revascularisation • Stroke **RELEVANT** • Readmission/Hospitalisation • Side effects/Adverse events
Search	• The databases to be searched are Medline, Embase and the Cochrane Library • Type of studies included: randomised controlled trials (RCTs) and if insufficient data available prospective cohort studies will be included. • Studies will be restricted to English language only

Review question	In people with an MI in the past who were not initiated on dual antiplatelet therapy (clopidogrel, prasugrel or ticagrelor in combination with aspirin), should this be initiated?
	• Abstracts will be excluded unless there are no other studies available for a particular outcome or clinical question • Phase I and II (non randomised) and cross-over studies are excluded • New search • No trial duration maximum limit.
Review strategy	**Cochrane Reviews** Cochrane reviews will be quality assessed and presented. Any papers included in the Cochrane, that were not reviewed in the original guideline and deemed to be important will be ordered and considered for inclusion. **Data analysis** The outcomes will be presented and analysed using Hazard Ratios (HR) or Relative Risk (RR) where appropriate. Hazard ratios are presented in preference to RR for outcomes that are influenced by trial duration i.e. mortality, reinfarction, regardless of the number of papers available for each calculation. Hazard ratios will be calculated wherever possible. The exceptions to this are: 1) when the quality of the HR data is low or; 2) key papers that influence current medical practice are excluded from the analysis because they only provide RR data. In such instances RR data will also be presented. Relative risk will be used for adverse events. Default minimal important differences (MIDs) for hazard ratios and relative risks will be used: 0.75 and 1.25. Meta-analysis will be conducted wherever possible (i.e. where similar studies can be combined). In the case in which we have missing data, available case analysis will be performed unless the GDG has good reason to perform intention-to-treat with imputation. Meta-analysis will be conducted where appropriate. **Heterogeneity / Subgroups** If heterogeneity is found, it will first be explored by performing sensitivity analysis and eliminating papers that have a high risk of bias. If heterogeneity is still present, the influence of the following subgroups will then be examined: ○ Type of MI (STEMI/NSTEMI) ○ Type of treatment of MI (PCI, CABG or medical) If heterogeneity can not be explained the RR results will be presented as random effects, rather than fixed effects

C.3.1.7 Antiplatelet therapy in people with an additional indication for anticoagulation

This section was updated and replaced in 2020. See www.nice.org.uk/guidance/ng185 for the 2020 evidence review.

Review question	What is the most clinically and cost effective combination of antiplatelet and anticoagulant therapies for people who have had an MI and an indication for anticoagulation?
Objective	To assess the most clinically and cost effective combination of antiplatelet and anticoagulant therapies in patients with an indication for long-term anticoagulant therapy, who have also had an MI.
Strata	The following strata will be considered in the analysis: • Dose of warfarin (moderate dose INR 2-2.9 and high dose INR 3-4.5)

Review question	What is the most clinically and cost effective combination of antiplatelet and anticoagulant therapies for people who have had an MI and an indication for anticoagulation?
	• Dose of rivaroxaban (low dose 5mg/d and prescribed dose 10mg/d) • Dose of dabigatran (low dose 100+150 mg/d and prescribed dose 220+300mg/d)
Criteria	**Population:** Direct population Adults (≥ 18 years) who have had an MI (type 1 universal definition) and comorbid condition needing oral anticoagulation. The following groups are included: ○ Patients with mechanical valve replacements, VTE needing continuing treatment (including left ventricular thrombus and ongoing deep venous thrombosis (DVT)) ○ Patients with atrial fibrillation (AF) who have had a MI and are taking new anticoagulant agents (these papers often report subgroup data so we can use these trials). Indirect population ○ Patients with an indication for anticoagulation and have CHD (but have not had an MI or unclear if they have) ○ Patients without an indication for anticoagulation but have CHD (stable angina, unstable angina or revascularisation) or MI (>75% OR <75% but remainder are a CHD population). • Note: In older ACS studies, a large proportion of unstable angina patients would now be classified in the direct population as NSTEMI (based on changes in ECG and enzyme levels) **Direct population = any comparison between any intervention on the list** **Indirect population = only comparisons where one comparator is a combination of anticoagulant and antiplatelet (single or dual) versus any other treatment in list.** **Intervention = Post discharge treatment.** Dual antiplatelet therapy + warfarin Dual antiplatelet therapy + rivaroxaban Dual antiplatelet therapy + dabigatran Dual antiplatelet therapy + apixaban Aspirin + apixaban Aspirin + warfarin Aspirin + rivaroxaban Aspirin + dabigatran Clopidogrel/prasugrel/ticagrelor + warfarin Clopidogrel/prasugrel/ticagrelor + rivaroxaban Clopidogrel/prasugrel/ticagrelor + dabigatran Clopidogrel/prasugrel/ticagrelor + apixaban **Comparison** Dual antiplatelet therapy alone Warfarin alone Rivaroxaban alone Dabigatran alone Abciximab alone Aspirin alone Clopidogrel/prasugrel/ticagrelor alone

Review question	What is the most clinically and cost effective combination of antiplatelet and anticoagulant therapies for people who have had an MI and an indication for anticoagulation?

	Note
	Dual antiplatelet therapy = aspirin + clopidogrel/ticagrelor/prasugrel
	
	Duration
	• Studies with all durations of follow up will be included in the review. The duration of treatment and follow up will be considered when evaluating the benefits and risks for these therapies: short term (≤30 days), intermediate term (31 days to 1 year), and long term (>1 year).
	• Duration will also be investigated if there is heterogeneity.
	
	Excluded:
	People who
	• Patients diagnosed as having a type 2, 3, 4a, 4b or 5 MI as per the universal definition of myocardial infarction.
	• AF populations, except where subgroups are reported or the MI population is >75%.
	• Study populations with ≥30% heart failure patients
	
	Study design:
	• Single or double blind randomised controlled trials
	• If not RCTs, prospective cohort studies will be included
	
	Outcomes:
	CRITICAL
	• Mortality (all cause, cardiac or sudden)
	• Quality of life (report all, inc EQ-5D (EuroQol), SF-36 (Short Form 36), SF6D (Short Form 6-Dimensions), SF-12 (Short Form 12-Dimensions), RAND-36 (Research and Development Medical Outcomes Study Short Form-36), HUI (Health Utilities Index), EQ-VAS (Euroqol visual analogue scale), 15D - 15 dimensions, QWB (Quality of Well Being), AQol (Assessment of Quality of Life))
	IMPORTANT
	• Re-infarction
	• Revascularisation
	• Stroke
	RELEVANT
	• Readmission/Hospitalisation
	• Side effects/Adverse events including:
	  ○ Adverse drug reactions (thrombocytopenia, allergic drug reaction)
	  ○ Bleeding (various definitions of minor and major bleeding have been used in published studies such as TIMI, GUSTO, PLATO, BARC, which are based on a decrease in haemoglobin levels or the number of transfusions administered)
	  ○ Stent thrombosis
	
	Settings:
	• Primary care
	• Secondary care
	• Tertiary care
	• Community settings in which NHS care is delivered

Review question	What is the most clinically and cost effective combination of antiplatelet and anticoagulant therapies for people who have had an MI and an indication for anticoagulation?
	Population size and directness: • No limitations on sample size.
Search	• The databases to be searched are Medline, Embase and the Cochrane Library • Type of studies included: randomised controlled trials (RCTs) and if limited data available prospective cohort studies will be included. • Where data on the direct population are available, an indirect population will be considered • Studies will be restricted to English language only • Abstracts will be excluded unless there are no other studies available for a particular outcome or clinical question • Phase I and II (non randomised) and cross-over studies are excluded • No trial duration maximum limit. • New search
Review strategy	**Cochrane Reviews** Cochrane reviews will be quality assessed and presented. Any papers included in the Cochrane, that were not reviewed in the original guideline and deemed to be important will be ordered and considered for inclusion. **Data analysis** The outcomes will be presented and analysed using Hazard Ratios (HR) or Relative Risk (RR) where appropriate. Hazard ratios are presented in preference to RR for outcomes that are influenced by trial duration i.e. mortality, reinfarction, regardless of the number of papers available for each calculation. Hazard ratios will be calculated wherever possible. The exceptions to this are: 1) when the quality of the HR data is low or; 2) key papers that influence current medical practice are excluded from the analysis because they only provide RR data. In such instances RR data will also be presented. Relative risk will be used for adverse events. Default minimal important differences (MIDs) for hazard ratios and relative risks will be used: 0.75 and 1.25. Meta-analysis will be conducted wherever possible (i.e. where similar studies can be combined). In the case in which we have missing data, available case analysis will be performed unless the GDG has good reason to perform intention-to-treat with imputation. Meta-analysis will be conducted where appropriate. **Heterogeneity / Subgroups** If heterogeneity is found, it will first be explored by performing sensitivity analysis and eliminating papers that have a high risk of bias. If heterogeneity is still present, the influence of the following subgroups will then be examined: ○ Duration of treatment (short term <30d, intermediate 30d-1yr, long term >1yr) ○ Indication for anticoagulant (mechanical heart values vs. VTE (including left ventricular thrombus and DVT, which should not be specified separately) (this group has a stronger need for anticoagulation) ○ type of treatment of MI (PCI or CABG or medical) ○ types of stents (bare metal stent vs. drug eluting stent) ○ for bleeding risk outcome look at age (<65 vs >65 years of age) If heterogeneity cannot be explained the RR results will be presented as random effects, rather than fixed effects

C.3.1.8 Beta-blockers

This section was partially updated in 2020. See www.nice.org.uk/guidance/ng185 for the 2020 evidence reviews.

Review question	What is the clinical and cost effectiveness of adding a beta-blocker versus placebo to improve outcome in people after a MI i) with and ii) without left ventricular dysfunction and is there an optimal duration?
Objectives	To assess the clinical and cost effectiveness of a beta-blocker in people who have had an MI who have preserved left ventricular function or left ventricular dysfunction and if so, identify the optimal duration of treatment.
Strata	• In people who have had an acute MI (0-72 hours) • In people who have had a sub-acute MI (>72 hours-1year) • In people who have had an MI in the past (≥1year)
Criteria	**Population:** Direct population: Adult individuals or groups who have had an MI (type 1 universal definition) (>75% post MI = direct population) Including: • Patients following the acute early phase, providing the patient is stable. • STEMI patients • NSTEMI patients • In older ACS studies, a large proportion of unstable angina patients would now be classified in the direct population as NSTEMI (based on changes in ECG and enzyme levels) • Indirect population: • If insufficient high quality data, extend this to include all patients with a history of CHD (stable angina, unstable angina, or revascularisation) and <75% post MI patients. (indirect population) • For indirect populations, we will accept a maximum of 30% heart failure patients **Intervention /Comparison** **PART 1 - duration** • Direct study design: beta-blocker vs. same beta-blocker (i.e. 6 months vs. 12 months) Indirect study design: beta-blocker vs. placebo (different follow-up time periods) **PART 2 - beta-blocker vs. placebo** • Direct study design: beta-blocker vs. placebo **Included:** Beta –blocker - include papers that use intravenous or oral beta-blocker in hospital but oral only after discharge • Acebutolol • Atenolol • Bisoprolol • Carvedilol • Celiprolol • Esmolol

Review question	What is the clinical and cost effectiveness of adding a beta-blocker versus placebo to improve outcome in people after a MI i) with and ii) without left ventricular dysfunction and is there an optimal duration?
	• Labetalol • Metoprolol • Nadolol • Nebivolol • Oxprenolol • Propranolol • Pindolol • Sotalol • Timolol **Duration:** Studies with all durations of follow up will be included in the review. **Excluded:** People who Patients diagnosed as having a type 2, 3, 4a, 4b or 5 MI as per the universal definition of myocardial infarction. Patients with heart failure that contribute to more than 25% of total population Patient with implanted cardiac defibrillators **Study design:** Include: for direct study designs: cohort studies + randomised control trials Include for: indirect studies designs: randomised controlled trials (not necessarily double-blind) Exclude: trials that compare different BB to one another, BB not prescribed in the UK. **Outcomes:** **CRITICAL** • Mortality (all cause, cardiac or sudden) • Quality of life (report all, inc EQ-5D (EuroQol), SF-36 (Short Form 36), SF6D (Short Form 6-Dimensions), SF-12 (Short Form 12-Dimensions), RAND-36 (Research and Development Medical Outcomes Study Short Form-36), HUI (Health Utilities Index), EQ-VAS (Euroqol visual analogue scale), 15D - 15 dimensions, QWB (Quality of Well Being), AQol (Assessment of Quality of Life)) **IMPORTANT** • Re-infarction • Revascularisation • Stroke **RELEVANT** • Readmission/Hospitalisation • Side effects/Adverse events Relevant: any adverse event, bradycardia (HR<60BPM)/brachycardia, tiredness, impotence, dizziness, vivid dreams **Settings:** • Primary care • Secondary care

Review question	What is the clinical and cost effectiveness of adding a beta-blocker versus placebo to improve outcome in people after a MI i) with and ii) without left ventricular dysfunction and is there an optimal duration?
	Population size and directness: • Only include papers that are sufficiently powered • Studies with indirect populations will be considered if low quality data or no data from direct populations are available.
Search	• The databases to be searched are Medline, Embase and the Cochrane Library • Type of studies included: randomised controlled trials (RCTs) and cohort studies • Studies will be restricted to English language only • Abstracts will be excluded unless there are no other studies available for a particular outcome or clinical question • Phase I and II (non randomised) and cross-over studies are excluded • Non-randomised controlled studies and open-label studies are excluded • 2006 to now • No trial duration limit.
Review strategy	**Cochrane Reviews** Cochrane reviews will be quality assessed and presented. Any papers included in the Cochrane, that were not reviewed in the original guideline and deemed to be important, will be ordered and considered for inclusion. **Systematic reviews** Systematic reviews where the data has been critically assessed will be used and updated if possible. This is considered for this review because of the large volume of papers published on beta-blockers. Data will be partially extracted from papers included in the previously published meta-analysis and full extractions from new papers published since. The quality of the papers will be extracted from the SR and using GRADE for the recent papers. Papers that have used unlicensed drugs from the UK will be removed from the meta-analysis in case they bias the outcome for the class effect. **Data analysis** The outcomes will be presented and analysed using Hazard Ratios (HR) or Relative Risk (RR) where appropriate. Hazard ratios are presented in preference to RR for outcomes that are influenced by trial duration i.e. mortality, reinfarction, regardless of the number of papers available for each calculation. The exceptions to this are: 1) when the quality of the HR data is low or; 2) key papers that influence current medical practice are excluded from the analysis because they only provide RR data. In such instances RR data will also be presented. Relative risk will be used for adverse events. Default minimal important differences (MIDs) of 0.75 and 1.25 will be used for hazard ratios and relative risk to ascertain precision. For decision making, MIDs for absolute changes in mortality and reinfarction is set at ±10% Meta-analysis will be conducted wherever possible (i.e. where similar studies can be combined). In the case in which we have missing data, available case analysis will be performed unless the GDG has good reason to perform intention-to-treat with imputation.

Review question	What is the clinical and cost effectiveness of adding a beta-blocker versus placebo to improve outcome in people after a MI i) with and ii) without left ventricular dysfunction and is there an optimal duration?
	Heterogeneity (sensitivity analysis and subgroups) If heterogeneity is found, it will first be explored by performing sensitivity analysis and eliminating papers that have a high risk of bias. If heterogeneity is still present, the influence of the following subgroups will then be examined: ○ LVSD status: LVSD vs. unselected LV function vs. without LVSD ○ COPD: No COPD vs. COPD ○ type of treatment of MI (PCI or CABG or medical) ○ STEMI vs. NSTEMI ○ Age <75 years vs. >75 years ○ Fat soluble vs. non-fat soluble beta-blockers ○ Ethnicity (Caucasian vs. non-Caucasian) If heterogeneity cannot be explained the RR results will be presented as random effects, rather than fixed effects

C.3.1.9 Beta-blocker initiation

Review protocol	Is there an optimal time for BB to be initiated in people who have had a MI?
Objectives	To assess whether there is an optimal time for beta-blockers to be started after an MI.
Strata	• with left ventricular systolic dysfunction (LVSD) + different time points • normal left ventricular systolic dysfunction (low risk patient) + different time points • unselected people (with or without LVSD) + different time points Chronic obstructive pulmonary disorder (COPD vs no COPD)) + different time points
Criteria	**Population:** Adult individuals or groups who have had an MI (type 1 universal definition) (>75% post MI = direct population) Including: • Patients following the acute early phase, providing the patient is stable. • STEMI patients • NSTEMI patients • In older ACS studies, a large proportion of unstable angina patients would now be classified in the direct population as NSTEMI (based on changes in ECG and enzyme levels) • If insufficient high quality data, extend this to include all patients with a history of CHD (stable angina, unstable angina, or revascularisation) and <75% post MI patients. (indirect population). • For indirect populations, we will accept a maximum of 25% heart failure patients **Intervention /Comparison** • Direct study design: BB vs. same BB (ideal study design would be giving BB on day 2 versus day 5) • If insufficient data include the following comparison • Indirect study design: BB vs. placebo (comparing papers that initiated treatment on different

Review protocol	Is there an optimal time for BB to be initiated in people who have had a MI?
	days) **Included:** Beta-blocker (include papers that use intravenous or oral BB in hospital but oral only after discharge) • Propranolol • Acebutolol • Atenolol • Bisoprolol • Carvedilol • Celiprolol • Esmolol • Labetalol • Metoprolol • Nadolol • Nebivolol • Oxprenolol • Pindolol • Sotalol • Timolol **Duration** • Studies with all durations of follow up will be included in the review. **Excluded:** People who • Patients diagnosed as having a type 2, 3, 4a, 4b or 5 MI as per the universal definition of myocardial infarction. • Patients with heart failure • Patient with implanted cardiac defibrillators **Study design:** • Include: for direct study designs: cohort studies + randomised control trials • Include for: indirect studies designs: double blind randomised controlled trials • Exclude: trials that compare different BB to one another **Outcomes:** **CRITICAL** • Mortality (all cause, cardiac or sudden) • Quality of life (report all, inc EQ-5D (EuroQol), SF-36 (Short Form 36), SF6D (Short Form 6-Dimensions), SF-12 (Short Form 12-Dimensions), RAND-36 (Research and Development Medical Outcomes Study Short Form-36), HUI (Health Utilities Index), EQ-VAS (Euroqol visual analogue scale), 15D - 15 dimensions, QWB (Quality of Well Being), AQol (Assessment of Quality of Life)) **IMPORTANT** • Re-infarction • Revascularisation

Review protocol	Is there an optimal time for BB to be initiated in people who have had a MI?
	• Stroke **RELEVANT** • Readmission/Hospitalisation • Side effects/Adverse events Relevant: adverse effects including: any adverse event, bradycardia/brachycardia, tiredness, impotence, dizziness, vivid dreams **Settings:** • Primary care • Secondary care • Tertiary care **Population size and directness:** • No limitations on sample size • Studies with indirect populations will be considered if low quality data or no data from direct populations are available.
Search strategy	• The databases to be searched are Medline, Embase and the Cochrane Library • Type of studies included: randomised controlled trials (RCTs) and post-hoc analysis of RCTs and cohort studies. • Studies will be restricted to English language only • Abstracts will be excluded unless there are no other studies available for a particular outcome or clinical question • Phase I and II (non randomised) and cross-over studies are excluded • Non-randomised controlled studies and open-label studies are excluded • 2006 to now • No trial duration limit.
Review strategy	**Cochrane Reviews** Cochrane reviews will be quality assessed and presented. Any papers included in the Cochrane, that were not reviewed in the original guideline and deemed to be important, will be ordered and considered for inclusion. **Data analysis** The outcomes will be presented and analysed using Hazard Ratios (HR) or Relative Risk (RR) where appropriate. Hazard ratios are presented in preference to RR for outcomes that are influenced by trial duration i.e. mortality, reinfarction, regardless of the number of papers available for each calculation. The exceptions to this are: 1) when the quality of the HR data is low or; 2) key papers that influence current medical practice are excluded from the analysis because they only provide RR data. In such instances RR data will also be presented. Relative risk will be used for adverse events. Default minimal important differences (MIDs) of 0.75 and 1.25 will be used for hazard ratios and relative risk. For decision making, MIDs for absolute changes in mortality and reinfarction is set at ±10% Meta-analysis will be conducted wherever possible (i.e. where similar studies can be combined).

Review protocol	Is there an optimal time for BB to be initiated in people who have had a MI?
	In the case in which we have missing data, available case analysis will be performed unless the GDG has good reason to perform intention-to-treat with imputation. **Heterogeneity** (sensitivity analysis and subgroups) If heterogeneity is found, it will first be explored by performing sensitivity analysis and eliminating papers that have a high risk of bias. If heterogeneity is still present, the influence of the following subgroups will then be examined: type of treatment of MI (PCI or CABG or medical) ○ STEMI vs NSTEMI ○ Age <75 years vs. >75 years ○ Fat soluble vs. non-fat soluble beta-blockers ○ Ethnicity (Caucasian vs. non-Caucasian) If heterogeneity cannot be explained the RR results will be presented as random effects, rather than fixed effects

C.4 Economic evidence reviews

Review question	All questions – health economic evidence
Objectives	To identify economic studies relevant to the review questions set out above.
Criteria	Populations, interventions and comparators as specified in the individual review protocols above. Must be a relevant economic study design (cost-utility analysis, cost-benefit analysis, cost-effectiveness analysis, cost-consequence analysis, comparative cost analysis).
Search strategy	An economic study search was undertaken using population specific terms and an economic study filter – see Appendix E.
Review strategy	Each study is assessed using the NICE economic evaluation checklist – NICE (2009) Guidelines Manual. **Inclusion/exclusion criteria** If a study is rated as both 'Directly applicable' and 'Minor limitations' (using the NICE economic evaluation checklist) then it should be included in the guideline. An evidence table should be completed and it should be included in the economic profile. If a study is rated as either 'Not applicable' or 'Very serious limitations' then it should be excluded from the guideline. It should not be included in the economic profile and there is no need to include an evidence table. If a study is rated as 'Partially applicable' and/or 'Potentially serious limitations' then there is discretion over whether it should be included. The health economist should make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the GDG if required. The ultimate aim being to include studies that are helpful for decision making in the context of the guideline and current NHS setting. Where exclusions occur on this basis, this should be noted in the relevant section of the guideline with references. Also exclude: • unpublished reports unless submitted as part of a call for evidence • abstract-only studies • letters • editorials • reviews of economic evaluations • foreign language articles

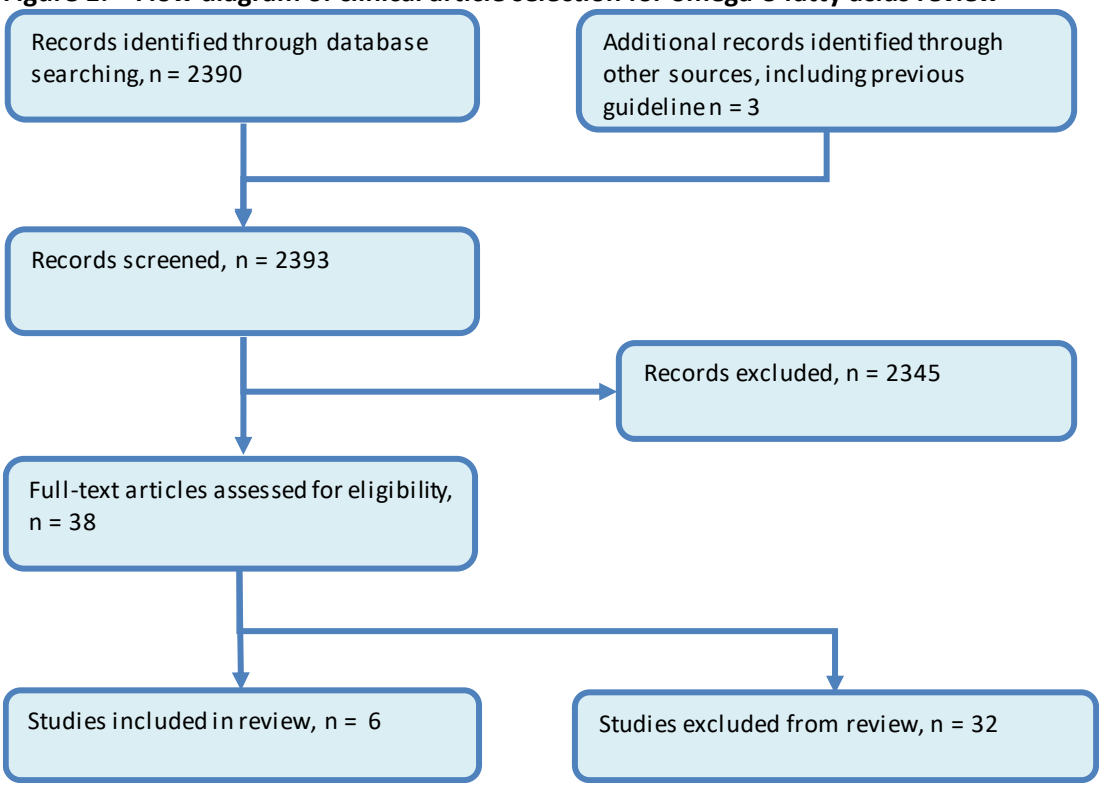
Review question	All questions – health economic evidence
	Where there is discretion The health economist should be guided by the following hierarchies. **Setting:** • UK NHS • OECD countries with predominantly public health insurance systems (e.g. France, Germany, Sweden) • OECD countries with predominantly private health insurance systems (e.g. USA, Switzerland) • Non-OECD settings (always 'Not applicable') **Economic study type:** • Cost-utility analysis • Other type of full economic evaluation (cost-benefit analysis, cost-effectiveness analysis, cost-consequence analysis) • Comparative cost analysis • Non-comparative cost analyses including cost of illness studies (always 'Not applicable') **Year of analysis:** The more recent the study, the more applicable it is. **Quality and relevance of effectiveness data used in the economic analysis:** The more closely the effectiveness data used in the economic analysis matches with the studies included for the clinical review the more useful the analysis will be to decision making for the guideline.

Appendix D: Clinical article selection

D.1 Lifestyle

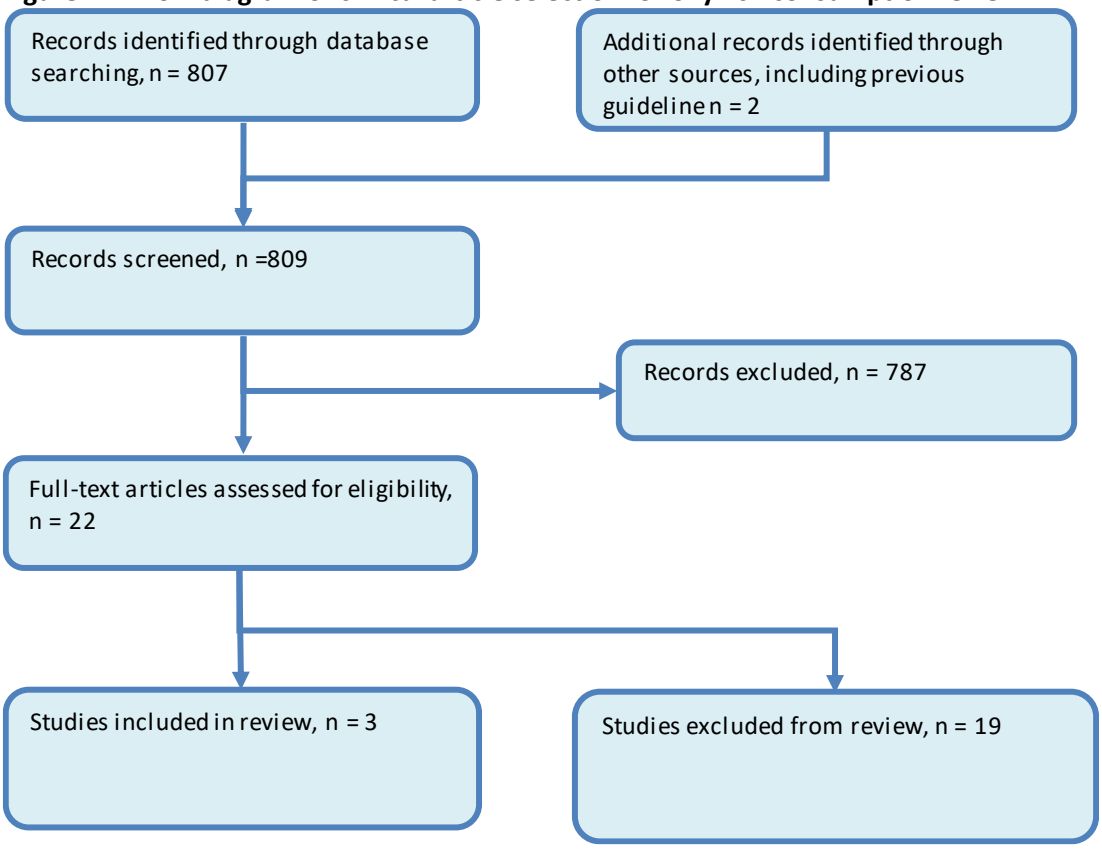
D.1.1 Omega-3 fatty acids

Figure 1: Flow diagram of clinical article selection for omega-3 fatty acids review



D.1.2 Oily fish consumption

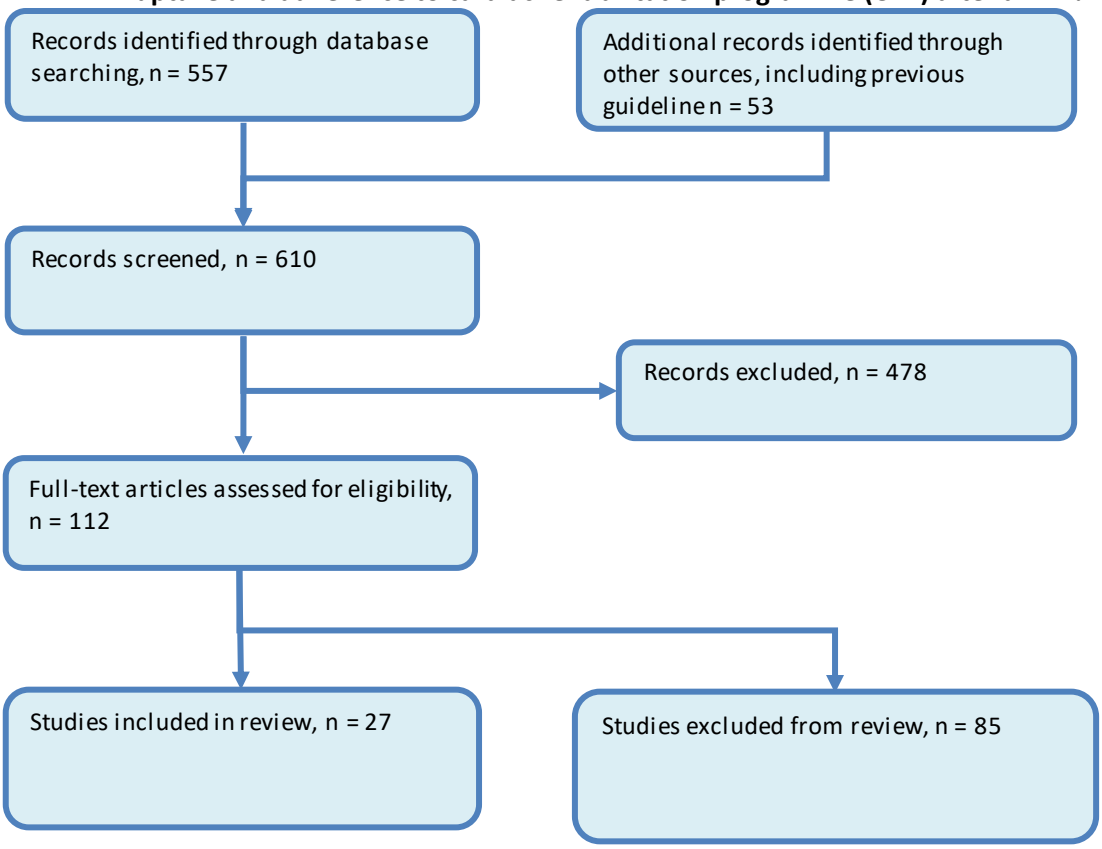
Figure 2: Flow diagram of clinical article selection for oily fish consumption review.



D.2 Cardiac rehabilitation

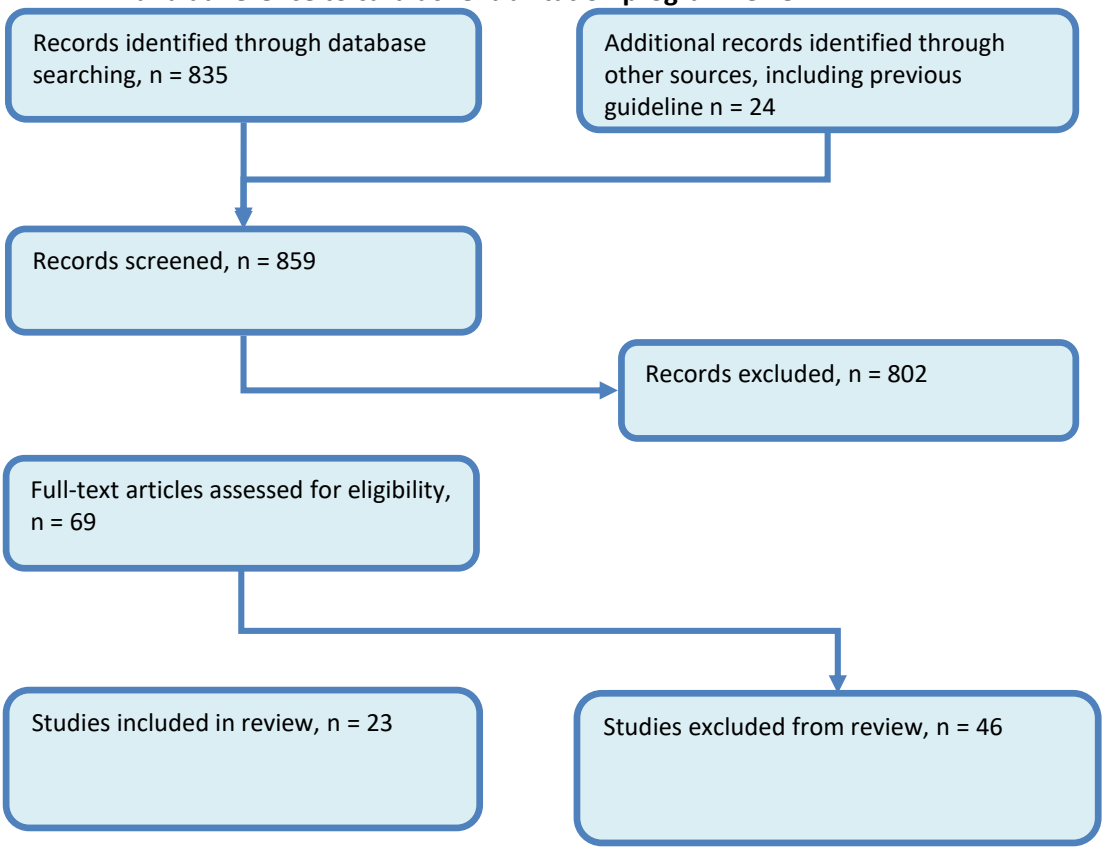
D.2.1 Barriers to the uptake of and adherence to cardiac rehabilitation

Figure 3: Flow diagram of clinical article selection for Which factors are associated with patients' uptake and adherence to cardiac rehabilitation programme (CRP) after an MI? review



D.2.2 Interventions to increase the uptake of and adherence to cardiac rehabilitation

Figure 4: Flow diagram of clinical article selection for interventions aimed at improving uptake and adherence to cardiac rehabilitation program review



D.3 Drug therapy

D.3.1 ACE inhibitors and ARBs

Figure 5: Flow diagram of article selection for 'What is the clinical and cost effectiveness of adding ACE inhibitors versus placebo to improve outcome in people after an MI and is there an optimal duration?'

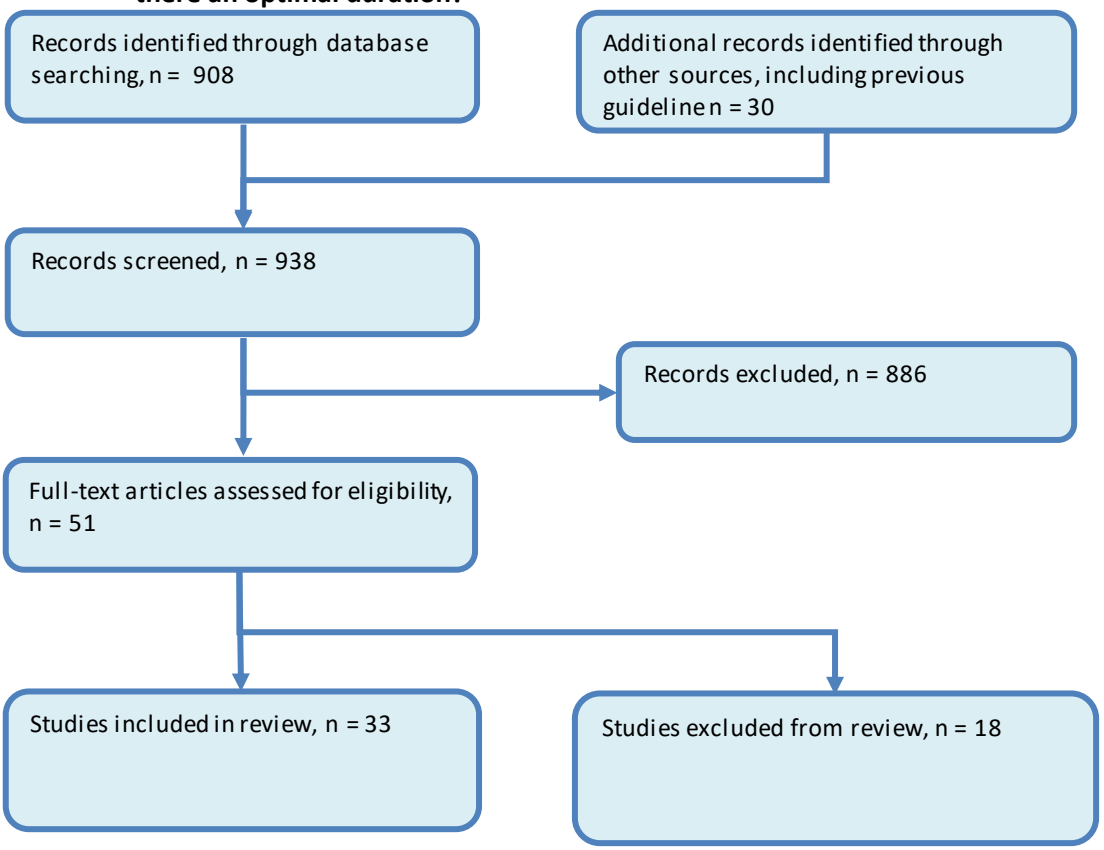


Figure 6: Flow diagram of clinical article selection for 'Is there an optimal time for ACE inhibitors to be initiated in people who have had a MI?'

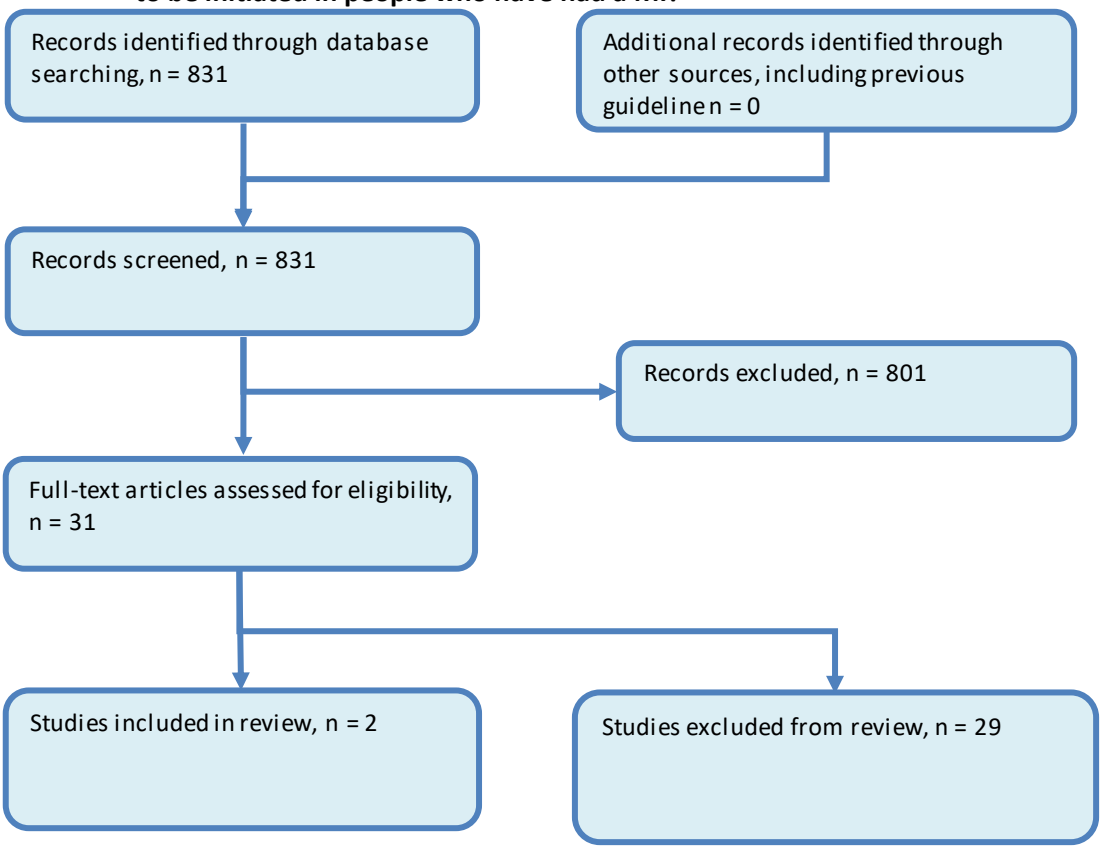


Figure 7: Flow diagram of clinical article selection for 'Is early dose titration of ACE inhibitors in hospital more clinically and cost effective than dose titration over an extended period of time in people who have had a MI?' review

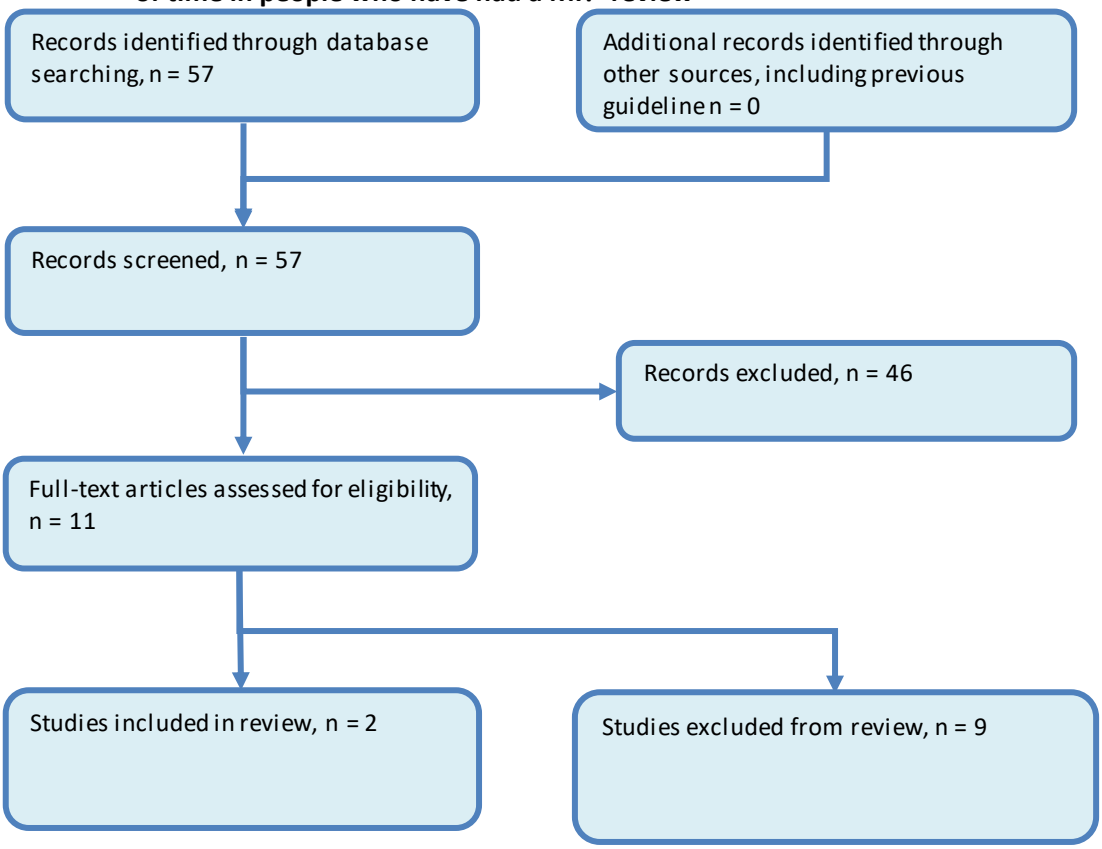
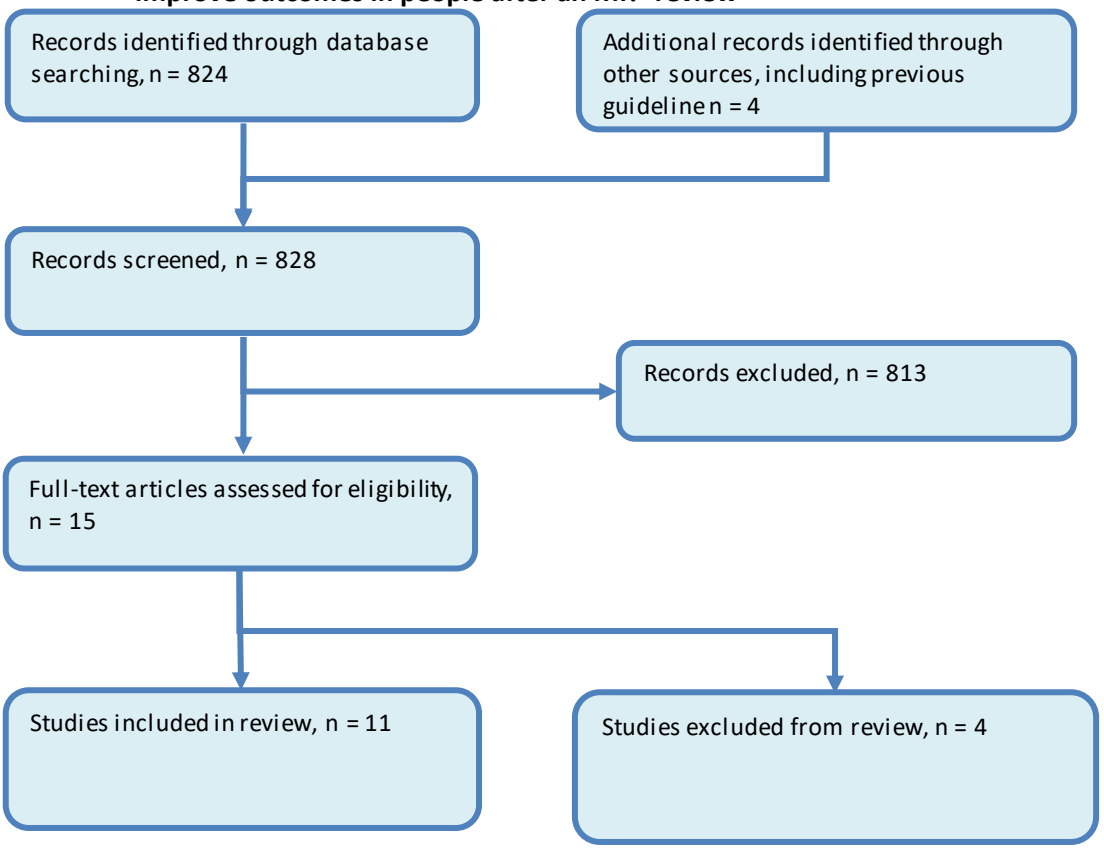


Figure 8: Flow diagram of clinical article selection for 'What is the clinical and cost effectiveness of adding ACE inhibitors versus ARBs or in combination versus ACE inhibitors to improve outcomes in people after an MI?' review



D.3.2 Antiplatelet therapy

Figure 9: Flow diagram of clinical article selection for 'What is the optimal duration clopidogrel should be continued in people after MI?' review

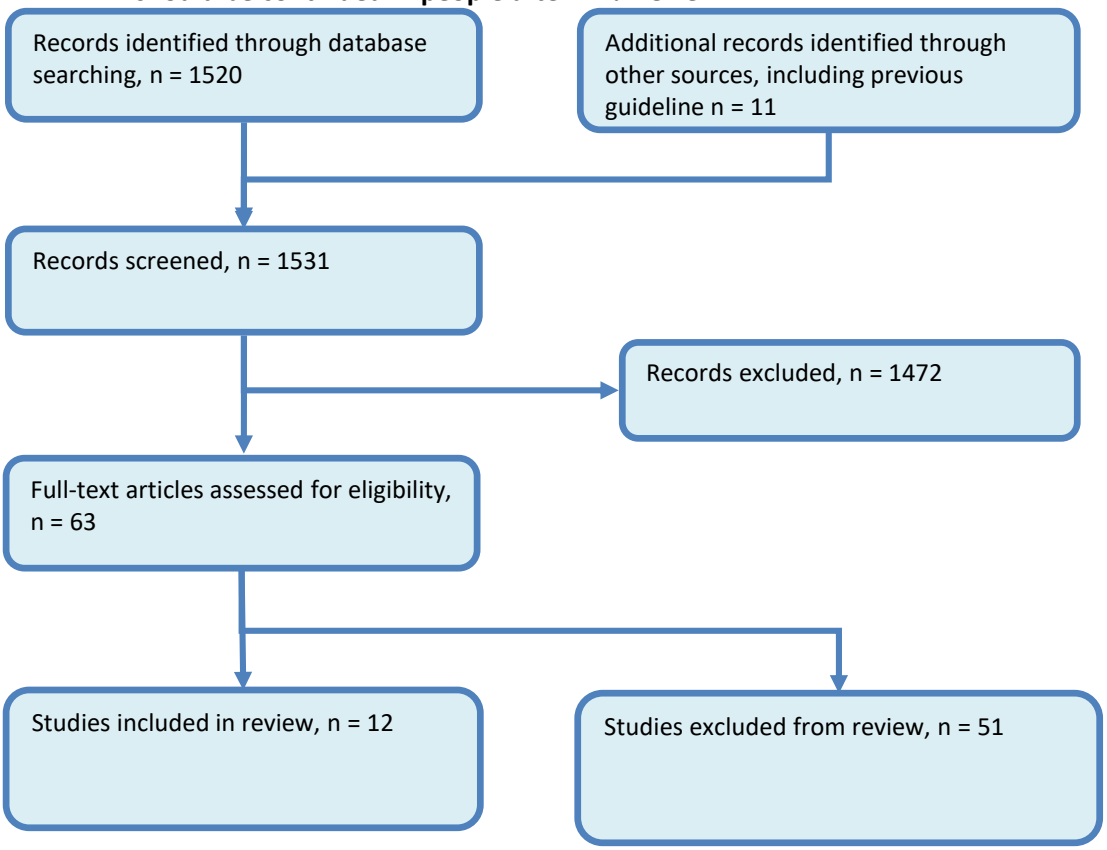


Figure 10: Flow diagram of clinical article selection for 'In people who had an MI in the past who were not initiated on dual antiplatelet therapy (clopidogrel, prasugrel or ticagrelor in combination with aspirin), should this be initiated?'

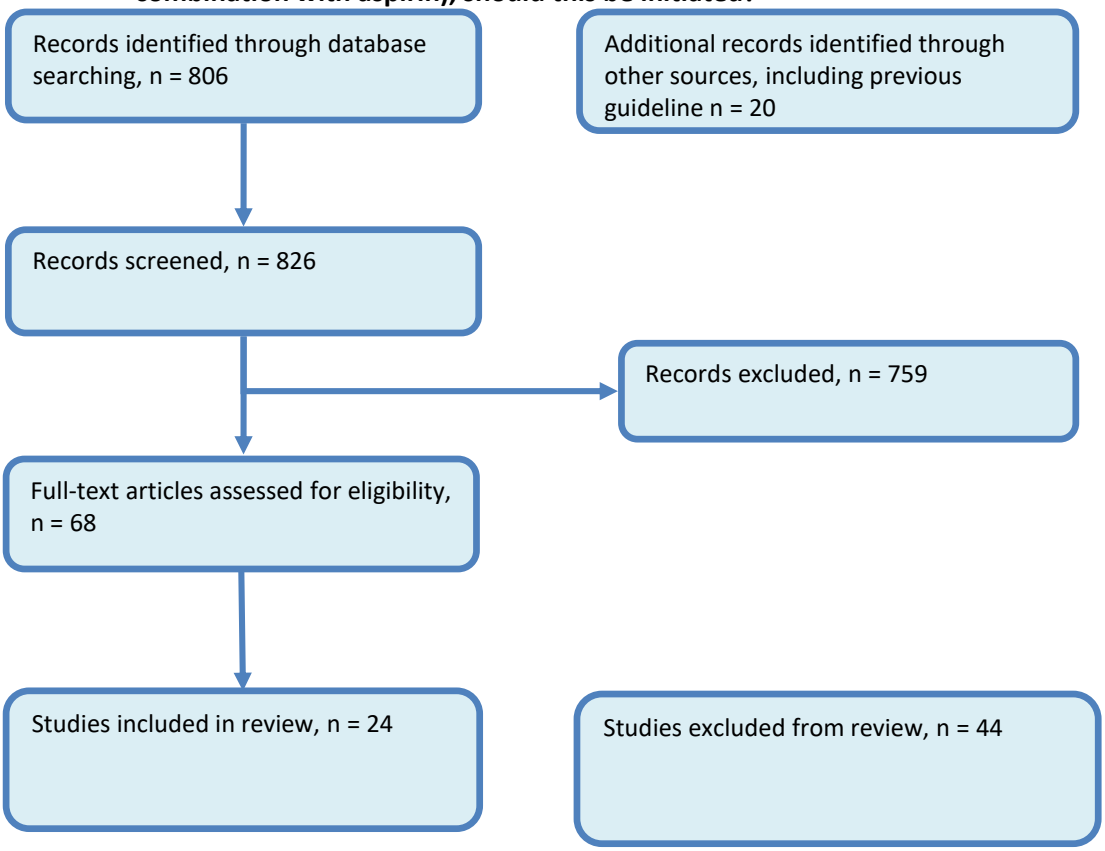
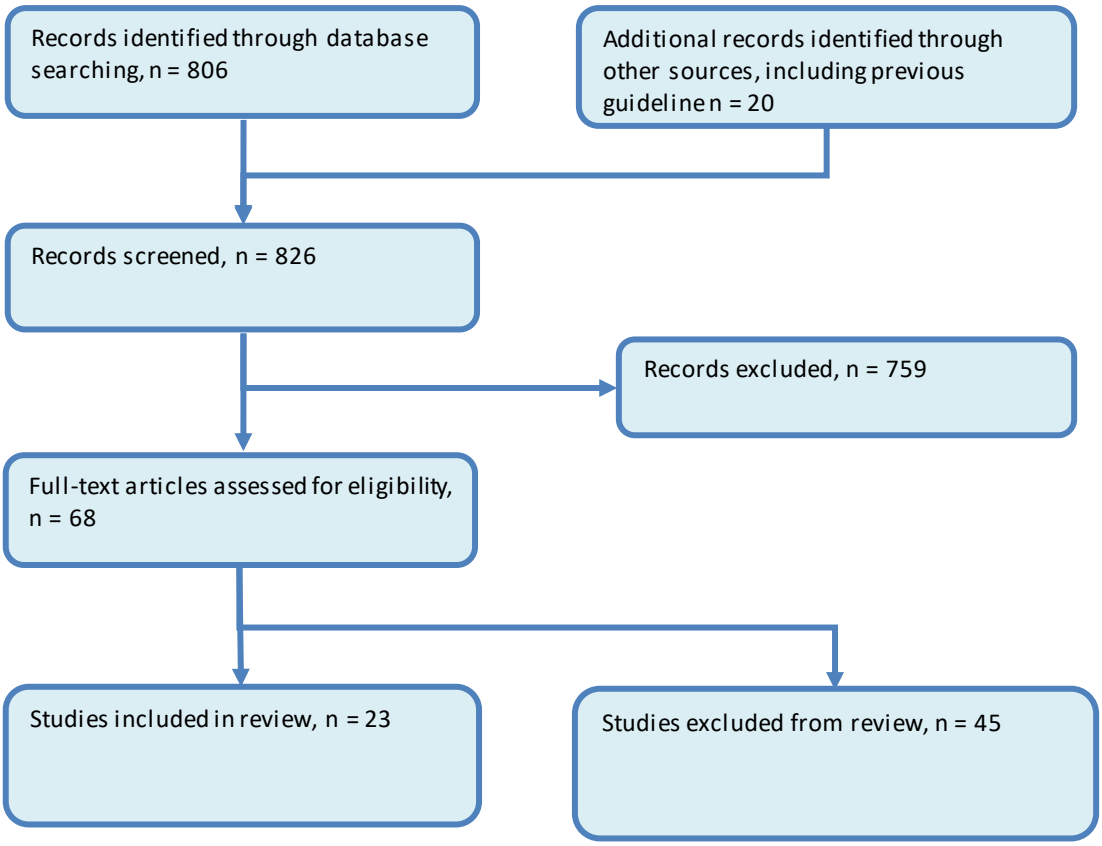


Figure 11: Flow diagram of clinical article selection for 'What is the most clinically and cost effective combination of antiplatelet and anticoagulant therapies for people who have had an MI and an indication for anticoagulation? '

This section was updated and replaced in 2020. See www.nice.org.uk/guidance/ng185 for the 2020 evidence review.



D.3.3 Beta-blockers

Figure 12: Flow diagram of clinical article selection for 'What is the clinical and cost effectiveness of adding a beta blocker versus placebo to improve outcome in people after a MI i) with and ii) without left ventricular dysfunction and is there an optimal duration?'

This section was partially updated in 2020. See www.nice.org.uk/guidance/ng185 for the 2020 evidence review.

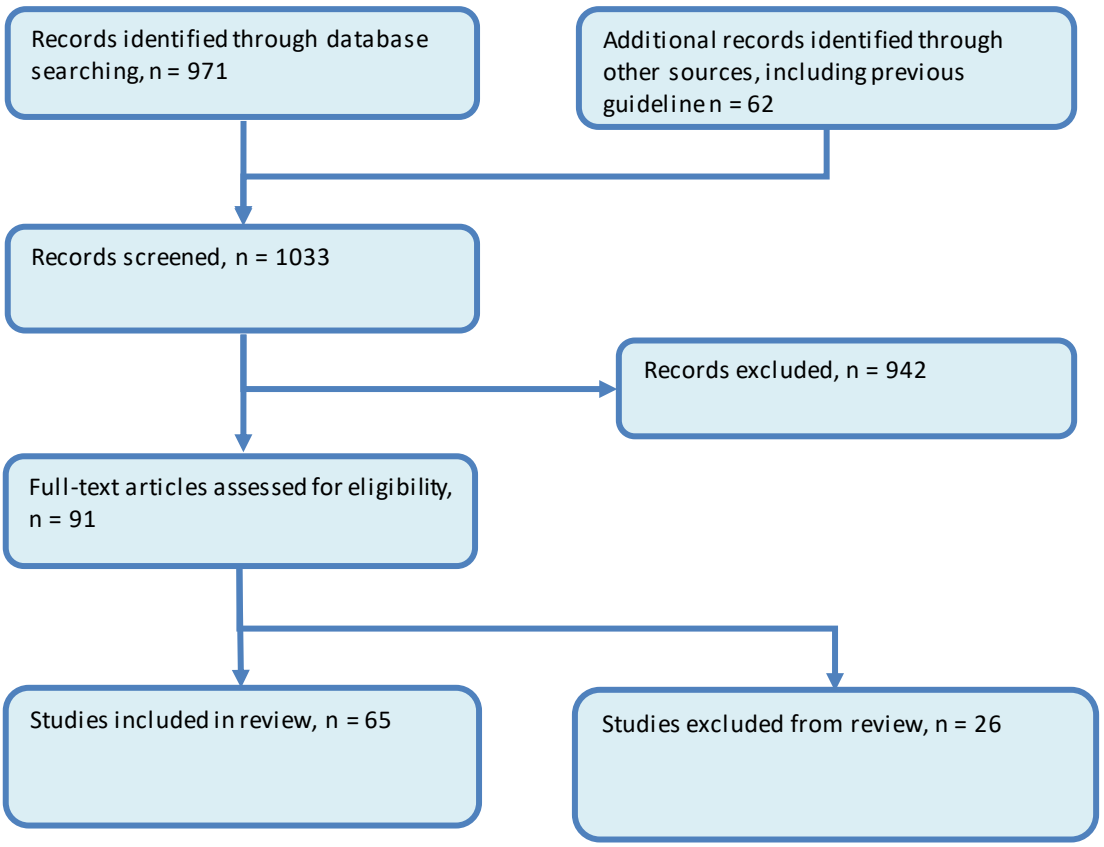
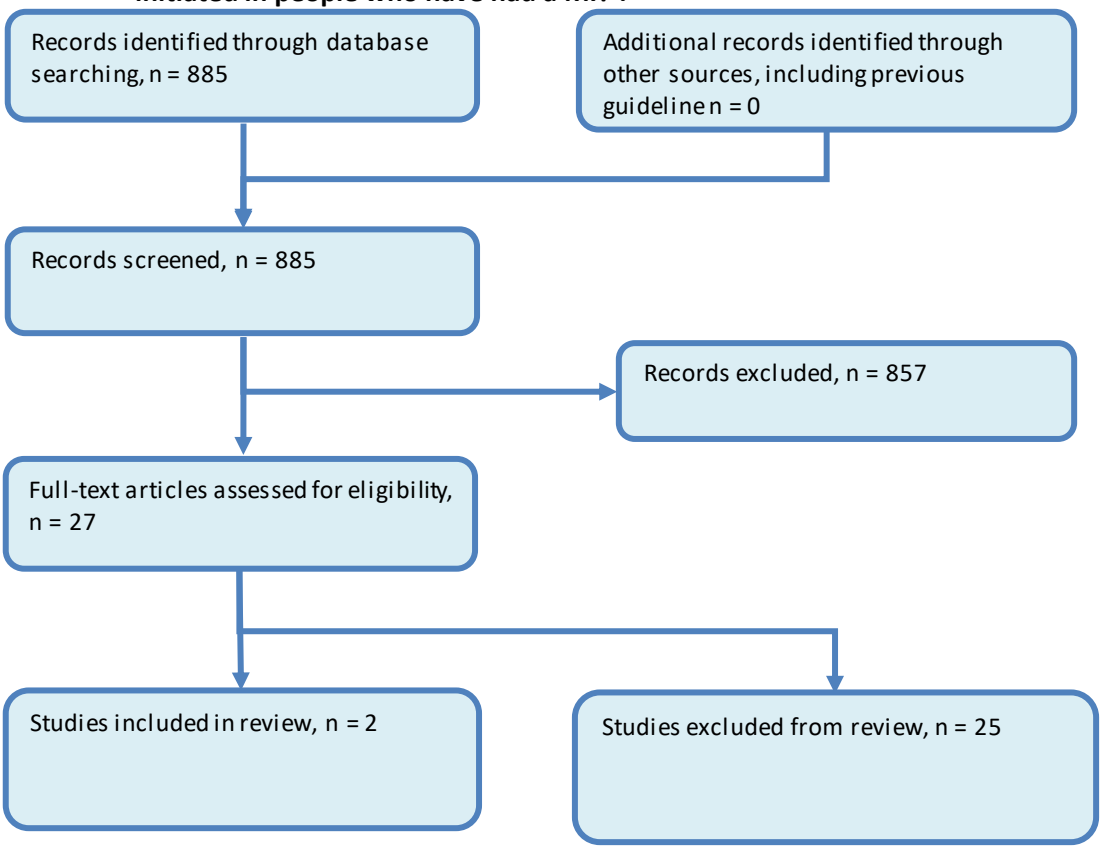
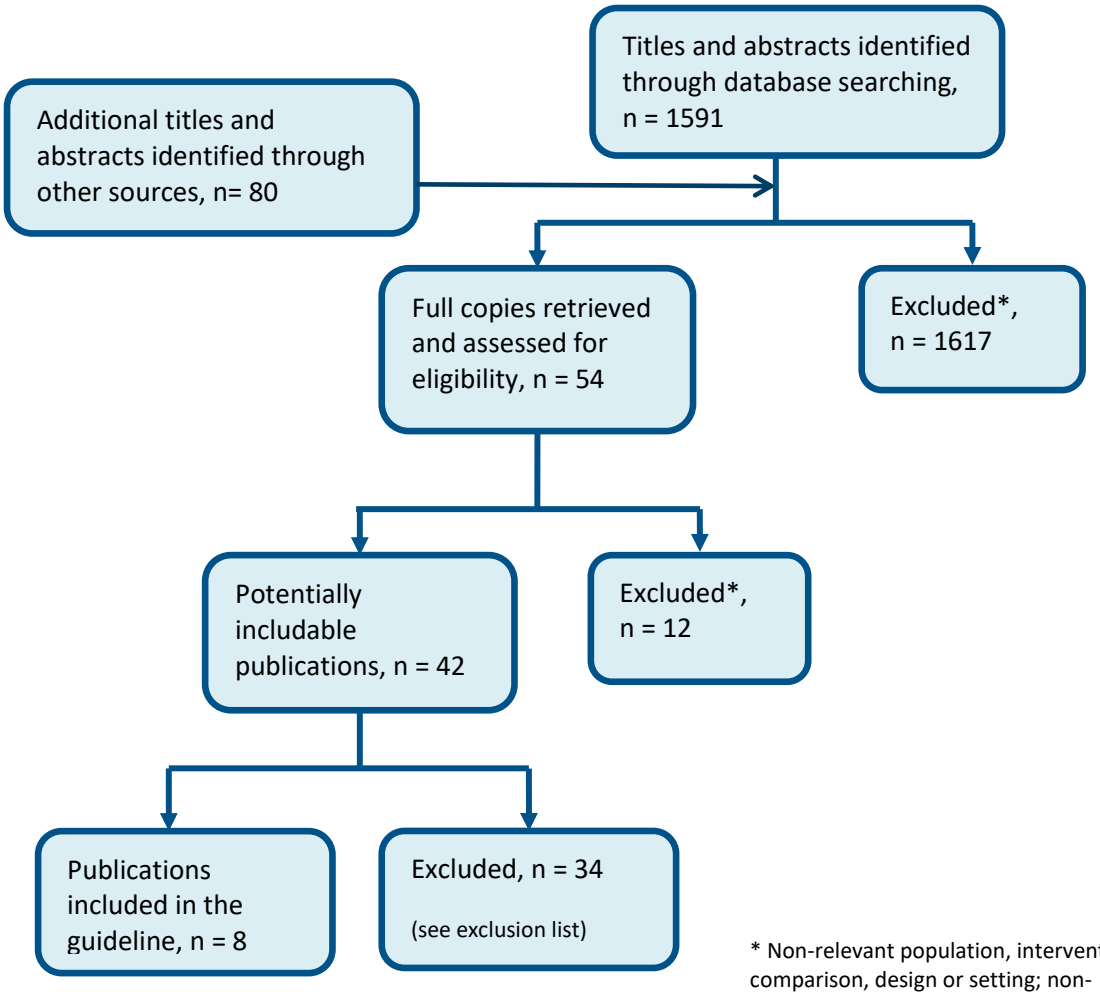


Figure 13: Flow diagram of clinical article selection for 'Is there an optimal time for BB to be initiated in people who have had a MI?'.



Appendix E: Economic article selection

Figure 14: Flow diagram of economic article selection for all review questions



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix F: Literature search strategies

Contents

Search strategies used for the myocardial infarction: secondary prevention guideline are outlined below and were run in accordance with the methodology in the NICE Guidelines Manual 2009.[420] All searches were run up to 25 March 2013 unless otherwise stated. Any studies added to the databases after this date were not included unless specifically stated in the text. Where possible searches were limited to retrieve material published in English.

Searches for the **clinical reviews** were run in Medline (OVID), Embase (OVID) and the Cochrane Library (Wiley). Additional searches were run in CINAHL (EBSCOHost), AMED (Ovid) and PsychInfo (Ovid) for some questions. Usually, searches were constructed in the following way:

- A PICO format was used for **intervention** searches where population (P) terms were combined with intervention (I) and sometimes comparison (C) terms. An intervention can be a drug, a procedure or a diagnostic test. Outcomes (O) are rarely used in search strategies for interventions. Search filters were also added to the search where appropriate.

- A PEO format was used for **prognosis** searches where population (P) terms were combined with exposure (E) terms and sometimes outcomes (O). Search filters were added to the search where appropriate.

Searches for the **health economic reviews** were run in Medline (Ovid), Embase (Ovid), the NHS Economic Evaluations Database (NHS EED), the Health Technology Assessment (HTA) database and the Health Economic Evaluation Database (HEED). HTA and NHS EED searches were carried out via the Centre for Reviews and Dissemination (CRD) interface. Searches in NHS EED and HEED were constructed only using population terms. For Medline and Embase an economic filter (instead of a study type filter) was added to the same clinical search strategy.

F.1 Population search strategies

Medline search terms

1	acute coronary syndrome/
2	exp myocardial infarction/
3	coronary thrombosis/
4	heart arrest/
5	(acute coronary adj2 syndrome*).ti,ab.
6	((myocardial or heart) adj infarct*).ti,ab.
7	(heart adj (attack* or event*)).ti,ab.
8	((heart or cardiac) adj arrest*).ti,ab.
9	(coronary adj2 thrombosis).ti,ab.
10	(stemi or st-segment or st segment or st-elevation or st elevation).ti,ab.
11	"non-st-segment elevation".ti,ab.
12	(non-stemi or nstemi or nonstemi).ti,ab.
13	"q wave myocardial infarction".ti,ab.
14	nste-acs.ti,ab.
15	(subendocardial adj3 infarct*).ti,ab.
16	or/1-15
17	letter/
18	editorial/
19	news/
20	exp historical article/
21	anecdotes as topic/
22	comment/
23	case report/
24	(letter or comment*).ti.
25	or/17-24
26	randomized controlled trial/ or random*.ti,ab.
27	25 not 26
28	animals/ not humans/
29	animals, laboratory/
30	exp animal experiment/
31	exp animal model/
32	exp rodentia/
33	(rat or rats or mouse or mice).ti.

34	or/27-33
35	16 not 34

Embase search terms

1	acute coronary syndrome/
2	exp heart infarction/
3	heart arrest/
4	exp coronary artery thrombosis/
5	st segment elevation/
6	st segment elevation myocardial infarction/
7	non st segment elevation acute coronary syndrome/
8	q wave/
9	(acute coronary adj2 syndrome*).ti,ab.
10	((myocardial or heart) adj infarct*).ti,ab.
11	(heart adj (attack* or event*)).ti,ab.
12	((heart or cardiac) adj arrest*).ti,ab.
13	(coronary adj2 thrombosis).ti,ab.
14	(stemi or st-segment or st segment or st-elevation or st elevation).ti,ab.
15	"non-st-segment elevation".ti,ab.
16	(non-stemi or nstemi or nonstemi).ti,ab.
17	"q wave myocardial infarction".ti,ab.
18	nste-acs.ti,ab.
19	(subendocardial adj3 infarct*).ti,ab.
20	or/1-19
21	letter.pt. or letter/
22	note.pt.
23	editorial.pt.
24	case report/ or case study/
25	(letter or comment*).ti.
26	or/21-25
27	randomized controlled trial/ or random*.ti,ab.
28	26 not 27
29	animal/ not human/
30	nonhuman/
31	exp animal experiment/
32	exp experimental animal/
33	animal model/
34	exp rodent/
35	(rat or rats or mouse or mice).ti.
36	or/28-35
37	20 not 36

Cochrane search terms

#1	MeSH descriptor Acute Coronary Syndrome, this term only
#2	MeSH descriptor Myocardial Infarction explode all trees
#3	MeSH descriptor Coronary Thrombosis, this term only

#4	MeSH descriptor Heart Arrest, this term only
#5	(coronary NEAR/2 thrombos*):ti,ab
#6	((myocardial or heart) NEXT infarct*):ti,ab
#7	(heart NEXT (attack* or event*)):ti,ab
#8	((heart or cardiac) NEXT arrest*):ti,ab
#9	(stemi or st-segment or (st segment) or st-elevation or (st elevation)):ti,ab
#10	"non-st-segment elevation":ti,ab
#11	(non-stemi or nstemi or nonstemi):ti,ab
#12	(Q NEXT wave NEXT myocardial NEXT infarction):ti,ab
#13	nste-acs:ti,ab
#14	(subendocardial NEAR/3 infarct*):ti,ab
#15	(acute NEXT coronary NEAR/2 syndrome*):ti,ab
#16	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)

AMED search terms

1	cardiovascular disease/ or coronary disease/ or myocardial infarction/
2	heart disease/ or heart arrest/
3	(acute coronary adj2 syndrome*).ti,ab.
4	((myocardial or heart) adj infarct*).ti,ab.
5	(heart adj attack*).ti,ab.
6	((heart or cardiac) adj (arrest* or event*)).ti,ab.
7	(coronary adj2 thrombosis).ti,ab.
8	(stemi or st-segment or st segment or st-elevation or st elevation).ti,ab.
9	non-st-segment elevation.ti,ab.
10	(non-stemi or nstemi or nonstemi).ti,ab.
11	q wave myocardial infarction.ti,ab.
12	nste-acs.ti,ab.
13	(subendocardial adj3 infarct*).ti,ab.
14	or/1-13

CINAHL search terms

S1	(MH "Acute Coronary Syndrome") OR (MH "Angina Pectoris+") OR (MH "Myocardial Infarction+") OR (MH "Coronary Thrombosis") OR (MH "Heart Arrest")
S2	acute coronary n2 syndrome* OR heart n1 attack* OR coronary n2 thrombosis
S3	((myocardial or heart) n1 infarct*)
S4	((heart or cardiac) n1 (arrest* or event*))
S5	(stemi or st-segment or st segment or st-elevation or st elevation)
S6	non-st-segment elevation or non-stemi or nstemi or nonstemi
S7	q wave myocardial infarction or nste-acs or subendocardial n3 infarct*
S8	S1 or S2 or S3 or S4 or S5 or S6 or S7
S9	PT anecdote or PT audiovisual or PT bibliography or PT biography or PT book or PT book review or PT brief item or PT cartoon or PT commentary or PT computer program or PT editorial or PT games or PT glossary or PT historical material or PT interview or PT letter or PT listservs or PT masters thesis or PT obituary or PT pamphlet or PT pamphlet chapter or PT pictorial or PT poetry or PT proceedings or PT “questions and answers” or PT response or PT software or PT teaching materials or PT website
S10	S8 NOT S9

PsychInfo search terms

1	exp heart disorders/
2	(acute coronary adj2 syndrome*).ti,ab.
3	((myocardial or heart) adj infarct*).ti,ab.
4	(heart adj attack*).ti,ab.
5	((heart or cardiac) adj (arrest* or event*)).ti,ab.
6	(coronary adj2 thrombosis).ti,ab.
7	(stemi or st-segment or st segment or st-elevation or st elevation).ti,ab.
8	"non-st-segment elevation".ti,ab.
9	(non-stemi or nstemi or nonstemi).ti,ab.
10	"q wave myocardial infarction".ti,ab.
11	nste-acs.ti,ab.
12	(subendocardial adj3 infarct*).ti,ab.
13	or/1-12

F.2 Study filter search terms

F.2.1 Systematic reviews (SRs) search terms

Medline search terms

1	meta-analysis/
2	meta-analysis as topic/
3	(meta analy* or metanaly* or metaanaly*).ti,ab.
4	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
5	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7	(search* adj4 literature).ab.
8	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9	cochrane.jw.
10	((indirect or mixed) adj2 comparison*).ti,ab.
11	or/1-10

Embase search terms

1	systematic review/
2	meta-analysis/
3	(meta analy* or metanaly* or metaanaly*).ti,ab.
4	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
5	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7	(search* adj4 literature).ab.
8	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9	((pool* or combined) adj2 (data or trials or studies or results)).ab.
10	cochrane.jw.

11	((indirect or mixed) adj2 comparison*).ti,ab.
12	or/1-11

F.2.2 Randomised controlled studies (RCTs) search terms

Medline search terms

1	randomized controlled trial.pt.
2	controlled clinical trial.pt.
3	randomi#ed.ab.
4	placebo.ab.
5	randomly.ab.
6	clinical trials as topic.sh.
7	trial.ti.
8	or/1-7

Embase search terms

1	random*.ti,ab.
2	factorial*.ti,ab.
3	(crossover* or cross over*).ti,ab.
4	((doubl* or singl*) adj blind*).ti,ab.
5	(assign* or allocat* or volunteer* or placebo*).ti,ab.
6	crossover procedure/
7	single blind procedure/
8	randomized controlled trial/
9	double blind procedure/
10	or/1-9

F.2.3 Observational studies search terms

Medline search terms

1	epidemiologic studies/
2	exp case control studies/
3	exp cohort studies/
4	cross-sectional studies/
5	case control.ti,ab.
6	(cohort adj (study or studies or analys*)).ti,ab.
7	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.
8	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.
9	or/1-8

Embase search terms

1	clinical study/
2	exp case control study/
3	family study/
4	longitudinal study/
5	retrospective study/

6	prospective study/
7	cross-sectional study/
8	cohort analysis/
9	follow-up/
10	cohort*.ti,ab.
11	9 and 10
12	case control.ti,ab.
13	(cohort adj (study or studies or analys*)).ti,ab.
14	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.
15	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.
16	or/1-8,11-15

F.2.4 Qualitative search terms

Medline search terms

1	qualitative research/
2	exp interviews as topic/
3	exp questionnaires/
4	health care surveys/
5	(qualitative or interview* or focus group* or theme* or questionnaire* or survey*).ti,ab.
6	or/1-5

Embase search terms

1	qualitative research/
2	exp interview/
3	exp questionnaire/
4	health care survey/
5	(qualitative or interview* or focus group* or theme* or questionnaire* or survey*).ti,ab.
6	or/1-5

CINAHL search terms

S1	qualitative or interview* or focus group* or theme* or questionnaire* or survey*
S2	(MH "Questionnaires+") OR (MH "Qualitative Validity+") OR (MH "Qualitative Studies+")
S3	(MH "Interviews+") OR (MH "Focus Groups") OR (MH "Surveys")
S4	S1 or S2 or S3

PsychInfo search terms

1	qualitative research/
2	exp interviews/ or interviewing/ or questioning/
3	exp questionnaires/ or exp surveys/
4	(qualitative or interview* or focus group* or theme* or questionnaire* or survey*).ti,ab.
5	or/1-4

F.2.5 Health economic search terms

Medline search terms

1	economics/
2	value of life/
3	exp "costs and cost analysis"/
4	exp economics, hospital/
5	exp economics, medical/
6	economics, nursing/
7	economics, pharmaceutical/
8	exp "fees and charges"/
9	exp budgets/
10	budget*.ti,ab.
11	cost*.ti.
12	(economic* or pharmaco?economic*).ti.
13	(price* or pricing*).ti,ab.
14	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
15	(financ* or fee or fees).ti,ab.
16	(value adj2 (money or monetary)).ti,ab.
17	or/1-16

Embase search terms

1	*health economics/
2	exp *economic evaluation/
3	exp *health care cost/
4	exp *fee/
5	budget/
6	funding/
7	budget*.ti,ab.
8	cost*.ti.
9	(economic* or pharmaco?economic*).ti.
10	(price* or pricing*).ti,ab.
11	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
12	(financ* or fee or fees).ti,ab.
13	(value adj2 (money or monetary)).ti,ab.
14	or/1-13

F.2.6 Quality of life search terms

Medline search terms

1	quality-adjusted life years/
2	sickness impact profile/
3	(quality adj2 (wellbeing or well being)).ti,ab.
4	sickness impact profile.ti,ab.
5	disability adjusted life.ti,ab.
6	(qal* or qtime* or qwb* or daly*).ti,ab.
7	(euroqol* or eq5d* or eq 5*).ti,ab.
8	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
9	(health utility* or utility score* or disutilit* or utility value*).ti,ab.

10	(hui or hui1 or hui2 or hui3).ti,ab.
11	(health* year* equivalent* or hye or hyes).ti,ab.
12	discrete choice*.ti,ab.
13	rosser.ti,ab.
14	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
15	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
16	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
17	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
18	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
19	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
20	or/1-19

Embase search terms

1	quality adjusted life year/
2	"quality of life index"/
3	short form 12/ or short form 20/ or short form 36/ or short form 8/
4	sickness impact profile/
5	(quality adj2 (wellbeing or well being)).ti,ab.
6	sickness impact profile.ti,ab.
7	disability adjusted life.ti,ab.
8	(qal* or qtime* or qwb* or daly*).ti,ab.
9	(euroqol* or eq5d* or eq 5*).ti,ab.
10	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
11	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
12	(hui or hui1 or hui2 or hui3).ti,ab.
13	(health* year* equivalent* or hye or hyes).ti,ab.
14	discrete choice*.ti,ab.
15	rosser.ti,ab.
16	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
17	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
18	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
19	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
20	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
21	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
22	or/1-21

F.3 Searches by specific questions

F.3.1 Omega 3

What is the clinical and cost effectiveness of omega 3 fatty acids supplementation in all people with myocardial infarction?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Myocardial	Omega 3		SRs	2006 – 25 March

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
infarction			RCTs Observational	2013

Omega 3 search terms

Medline search terms

1	fish oils/
2	cod liver oil/
3	plant oils/
4	flax/
5	brassica rapa/
6	perilla/
7	linseed oil/
8	alpha-linolenic acid/
9	docosahexaenoic acids/
10	eicosapentanoic acid/
11	triglycerides/
12	fatty acids, omega-3/
13	fatty acids, unsaturated/
14	(a-linolenic acid* or ala or alpha-linolenic acid* or linolenate or linolenic acid*).ti,ab.
15	(eicosapentaenoic acid* or epa or timnodonic acid* or eicosapentaenoate or icosapentanoate).ti,ab.
16	(docosahexaenoic acid* or dha or docosahexaenoate).ti,ab.
17	(docosapentaenoic acid* or dpa or docosapentaenoate).ti,ab.
18	((n-3 or n3) adj fatty acid*).ti,ab.
19	(omega-3 or omega3).ti,ab.
20	(omacor or maxepa).ti,ab.
21	(pufa or poluyunsaturated fa*).ti,ab.
22	((plant or algal or cod liver) adj oil*).ti,ab.
23	(flaxseed or linseed or rapeseed or canola or perilla or flax or linum).ti,ab.
24	((marine or fish) adj2 (lipid* or oil* or triglyceride*)).ti,ab.
25	or/1-24

Embase search terms

1	fish oil/
2	cod liver oil/
3	vegetable oil/
4	flax/ or linseed oil/
5	rapeseed oil/
6	perilla oil/
7	linolenic acid/
8	docosahexaenoic acid/
9	icosapentaenoic acid/
10	docosapentaenoic acid/
11	triacylglycerol/

12	omega 3 fatty acid/
13	polyunsaturated fatty acid/
14	(a-linolenic acid* or ala or alpha-linolenic acid* or linolenate or linolenic acid*).ti,ab.
15	(eicosapentaenoic acid* or epa or timnodonic acid* or eicosapentaenoate or icosapentanoate).ti,ab.
16	(docosahexaenoic acid* or dha or docosahexaenoate).ti,ab.
17	(docosapentaenoic acid* or dpa or docosapentaenoate).ti,ab.
18	((n-3 or n3) adj fatty acid*).ti,ab.
19	(omega-3 or omega3).ti,ab.
20	(omacor or maxepa).ti,ab.
21	(pufa or poluyunsaturated fa*).ti,ab.
22	((plant or algal or cod liver) adj oil*).ti,ab.
23	(flaxseed or linseed or rapeseed or canola or perilla or flax or linum).ti,ab.
24	((marine or fish) adj2 (lipid* or oil* or triglyceride*)).ti,ab.
25	or/1-24

Cochrane search terms

#1	MeSH descriptor Fish Oils explode all trees
#2	MeSH descriptor Dietary Fats, Unsaturated, this term only
#3	MeSH descriptor Triglycerides, this term only
#4	MeSH descriptor Plant Oils, this term only
#5	MeSH descriptor Flax, this term only
#6	MeSH descriptor Brassica rapa, this term only
#7	MeSH descriptor Perilla, this term only
#8	MeSH descriptor Linseed Oil, this term only
#9	(a-Linolenic acid* or ala or alpha-linolenic acid* or linolenate or linolenic acid*):ti,ab
#10	(eicosapentaenoic acid* or epa or timnodonic acid* or eicosapentaenoate or icosapentanoate):ti,ab
#11	(docosahexaenoic acid* or dha or docosahexaenoate):ti,ab
#12	(docosapentaenoic acid* or dpa or docosapentaenoate):ti,ab
#13	((n-3 or n3) NEXT (fatty acid*)):ti,ab
#14	(omega-3 or omega3):ti,ab
#15	(omacor or maxepa):ti,ab
#16	(pufa or poluyunsaturated fa*):ti,ab
#17	((plant or algal or cod liver) NEXT oil*):ti,ab
#18	(flaxseed or linseed or rapeseed or canola or perilla or flax or linum):ti,ab
#19	((marine or fish) NEAR/2 (lipid* or oil* or triglyceride*)):ti,ab
#20	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19)

AMED search terms

1	fish oils/
2	plant oils/
3	fatty acids/
4	triglycerides/
5	(a-linolenic acid* or ala or alpha-linolenic acid* or linolenate or linolenic acid*).ti,ab.
6	(eicosapentaenoic acid* or epa or timnodonic acid* or eicosapentaenoate or

	icosapentanoate).ti,ab.
7	(docosahexaenoic acid* or dha or docosahexaenoate).ti,ab.
8	(docosapentaenoic acid* or dpa or docosapentaenoate).ti,ab.
9	((n-3 or n3) adj fatty acid*).ti,ab.
10	(omega-3 or omega3).ti,ab.
11	(omacor or maxepa).ti,ab.
12	(pufa or poluyunsaturated fa*).ti,ab.
13	((plant or algal or cod liver) adj oil*).ti,ab.
14	(flaxseed or linseed or rapeseed or canola or perilla or flax or linum).ti,ab.
15	((marine or fish) adj2 (lipid* or oil* or triglyceride*)).ti,ab.
16	or/1-15

F.3.2 Fish diet

What is the clinical and cost effectiveness of an oily fish diet in all people with myocardial infarction?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Myocardial infarction	Fish		SRs RCTs Observational	2006 – 25 March 2013

Fish search terms

Medline search terms

1	exp fishes/
2	exp seafood/
3	exp crustacea/
4	diet, mediterranean/
5	fish*.ti,ab.
6	crab*.ti,ab.
7	(mediterranean adj2 diet*).ti,ab.
8	or/1-7

Embase search terms

1	exp fish/
2	exp crustacea/
3	seafood/
4	shellfish/
5	mediterranean diet/
6	fish*.ti,ab.
7	crab*.ti,ab.
8	(mediterranean adj2 diet*).ti,ab.
9	or/1-8

Cochrane search terms

#1	MeSH descriptor: [Fishes] explode all trees

#2	MeSH descriptor: [Seafood] explode all trees
#3	MeSH descriptor: [Crustacea] explode all trees
#4	MeSH descriptor: [Diet, Mediterranean] this term only
#5	fish*:ti,ab
#6	crab*:ti,ab
#7	(mediterranean near/2 diet*):ti,ab
#8	#1 or #2 or #3 or #4 or #5 or #6 or #7

AMED search terms

1	fish*.ti,ab.
2	crab*.ti,ab.
3	(mediterranean adj2 diet*).ti,ab.
4	diet mediterranean/
5	fishes/
6	or/1-5

F.3.3 Cardiac rehabilitation: interventions

Searches for the following question were run as two searches:

Which interventions designed to increase engagement in and/or adherence to cardiac rehabilitation programs are effective and cost effective in people who have had an MI?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Myocardial infarction	Cardiac rehabilitation adherence		SRs RCTs Observational	2006 – 25 March 2013

Cardiac rehabilitation adherence search terms

Medline search terms

1	rehabilitation centers/ or exp rehabilitation/ or rehabilitation nursing/
2	exercise therapy/
3	"Recovery of Function"/
4	rehabilitat*.ti,ab.
5	((exercise* or fitness) adj3 (therap* or training or program* or treatment or intervent*)).ti,ab.
6	managed care programs/
7	((multifactor* or multifacet* or managed care) adj program*).ti,ab.
8	patient education as topic/
9	health education/
10	((patient* or health) adj2 educat*).ti,ab.
11	counseling/
12	counsel*.ti,ab.
13	exp psychotherapy/
14	(psychotherap* or psychosocial*).ti,ab.
15	(psycholog* adj2 intervent*).ti,ab.
16	(behavi* adj3 (modify or modificat* or therap* or change)).ti,ab.

17	(Cognitive adj2 therap*).ti,ab.
18	cbt.ti,ab.
19	((lifestyle or life-style) adj3 (intervent* or program* or treatment*)).ti,ab.
20	self care/
21	(self adj3 (manage* or care or motivat*)).ti,ab.
22	or/1-21
23	health services accessibility/
24	patient compliance/
25	"referral and consultation"/
26	patient satisfaction/
27	patient participation/
28	motivation/
29	(enrollment or enrolment or enroling or enrolling).ti,ab.
30	participat*.ti,ab.
31	motivat*.ti,ab.
32	uptake.ti,ab.
33	referral.ti,ab.
34	(complian* or adheren* or non-complian* or noncomplian* or non adheren * or nonadheren*).ti,ab.
35	(attend* or non-attend*).ti,ab.
36	barrier*.ti,ab.
37	(engaging or engagement).ti,ab.
38	or/23-37
39	22 and 38

Embase search terms

1	exp *rehabilitation/ or *rehabilitation care/ or *rehabilitation center/
2	*rehabilitation medicine/ or rehabilitation nursing/
3	*kinesiotherapy/ or exercise recovery/ or movement therapy/
4	*convalescence/
5	rehabilitat*.ti,ab.
6	((exercise* or fitness) adj3 (therap* or training or program* or treatment or intervent*)).ti,ab.
7	((multifactor* or multifacet* or managed care) adj program*).ti,ab.
8	*health education/ or *patient education/
9	((patient* or health) adj2 educat*).ti,ab.
10	*counseling/ or *patient counseling/ or patient guidance/
11	counsel*.ti,ab.
12	exp *psychotherapy/
13	(psychotherap* or psychosocial*).ti,ab.
14	(psycholog* adj2 intervent*).ti,ab.
15	(behavi* adj3 (modify or modificat* or therap* or change)).ti,ab.
16	(cognitive adj2 therap*).ti,ab.
17	cbt.ti,ab.
18	((lifestyle or life-style) adj3 (intervent* or program* or treatment*)).ti,ab.
19	*self care/
20	(self adj3 (manage* or care or motivat*)).ti,ab.

21	or/1-20
22	exp *telehealth/ or *health care delivery/
23	exp *patient attitude/
24	*patient referral/
25	*motivation/
26	(enrollment or enrolment or enroling or enrolling).ti,ab.
27	participat*.ti,ab.
28	motivat*.ti,ab.
29	uptake.ti,ab.
30	referral.ti,ab.
31	(complian* or adheren* or non-complian* or noncomplian* or non adheren * or nonadheren*).ti,ab.
32	(attend* or non-attend*).ti,ab.
33	barrier*.ti,ab.
34	(engaging or engagement).ti,ab.
35	or/22-34
36	21 and 35

Cochrane search terms

#1	MeSH descriptor Rehabilitation Centers, this term only
#2	MeSH descriptor Rehabilitation explode all trees
#3	MeSH descriptor Rehabilitation Nursing, this term only
#4	MeSH descriptor Exercise Therapy, this term only
#5	MeSH descriptor Recovery of Function, this term only
#6	rehabilitat*:ti,ab
#7	((exercise* or fitness) NEAR/3 (therap* or training or program* or treatment or intervent*)):ti,ab
#8	MeSH descriptor Managed Care Programs, this term only
#9	((multifactor* or multifacet* or managed care) NEXT program*):ti,ab
#10	MeSH descriptor Patient Education as Topic, this term only
#11	MeSH descriptor Health Education, this term only
#12	((patient* or health) NEAR/2 educat*):ti,ab
#13	MeSH descriptor Counseling, this term only
#14	counsel*:ti,ab
#15	MeSH descriptor Psychotherapy explode all trees
#16	(psychotherap* or psychosocial*):ti,ab
#17	(psycholog* NEAR/2 intervent*):ti,ab
#18	(behavi* NEAR/3 (modify or modificat* or therap* or change)):ti,ab
#19	(cognitive NEAR/2 therap*):ti,ab
#20	cbt:ti,ab
#21	((lifestyle or life-style) NEAR/3 (intervent* or program* or treatment*)):ti,ab
#22	MeSH descriptor Self Care, this term only
#23	(self NEAR/3 (manage* or care or motivat*)):ti,ab
#24	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23)
#25	MeSH descriptor Health Services Accessibility, this term only

#26	MeSH descriptor Patient Compliance, this term only
#27	MeSH descriptor Referral and Consultation, this term only
#28	MeSH descriptor Patient Satisfaction explode all trees
#29	MeSH descriptor Patient Participation, this term only
#30	MeSH descriptor Motivation, this term only
#31	(enrollment or enrolment or enroling or enrolling):ti,ab
#32	participat*:ti,ab
#33	motivat*:ti,ab
#34	uptake:ti,ab
#35	referral:ti,ab
#36	(complian* or adheren* or non-complian* or noncomplian* or non adheren * or nonadheren*):ti,ab
#37	(attend* or non-attend*):ti,ab
#38	barrier*:ti,ab
#39	(engaging or engagement):ti,ab
#40	(#25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39)
#41	(#24 AND #40)

CINAHL search terms

S1	(MH "Rehabilitation+") OR (MH "Rehabilitation Centers") OR (MH "Home Rehabilitation+") OR (MH "Rehabilitation Nursing") OR (MH "Therapeutic Exercise") OR (MH "Managed Care Programs")
S2	rehabilitat*
S3	((exercise* or fitness) n3 (therap* or training or program* or treatment or intervent*))
S4	((multifactor* or multifacet* or managed care) n1 program*)
S5	(MH "Patient Education") OR (MH "Patient Discharge Education") OR (MH "Health Education") OR (MH "Counseling") OR (MH "Psychotherapy+") OR (MH "Self Care")
S6	((patient* or health) n2 educat*)
S7	counsel* OR psychotherap* OR psychosocial*
S8	psycholog* n2 intervent* OR cognitive n2 therap* OR cbt
S9	(behavi* n3 (modify or modificat* or therap* or change))
S10	((lifestyle or life-style) n3 (intervent* or program* or treatment*))
S11	(self n3 (manage* or care or motivat*))
S12	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11
S13	(MH "Health Services Accessibility") OR (MH "Telehealth+") OR (MH "Patient Compliance") OR (MH "Referral and Consultation+") OR (MH "Patient Satisfaction") OR (MH "Consumer Participation") OR (MH "Motivational Interviewing") OR (MH "Motivation")
S14	enrollment OR enrolment OR enroling OR enrolling
S15	participat* OR motivat* OR uptake OR referral
S16	(complian* or adheren* or non-complian* or noncomplian* or non adheren * or nonadheren*)
S17	attend* OR non-attend* OR barrier*
S18	engaging OR engagement
S19	S13 or S14 or S15 or S16 or S17 or S18
S20	S12 and S19

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Cardiac rehabilitation	Adherence		SRs RCTs Observational	2006 – 25 March 2013

Medline search terms

1	exp heart diseases/rh [rehabilitation]
2	((cardiac or heart) adj2 rehab*).ti,ab.
3	1 or 2
4	health services accessibility/
5	patient compliance/
6	"referral and consultation"/
7	patient satisfaction/
8	patient participation/
9	motivation/
10	(enrollment or enrolment or enroling or enrolling).ti,ab.
11	participat*.ti,ab.
12	motivat*.ti,ab.
13	uptake.ti,ab.
14	referral.ti,ab.
15	(complian* or adheren* or non-complian* or noncomplian* or non adheren* or nonadheren*).ti,ab.
16	(attend* or non-attend*).ti,ab.
17	barrier*.ti,ab.
18	(engaging or engagement).ti,ab.
19	or/4-18
20	3 and 19

Embase search terms

1	heart rehabilitation/
2	((cardiac or heart) adj2 rehab*).ti,ab.
3	exp *heart disease/rh [rehabilitation]
4	or/1-3
5	exp *telehealth/ or *health care delivery/
6	exp *patient attitude/
7	*patient referral/
8	*motivation/
9	(enrollment or enrolment or enroling or enrolling).ti,ab.
10	participat*.ti,ab.
11	motivat*.ti,ab.
12	uptake.ti,ab.
13	referral.ti,ab.
14	(complian* or adheren* or non-complian* or noncomplian* or non adheren * or nonadheren*).ti,ab.
15	(attend* or non-attend*).ti,ab.
16	barrier*.ti,ab.

17	(engaging or engagement).ti,ab.
18	or/5-17
19	4 and 18

CINAHL search terms

S1	(MH "Rehabilitation, Cardiac+") OR (MH "Heart Diseases+/RH")
S2	((cardiac or heart) n2 rehab*)
S3	S1 or S2
S4	(MH "Health Services Accessibility") OR (MH "Telehealth+") OR (MH "Patient Compliance") OR (MH "Referral and Consultation+") OR (MH "Patient Satisfaction") OR (MH "Consumer Participation") OR (MH "Motivational Interviewing") OR (MH "Motivation")
S5	enrollment OR enrolment OR enroling OR enrolling
S6	participat* OR motivat* OR uptake OR referral
S7	(complian* or adheren* or non-complian* or noncomplian* or non adheren * or nonadheren*)
S8	attend* OR non-attend* OR barrier*
S9	engaging OR engagement
S10	S4 or S5 or S6 or S7 or S8 or S9
S11	S3 and S10

F.3.4 Cardiac rehabilitation: barriers

Searches for the following question were run as two searches:

Which factors are associated with a person's uptake and adherence to cardiac rehabilitation programme (CRP) after an MI?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Myocardial infarction	Cardiac rehabilitation adherence		Qualitative	2006 – 25 March 2013

Cardiac rehabilitation adherence search terms

See cardiac rehabilitation: interventions question for cardiac rehabilitation adherence terms for Medline, Embase and CINAHL.

PsychInfo search terms

1	exp rehabilitation/ or exp rehabilitation centers/
2	exercise/ or movement therapy/
3	rehabilitat*.ti,ab.
4	((exercise* or fitness) adj3 (therap* or training or program* or treatment or intervent*)).ti,ab.
5	((multifactor* or multifacet* or managed care) adj program*).ti,ab.
6	health education/ or client education/
7	((patient* or health) adj2 educat*).ti,ab.
8	counseling/ or psychotherapeutic counseling/ or rehabilitation counseling/
9	counsel*.ti,ab.
10	exp psychotherapy/
11	(psychotherap* or psychosocial*).ti,ab.

12	(psycholog* adj2 intervent*).ti,ab.
13	(behavi* adj3 (modify or modificat* or therap* or change)).ti,ab.
14	(cognitive adj2 therap*).ti,ab.
15	exp cognitive behavior therapy/ or cognitive therapy/
16	cbt.ti,ab.
17	((lifestyle or life-style) adj3 (intervent* or program* or treatment*)).ti,ab.
18	(self adj3 (manage* or care or motivat*)).ti,ab.
19	self care skills/
20	or/1-19
21	exp compliance/
22	client participation/ or treatment barriers/
23	client satisfaction/
24	motivation/ or incentives/
25	readiness to change/
26	(enrollment or enrolment or enroling or enrolling).ti,ab.
27	participat*.ti,ab.
28	motivat*.ti,ab.
29	uptake.ti,ab.
30	referral.ti,ab.
31	(complian* or adheren* or non-complian* or noncomplian* or non adheren * or nonadheren*).ti,ab.
32	(attend* or non-attend*).ti,ab.
33	barrier*.ti,ab.
34	(engaging or engagement).ti,ab.
35	or/21-34
36	20 and 35

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Cardiac rehabilitation	Adherence		Qualitative	2006 – 25 March 2013

See cardiac rehabilitation: interventions question for terms for Medline, Embase and CINAHL.

PsychInfo search terms

1	((cardiac or heart) adj2 rehab*).ti,ab.
2	exp compliance/
3	client participation/ or treatment barriers/
4	client satisfaction/
5	motivation/ or incentives/
6	readiness to change/
7	(enrollment or enrolment or enroling or enrolling).ti,ab.
8	participat*.ti,ab.
9	motivat*.ti,ab.
10	uptake.ti,ab.
11	referral.ti,ab.

12	(complian* or adheren* or non-complian* or noncomplian* or non adheren * or nonadheren*).ti,ab.
13	(attend* or non-attend*).ti,ab.
14	barrier*.ti,ab.
15	(engaging or engagement).ti,ab.
16	or/2-15
17	1 and 16

F.3.5 ACE inhibitors

Searches for the following two questions were run as one search:

What is the clinical and cost effectiveness of adding ACE inhibitors versus placebo to improve outcome in people after an MI and is there an optimal duration?

What is the clinical and cost effectiveness of adding ACE inhibitors versus ARBs or in combination versus ACE inhibitors to improve outcomes in people after an MI?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Myocardial infarction	ACEi/ARB		SRs RCTs	2006 – 25 March 2013

ACEi/ARB search terms

Medline search terms

1	exp angiotensin-converting enzyme inhibitors/
2	((ace or acei or ((angiotensin adj converting adj2 enzyme*) or ace or kininase)) adj2 (inhibit* or antagonist*)).ti,ab.
3	(captopril or ecopace or kaplon or capoten or co-zidocapt or capto-co or capozide or cilazapril or vascace or enalapril or ednyt or innovace or innozide or fosinopril or imidapril or tanatril or lisinopril or zestril or carace or zestoretic or moexipril or perdix or perindopril or coversyl or quinapril or quinil or accupro or accuretic or ramipril or tritace or triapin or trandolapril or gopten or tarka).ti,ab.
4	exp angiotensin ii type 1 receptor blockers/ or angiotensin ii type 2 receptor blockers/
5	((angiotensin adj3 (receptor* adj2 (antagonist* or blocker*))) or arb or arbs).ti,ab.
6	(candesartan or amias or eprosartan or teveten or irbesartan or aprovel or coaprovel or losartan or cozaar or cozaar-comp or olmesartan or olmetec or sevikar or telmisartan or micardis or valsartan or diovan or co-diovan).ti,ab.
7	or/1-6

Embase search terms

1	exp *dipeptidyl carboxypeptidase inhibitor/
2	((ace or acei or ((angiotensin adj converting adj2 enzyme*) or ace or kininase)) adj2 (inhibit* or antagonist*)).ti,ab.
3	(captopril or ecopace or kaplon or capoten or co-zidocapt or capto-co or capozide or cilazapril or vascace or enalapril or ednyt or innovace or innozide or fosinopril or imidapril or tanatril or lisinopril or zestril or carace or zestoretic or moexipril or perdix or perindopril or coversyl or quinapril or quinil or accupro or accuretic or ramipril or tritace or triapin or trandolapril or gopten or tarka).ti,ab.
4	exp *angiotensin receptor antagonist/

5	((angiotensin adj3 (receptor* adj2 (antagonist* or blocker*))) or arb or arbs).ti,ab.
6	(candesartan or amias or eprosartan or teveten or irbesartan or aprovel or coaprovel or losartan or cozaar or cozaar-comp or olmesartan or olmetec or sevikar or telmisartan or micardis or valsartan or diovan or co-diovan).ti,ab.
7	or/1-6

Cochrane search terms

#1	MeSH descriptor Angiotensin-Converting Enzyme Inhibitors explode all trees
#2	((ace or acei or ((angiotensin adj converting NEAR/2 enzyme*) or ace or kininase)) NEAR/2 (inhibit* or antagonist*)):ti,ab
#3	(captopril or ecopace or kaplon or capoten or co-zidocapt or capto-co or capozide or cilazapril or vascace or enalapril or ednyt or innovace or innozide or fosinopril or imidapril or tanatril or lisinopril or zestril or carace or zestoretic or moexipril or perdix or perindopril or coversyl or quinapril or quinil or accupro or accuretic or ramipril or tritace or triapin or trandolapril or gopten or tarka):ti,ab
#4	MeSH descriptor Angiotensin Receptor Antagonists explode all trees
#5	((angiotensin NEAR/3 (receptor* NEAR/2 (antagonist* or blocker*))) or arb or arbs):ti,ab
#6	(candesartan or amias or eprosartan or teveten or irbesartan or aprovel or coaprovel or losartan or cozaar or cozaar-comp or olmesartan or olmetec or sevikar or telmisartan or micardis or valsartan or diovan or co-diovan):ti,ab
#7	(#1 OR #2 OR #3 OR #4 OR #5 OR #6)

F.3.6 ACE inhibitor initiation

Is there an optimal time for ACE inhibitors to be initiated in people who have had a MI?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Myocardial infarction	ACEi AND timing of initiation		SRs RCTs	No date restriction. Search run to 25 March 2013

See ACEi question for ACEi search terms.

Timing of initiation search terms

Medline search terms

1	time factors/
2	((time or timing or early or earlier or late or later) adj2 (initiat* or start* or treat* or therap* or administ*)).ti,ab.
3	or/1-2

Embase search terms

1	*time/
2	therapy delay/
3	((time or timing or early or earlier or late or later) adj2 (initiat* or start* or treat* or therap* or administ*)).ti,ab.
4	or/1-3

Cochrane search terms

#1	MeSH descriptor: [Time Factors] explode all trees

#2	((time or timing or early or earlier or late or later) near/2 (initiat* or start* or treat* or therap* or administ*)):ti,ab
#3	(#1 OR #2)

F.3.7 ACE inhibitor titration

Is early dose titration of ACE inhibitors in hospital more clinically and cost effective than dose titration over an extended period of time in people who have had a MI?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
ACEi	Titration		SRs RCTs	No date restriction. Search run to 25 March 2013

See ACEi question for ACEi search terms.

Titration search terms

Medline search terms

1	titrimetry/
2	(titrat* or titrimetr* or uptitrat* or up-titrat*).ti,ab.
3	or/1-2

Embase search terms

1	titrimetry/
2	(titrat* or titrimetr* or uptitrat* or up-titrat*).ti,ab.
3	or/1-2

Cochrane search terms

#1	MeSH descriptor: [Titrimetry] explode all trees
#2	(titrat* or titrimetr* or uptitrat* or up-titrat*):ti,ab
#3	#1 or #2

F.3.8 Clopidogrel

What is the optimal duration that clopidogrel should be continued in people after MI?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Myocardial infarction	Clopidogrel		SRs RCTs	2006 – 25 March 2013

Clopidogrel search terms

Medline search terms

1	(clopidogrel or plavix).ti,ab.

Embase search terms

1	clopidogrel/

2	(clopidogrel or plavix).ti,ab.
3	or/1-2

Cochrane search terms

#1	(clopidogrel or plavix):ti,ab

F.3.9 Antiplatelets

In people with an MI in the past who were not initiated on dual antiplatelet therapy (clopidogrel, prasugrel or ticagrelor in combination with aspirin), should this be initiated?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Myocardial infarction	Dual antiplatelet therapy		SRs RCTs Observational	No date restriction. Search run to 25 March 2013

Dual antiplatelet therapy search terms

Medline search terms

1	aspirin/
2	(aspirin or acetylsalicylic acid).ti,ab.
3	or/1-2
4	(clopidogrel or plavix).ti,ab.
5	(ticagrelor or brilique).ti,ab.
6	(prasugrel or efient or effient or prasita).ti,ab.
7	platelet aggregation inhibitors/
8	or/4-7
9	3 and 8

Embase search terms

1	acetylsalicylic acid plus clopidogrel/
2	(aspirin or acetylsalicylic acid).ti,ab.
3	acetylsalicylic acid/
4	or/2-3
5	prasugrel/
6	clopidogrel/
7	ticagrelor/
8	(clopidogrel or plavix).ti,ab.
9	(ticagrelor or brilique).ti,ab.
10	(prasugrel or efient or effient or prasita).ti,ab.
11	or/5-10
12	4 and 11
13	1 or 12

Cochrane search terms

#1	MeSH descriptor Aspirin, this term only
#2	(aspirin or aacetylsalicylic acid):ti,ab

#3	(#1 OR #2)
#4	(clopidogrel or plavix):ti,ab
#5	(ticagrelor or brilique):ti,ab
#6	(prasugrel or efient or effient or prasita):ti,ab
#7	MeSH descriptor Platelet Aggregation Inhibitors, this term only
#8	(#4 OR #5 OR #6 OR #7)
#9	(#3 AND #8)

F.3.10 Anticoagulants

What is the most effective and cost effective combination of antiplatelet and anticoagulant therapies for people with MI and an indication for anticoagulation?

This section was updated and replaced in 2020. See www.nice.org.uk/guidance/ng185 for the 2020 evidence review.

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Myocardial infarction	Anticoagulants ± antiplatelets		SRs RCTs	No date restriction. Search run to 25 March 2013

Anticoagulants ± antiplatelets search terms

Medline search terms

1	aspirin/
2	aspirin.ti,ab.
3	platelet aggregation inhibitors/
4	(clopidogrel or plavix).ti,ab.
5	(ticagrelor or brilique).ti,ab.
6	(prasugrel or efient or effient or prasita).ti,ab.
7	(antiplatelet* adj2 (dual or therap* or treat*)).ti,ab.
8	or/1-7
9	warfarin/
10	warfarin.ti,ab.
11	anticoagulants/
12	(rivaroxaban or xarelto).ti,ab.
13	(dabigatran or pradaxa).ti,ab.
14	apixaban.ti,ab.
15	or/9-14
16	(9 or 10) and (12 or 13 or 14)
17	12 and (9 or 10 or 13 or 14)
18	13 and (9 or 10 or 12 or 14)
19	14 and (9 or 10 or 12 or 13)
20	(8 and 15) or 16 or 17 or 18 or 19

Embase search terms

1	acetylsalicylic acid/

2	clopidogrel/
3	acetylsalicylic acid plus clopidogrel/
4	ticagrelor/
5	prasugrel/
6	antithrombocytic agent/
7	aspirin.ti,ab.
8	(clopidogrel or plavix).ti,ab.
9	(ticagrelor or brilique).ti,ab.
10	(prasugrel or efient or effient or prasita).ti,ab.
11	(antiplatelet* adj2 (dual or therap* or treat*)).ti,ab.
12	or/1-11
13	warfarin/
14	warfarin.ti,ab.
15	rivaroxaban/
16	(rivaroxaban or xarelto).ti,ab.
17	dabigatran/ or dabigatran etexilate/
18	(dabigatran or pradaxa).ti,ab.
19	apixaban/
20	apixaban.ti,ab.
21	or/13-20
22	(13 or 14) and (15 or 16 or 17 or 18 or 19 or 20)
23	(15 or 16) and (13 or 14 or 17 or 18 or 19 or 20)
24	(17 or 18) and (13 or 14 or 15 or 16 or 19 or 20)
25	(19 or 20) and (13 or 14 or 15 or 16 or 17 or 18)
26	(12 and 21) or 22 or 23 or 24 or 25

Cochrane search terms

#1	MeSH descriptor Aspirin, this term only
#2	MeSH descriptor Platelet Aggregation Inhibitors, this term only
#3	aspirin:ti,ab
#4	(clopidogrel or plavix):ti,ab
#5	(ticagrelor or brilique):ti,ab
#6	(prasugrel or efient or effient or prasita):ti,ab
#7	(antiplatelet* NEAR/2 (dual or therap* or treat*)):ti,ab
#8	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
#9	MeSH descriptor Anticoagulants, this term only
#10	warfarin:ti,ab
#11	MeSH descriptor Warfarin, this term only
#12	(rivaroxaban or xarelto):ti,ab
#13	(dabigatran or pradaxa):ti,ab
#14	apixaban:ti,ab
#15	(#9 OR #10 OR #11 OR #12 OR #13 OR #14)
#16	(#8 AND #15)
#17	((#10 OR #11) AND (#12 OR #13 OR #14))
#18	(#12 AND (#10 OR #11 OR #13 OR #14))

#19	(#13 AND (#10 OR #11 OR #12 OR #14))
#20	(#14 AND (#10 OR #11 OR #12 OR #13))
#21	(#16 OR #17 OR #18 OR #19 OR #20)

F.3.11 Beta blockers

Searches for the following two questions were run as one search:

What is the clinical and cost effectiveness of adding a beta blocker versus placebo to improve outcome in people after a MI i) with and ii) without left ventricular dysfunction and is there an optimal duration?

Is there an optimal time for beta-blockers to be initiated in people who have had a MI?

This section was partially updated in 2020. See www.nice.org.uk/guidance/ng185 for the 2020 evidence review.

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Myocardial infarction	Beta blockers		SRs RCTs Observational	2006 – 25 March 2013

Beta blockers search terms

Medline search terms

1	exp adrenergic beta-antagonists/
2	(propranolol or angilol or angilol or inderal-la or half-inderal or inderal or bedranol or prograne or slo-pro or acebutolol or sectral or atenolol or tenormin or bisoprolol or cardicor or emcor or carvedilol or eucardic or celiprolol or celectol or co-tenidone or tenoret or tenoretic or esmolol or brevibloc or labetalol or trandate or metoprolol or betaloc or lopresor or nadolol or corgard or nebivolol or nebilet or hypoloc or oxprenolol or trasicor or slow-trasicor or pindolol or visken or sotalol or beta-cardone or sotacor or timolol or betim).ti,ab.
3	(beta adj3 block*).ti,ab.
4	(b adj3 block*).ti,ab.
5	(beta adj2 antagonist*).ti,ab.
6	or/1-5

Embase search terms

1	exp *beta adrenergic receptor blocking agent/
2	(propranolol or angilol or angilol or inderal-la or half-inderal or inderal or bedranol or prograne or slo-pro or acebutolol or sectral or atenolol or tenormin or bisoprolol or cardicor or emcor or carvedilol or eucardic or celiprolol or celectol or co-tenidone or tenoret or tenoretic or esmolol or brevibloc or labetalol or trandate or metoprolol or betaloc or lopresor or nadolol or corgard or nebivolol or nebilet or hypoloc or oxprenolol or trasicor or slow-trasicor or pindolol or visken or sotalol or beta-cardone or sotacor or timolol or betim).ti,ab.
3	(beta adj3 block*).ti,ab.
4	(b adj3 block*).ti,ab.
5	(beta adj2 antagonist*).ti,ab.
6	or/1-5

Cochrane search terms

#1	MeSH descriptor Adrenergic beta-Antagonists explode all trees
#2	(propranolol or angilol or angilol or inderal-la or half-inderal or inderal or bedranol or prograne or slo-pro or acebutolol or sectral or atenolol or tenormin or bisoprolol or cardicor or emcor or carvedilol or eucardic or celiprolol or celectol or co-tenidone or tenoret or tenoretic or esmolol or brevibloc or labetalol or trandate or metoprolol or betaloc or lopresor or nadolol or corgard or nebivolol or nebilet or hypoloc or oxprenolol or trasicor or slow-trasicor or pindolol or visken or sotalol or beta-cardone or sotacor or timolol or betim):ti,ab
#3	(beta NEAR/3 block*):ti,ab
#4	(b NEAR/3 block*):ti,ab
#5	(beta NEAR/2 antagonist*):ti,ab
#6	(#1 OR #2 OR #3 OR #4 OR #5)

F.4 Economics searches

F.4.1 Economics search

Economic searches were conducted in Medline, Embase, HEED and CRD for NHS EED and HTA.

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Myocardial Infarction			Health economic	Medline and Embase 2011 – 25 March 2013 HEED and CRD (NHS EED and HTA) 2006 – 25 March 2013

CRD search terms

#1	MeSH DESCRIPTOR acute coronary syndrome IN NHSEED,HTA
#2	MeSH DESCRIPTOR myocardial infarction EXPLODE ALL TREES IN NHSEED,HTA
#3	MeSH DESCRIPTOR coronary thrombosis IN NHSEED,HTA
#4	MeSH DESCRIPTOR heart arrest IN NHSEED,HTA
#5	("acute coronary" adj2 syndrome*) IN NHSEED, HTA
#6	((myocardial or heart) adj infarct*) IN NHSEED, HTA
#7	(heart adj (attack* or event*)) IN NHSEED, HTA
#8	((heart or cardiac) adj arrest*) IN NHSEED, HTA
#9	(coronary adj2 thrombosis) IN NHSEED, HTA
#10	(stemi or st-segment or "st segment" or st-elevation or "st elevation") OR ("non-ST-segment elevation") OR (non-stemi or nstemi or nonstemi) OR ("q wave myocardial infarction") OR (nste-acs) IN NHSEED, HTA
#11	(subendocardial adj3 infarct*) IN NHSEED, HTA
#12	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11

HEED search terms

1	ax=acute coronary syndrome or acute coronary syndromes
2	ax=myocardial infarction or myocardial infarct or myorcardial infarcts
3	ax=coronary thrombosis
4	ax=heart infarction or heart infarct or heart infarcts
5	ax=heart attack or heart attacks

6	ax=heart arrest or heart arrests
7	ax=cardiac arrest or cardiac arrests
8	ax=heart event or heart events
9	ax=stemi or 'st segment' or 'st elevation'
10	ax=non-st-segment elevation
11	ax=non-stemi or nstemi or nonstemi
12	ax=q wave myocardial infarction
13	ax=nste-acs
14	ax=subendocardial and infarct*
15	cs=1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14

F.4.2 Quality of life search

Quality of life searches were conducted in Medline and Embase

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Myocardial Infarction			Quality of life	2006 – 25 March 2013

Appendix G: Clinical evidence tables

G.1 Summary of patient barriers to the uptake of and adherence to cardiac rehabilitation

Barriers	General population	Needs of ethnic minorities	Differences in gender	Differences in older /younger aged patients	Needs of those from low socioeconomic background	Employment issues Language barriers
Not understanding the importance of a CRP and what it entails	Madden 2011: patients did not know what a CR service was or why it was important; lack of perceived status of service (suggested by nurses rather than prescribed by cardiologists) McCorry 2009: manner of invitation did not indicate it was important to attend: "you had the option to go...If they had pushed it... I would probably have gone ...at	South Asians: not sure what CRP entails [210]	Women: like being independent, having to cope alone , dislike of asking for external help , frustration at loss of independence leading to lack of perceived need for CRP; poor understanding of programme (e.g. thinking it was for other people, not for them); thinking it was not needed if had family support [488] Dismissing doctors' advice (e.g. to give up smoking)[488] Tended to ascribe condition to stress or family tendency not alterable factors[488] MacInnes 2005: belief that illness was inevitable: " I	Older adults (over 65 years): continued only until felt back to normal or no longer challenged by programme[584] Tolmie 2009: older adults (over 65 years): "I've only got one life and I...intend to use it as it suits me"[584] Only 2 (younger) patients identified lifestyle factors as contributing to the MI [374]		

Barriers	General population	Needs of ethnic minorities	Differences in gender	Differences in older /younger aged patients	Needs of those from low socioeconomic background	Employment issues Language barriers
	least once"[374] McCorry 2009: CR exercises perceived as a course to get back to normal (rather than long term behaviour change)[374] Jones 2007: In denial about heart attack Clark 2004: Stress identified as cause rather than smoking, diet, sedentary lifestyle or obesity McCorry 2009: participants attributed MI to factors outside their control (e.g. fate, familial disposition) or		don't think heart attacks can be prevented[352]			

Barriers	General population	Needs of ethnic minorities	Differences in gender	Differences in older /younger aged patients	Needs of those from low socioeconomic background	Employment issues Language barriers
	stressful/ emotional circumstances; "If it's your time, it's your time. When you've got to go, you've got to go"[374] Clark 2004: saw themselves as relatively helpless in combating CHD Pell 1998: perception that attendance would result in little benefit; felt better/fine McCorry 2009: "didn't feel I needed the support...just to reassure you... wouldn't do anything for you medically...if you are feeling OK					

Barriers	General population	Needs of ethnic minorities	Differences in gender	Differences in older /younger aged patients	Needs of those from low socioeconomic background	Employment issues Language barriers
	you can do without it"[374] McCorry 2009: adherence to medication perceived to give greater control of health ; CRP no additional value[374] McCorry 2009: feeling that heart problem had cleared up (i.e. did not see MI as a symptom of underlying heart disease)[374] Jones 2007: doing alternative types of exercise instead; had made a good recovery and did not see need for, or potential benefits from,					

Barriers	General population	Needs of ethnic minorities	Differences in gender	Differences in older /younger aged patients	Needs of those from low socioeconomic background	Employment issues Language barriers
	programme [298] Clark 2004: saw service as poorly organised and did not meet expectations [109] Jackson 2012 Believe that CRP will have little benefit on their recovery and that only medical or surgical intervention could improve health. Low expectations. Uncertainty about future health, risk of further MI and the extent they could regain their former way of life. Belief that CRP would make little difference to their					

Barriers	General population	Needs of ethnic minorities	Differences in gender	Differences in older /younger aged patients	Needs of those from low socioeconomic background	Employment issues Language barriers
	health or co-morbidities. Struggled to understand the Heart Manual, causing misunderstandings, anxiety and misjudgements and maladjustment.[287]					
Location/ transport/ mobility/ distance difficulties	Madden 2011: geographical location of services [354] O'Driscoll 2007: staff unclear if hospital could provide transport Pell 1998: parking/ lack of access to suitable transport/ cost of transport; community venue easier to attend Jones 2007:	South Asians: transport difficulties, mobility, distance to travel. lack of access to a car[210] South Asian women fearful of racial abuse when waiting outdoors for a taxi provided by CRP; being in the presence of young male taxi drivers unacceptable for younger females; anxious about attending sessions	Radley 1998: public transport arrangements not suitable Women: Transport barriers[488]		Lack of transport[48]	

Barriers	General population	Needs of ethnic minorities	Differences in gender	Differences in older /younger aged patients	Needs of those from low socioeconomic background	Employment issues Language barriers
	heavy traffic, lack of parking, irregular bus services, location inconvenient Rivett 2009: Unhappy with city centre location; Lack of transport Jones 2009: difficulty parking Jackson2012 Transport difficulties (data saturation). [287]	held in high crime areas[210]				
Referral issues/insufficient information	Madden 2011: Lack of information on which to base a choice between hospital and home-based programme (e.g. different course content); lack of referral; patients who had to find rehab programme rather than being	Galdas 2012 (SR): South Asians: lack of referral, did not know CRP available, waiting to be formally invited	Radley 1998: women not offered the opportunity to attend			

Barriers	General population	Needs of ethnic minorities	Differences in gender	Differences in older /younger aged patients	Needs of those from low socioeconomic background	Employment issues Language barriers
	offered it lost motivation [354] Jones 2007: patients had not been invited; misunderstanding (having been given information on times of programmes but had not got an appointment with a specific start date) Jackson 2012 Not being informed or invited and non-availability. Inadequate information on whether to attend cardiac rehabilitation or coronary heart disease groups [287]					
Time constraints	Madden 2011: restricted choice of times to attend	Galdas 2012 (SR): South Asians: lack of time		Tolmie 2009: older adults (over 65 years): desire to reduce time already being		Madden 2011: inflexible working

Barriers	General population	Needs of ethnic minorities	Differences in gender	Differences in older /younger aged patients	Needs of those from low socioeconomic background	Employment issues Language barriers
	hospital programme; clash with family commitments [354] O'Driscoll 2007: twice a week is quite a tall order really Pell 1998: conflicting domestic commitments (dependent family member); dislike of class times McCorry 2009: "didn't want to be running to places where I hadn't time to go..." Jones 2007: carer: unable to leave partner for extended periods required for hospital programme;			spent attending clinics/ appointments		hours[354] Pell 1998: conflicting work commitments

Barriers	General population	Needs of ethnic minorities	Differences in gender	Differences in older /younger aged patients	Needs of those from low socioeconomic background	Employment issues Language barriers
	return to work made attendance difficult; unwilling to go out in the evening; only able to attend in the evening as relied on working daughter for transport; time unsuitable as cannot exercise after meals due to indigestion; wife having to take too much time off work to take patient to hospital [374] Rivett 2009: Family demands; Work demands; Lack of time Jackson 2012: Mostly because of work [287]					
Needs not	Madden 2011:					

Barriers	General population	Needs of ethnic minorities	Differences in gender	Differences in older /younger aged patients	Needs of those from low socioeconomic background	Employment issues Language barriers
being met by CR staff	staff running home-based service not medical and unable o answer the patient's questions; problems of staff leave, retention, sickness, lack of like-for-like maternity cover, NHS restructuring and short-term financial crisis.[354] O'Driscoll 2007: lack of staff leading to information overload, un-interactive and didactic teaching with rapid pace and sometimes vague and too general with limited clarifications; contradicting or omitted advice;					

Barriers	General population	Needs of ethnic minorities	Differences in gender	Differences in older /younger aged patients	Needs of those from low socioeconomic background	Employment issues Language barriers
	lack of psychologist to provide support (e.g. for depression, stress management) Clark 2004: saw professionals as providing inconsistent information that was inappropriately timed, as coercive, overly negative or too intense [374] Jackson 2012: Expressed frustration at the lack of CRP support.[287]					
Reluctant to exercise and unmotivated	Pell 1998: dislike of exercise Jones 2007: has never done any exercise so does	Galdas 2012 (SR): female South Asian participants lacked motivation to exercise on their own		Tolmie 2009: older adults (over 65 years): classes had little time for social interaction; the leader turned on the music and		Madden 2011: work constraints meant that some patients

Barriers	General population	Needs of ethnic minorities	Differences in gender	Differences in older /younger aged patients	Needs of those from low socioeconomic background	Employment issues Language barriers
	not know what to expect or how to do it Jones 2009: patients worried about exercising on their own in home programme and reluctant to push themselves Madden 2011: bored/ depressed doing exercises alone at home[354] Jones 2007: lack of motivation; would not have been motivated on home programme Rivett 2009: Lack of motivation			left participants to it so little motivation to continue attendance		could not join group, but found it hard to do exercises on their own and said that group would have helped motivation; others thought home-based programme more suitable for those not working and hard to fit exercises into tiring work day[354]
Unsure if it is safe to		Galdas 2012 (SR): South Asian women				

Barriers	General population	Needs of ethnic minorities	Differences in gender	Differences in older /younger aged patients	Needs of those from low socioeconomic background	Employment issues Language barriers
exercise (location)		reluctant to exercise outdoors and unaccompanied: found it difficult to identify safe and suitable walking routes in inner-city areas or to arrange for a family member to accompany them				
Costs	Rivett 2009: Too expensive				Beauchamp 2010: neighbourhood deprivation and unemployment; programme cost	
Religious reasons		Galdas 2012 (SR): Gujarati Hindu participants and South Asian Muslims felt that MI and recovery were tied to fate or the will of God (external locus of control); low perceived control of patients towards rehabilitation and therefore low adherence to CR advice	Galdas 2012 (SR): mixed gender classes problematic for Muslim women due to need to wear appropriate clothing in mixed groups and embarrassment about exercising in front of others. Early afternoon or Friday CRP sessions conflicted with call to prayer for Muslim women			

Barriers	General population	Needs of ethnic minorities	Differences in gender	Differences in older /younger aged patients	Needs of those from low socioeconomic background	Employment issues Language barriers
Lack of family support	O'Driscoll 2007: not all patients informed that family members welcome to attend rehab programme; constraints if room not big enough for patients and relatives Rivett 2009: Lack of female support	Galdas 2012 (SR): South Asian families less inclined to encourage family members to participate in regular exercise as recommended by CRP providers; male patients received more family support during rehabilitation while female patients attempted to modify their lifestyle with limited help. male patients received more family support during rehabilitation while female patients attempted to modify their lifestyle with limited help, some South Asian women reported they would need their husband's agreement to attend CRP		Tolmie 2009: older adults (over 65 years): comments from a family member who believed the person wasn't "at that stage" and "wouldn't gain anything"		

Barriers	General population	Needs of ethnic minorities	Differences in gender	Differences in older /younger aged patients	Needs of those from low socioeconomic background	Employment issues Language barriers
Comorbidities	O'Driscoll 2007: limited level of concentration Pell 1998: clinical problems (e.g. worsening cardiac symptoms or other health problems) McCorry 2009: "with the pain, with the arthritis you can't do an awful lot...you get tired and then you get weak" [374] McCorry 2009: symptoms put down to other comorbidites (e.g. asthma) Jones 2007: health problems affecting ability to do exercise (e.g. emphysema, arthritis, back pain, angina,		Women: previous cardiac problems (felt they had sufficient knowledge on condition already) and/or comorbidities (e.g. prioritised spondylitis over cardiac condition)[488]	Tolmie 2009: older adults (over 65 years): physically restricting or socially embarrassing problems (e.g. arthritis, incontinence)		Beauchamp 2010: depression

Barriers	General population	Needs of ethnic minorities	Differences in gender	Differences in older /younger aged patients	Needs of those from low socioeconomic background	Employment issues Language barriers
	waiting for hip replacement) [374] Rivett 2009: Injury or illness Jackson 2012 physical discomfort and disability.[287]					
Clothing		Galdas 2012 (SR): clothing requirements for exercise incompatible with traditional South Asian dress including long headscarves; reluctance to adapt to Western norms for exercise attire				
Feeling that exercise is inappropriate	Pell 1998: dislike of exercise level McCorry 2009: belief that keeping active through everyday activities was	Galdas 2012 (SR): South Asians feeling no immediate benefit from exercise; belief that they were too old to exercise; having more exercise forced on them than they were prepared		Tolmie 2009: older adults (over 65 years): belief that exercise regime was too strenuous / outwith the person's capabilities; day to day activities enough; severe pain or exhaustion during or after exercise session so too		

Barriers	General population	Needs of ethnic minorities	Differences in gender	Differences in older /younger aged patients	Needs of those from low socioeconomic background	Employment issues Language barriers
	sufficient[374] McCorry 2009: feeling that existing management sufficient: "I survived for 12 years... I didn't think it was worth my while going in [to CR]"[374] Jones 2007: home exercises too easy Rivett 2009: Joined other facilities Pell 1998: perception that attendance would result in increased risk/advised against McCorry 2009: concerns about straining heart or	to do Galdas 2012 (SR): South Asian women had long-standing beliefs that exercise brings on chest pain		frightened to try again; low-level exercise programmes felt not to provide any more benefit than routine everyday activities; negative beliefs about ageing process and extent to which health/ quality of life could be improved; belief that surgery/ drugs/ radiological interventions more effective than lifestyle change, and beyond these interventions, little could be done McCorry 2009: some younger participants thought CRP not appropriate for them because attendees perceived to be elderly and exercises not appropriate for younger people Jones 2007: patients aged between 52 and 60 thought that the other patients were all old people and did not feel		

Barriers	General population	Needs of ethnic minorities	Differences in gender	Differences in older /younger aged patients	Needs of those from low socioeconomic background	Employment issues Language barriers
	becoming breathless; "don't know whether I'm doing myself any harm or whether I'm doing myself any good". Activity that caused participants to breather more heavily was not thought to be appropriate: "I'm afraid really to overdo things , cause I don't want to put a strain on my heart obviously"[374]			comfortable with this		
Programme culturally insensitive		Galdas 2012 (SR): Dietary advice inappropriate to South Asians (e.g. recommending dhal which was perceived to be food for poor people); embarrassment about advice about	Galdas 2012 (SR): South Asian women embarrassed about advice about sexual relations			Galdas 2012 (SR): South Asians: inability to speak English, lack of audio- or video-taped information in preferred

Barriers	General population	Needs of ethnic minorities	Differences in gender	Differences in older /younger aged patients	Needs of those from low socioeconomic background	Employment issues
						Language barriers
		sexual relations, assumptions made by health professionals on basis of person's appearance				language or use of interpreter, lack of direct communication with patients so lack of opportunity to emphasis importance of family involvement in rehabilitation. Reliance on family members to interpret could go against usual family roles and privacy; children tended to avoid conveying negative aspects and seriousness of parents' cardiac condition to reduce distress
Attitude/ remarks of	McCorry 2009: if heart attack was		Radley 1998: doctor told one woman that	Tolmie 2009: older adults (over 65 years): consultant	Beauchamp 2010: strength of	

Barriers	General population	Needs of ethnic minorities	Differences in gender	Differences in older /younger aged patients	Needs of those from low socioeconomic background	Employment issues Language barriers
health professionals	described as "mild" (and person perceived they were back to normal)[374]		attendance "wasn't necessary"	who made the person feel "worthless"; member of CRP who told them they didn't think there was much they could do for the patient	recommendation from professionals; scepticism from professionals about ability of lower SES patients to make lifestyle change	
No desire to extend lifespan				Tolmie 2009: older adults (over 65 years): "not really keen on staying too long...rather live a natural life than to ... linger on and become a burden to people...when it's done, it's done"		
Ambience of CR centre	Jones 2007: Overcrowded; did not enjoy it Rivett 2009: Too crowded; Lack of enjoyment Clark 2004: thought programme was too narrow, too short, insufficiently taxing and unlikely to benefit	Galdas 2012 (SR): South Asians: preference for private home-based CR programme. Female South Asian participants lacked confidence to take part in group exercise activities Galdas 2012 (SR): female South Asian participants lacked confidence to take part in group				

Barriers	General population	Needs of ethnic minorities	Differences in gender	Differences in older /younger aged patients	Needs of those from low socioeconomic background	Employment issues Language barriers
	them; saw attenders as old, illness-focused and "needy" [374] Clark 2005: surprise that CRP was principally group-based Pell 1998: dislike of large mixed-sex classes Clark 2005: initially uncomfortable exercising in group "concerned about doing exercises in front of other people in case I make a fool of myself"; "stayed at the back ... so nobody would watch us"; concerned that programme would be tailored	exercise activities Radley 1998: woman did not like group arrangement (would have preferred one-to-one sessions); being the only woman in a group of mostly younger men made women self-conscious and hindered involvement				

Barriers	General population	Needs of ethnic minorities	Differences in gender	Differences in older /younger aged patients	Needs of those from low socioeconomic background	Employment issues Language barriers
	to the needs of others to the neglect of their own needs Blake 2009: never been in a gym before Jackson2012Do not like the group.[287]					
Uncomfortable seeking help or had lack of support	Jackson 2112 Reticence about highlighting health service difficulties and reluctance to ask for support. Deterred by perceived judgement, staff attitudes regarding issues, for example smoking or their motivation.[287] Jackson 2012					

Barriers	General population	Needs of ethnic minorities	Differences in gender	Differences in older /younger aged patients	Needs of those from low socioeconomic background	Employment issues Language barriers
	Follow-up support was too late, too brief or did not addressed key needs particularly regarding mental, emotional, and for some cognitive issues. Lack of long-term support.[287]					

G.1.1 Summary of patient barriers to the uptake of and adherence to cardiac rehabilitation

Facilitators	General population	Needs of ethnic minorities	Differences in gender	Differences in older /younger aged patients	Needs of those from low socioeconomic background	Employment issues Language-barriers
Motivation: Desire to reduce risk of secondary MI	Martin 2012: understanding among participants of health benefits of continuing to adhere to physical activity – this should be	Galdas 2012 (SR): some South Asians (e.g. Sikhs) felt that MI was an indication from God that they had not looked after their health, so willing to make lifestyle changes to	Women: being able to do something to control the condition; able to identify causes of condition and appreciate importance of appropriate lifestyle control (smoking, diet, exercise)[488]			

Facilitators	General population	Needs of ethnic minorities	Differences in gender	Differences in older /younger aged patients	Needs of those from low socioeconomic background	Employment issues Language-barriers
	reinforced by staff; continued participation as an insurance policy against being in stage they had just left; keeping on the straight and narrow Clark 2004: saw attendance as rational choice [374] Clark 2004: saw their CHD event as a warning that they should change their behaviour [374]	take personal responsibility and guard against future problems				
Motivation: Desire to achieve goals	Jones 2007: did exercises so he could return to work; "hope to improve by...doing it"		Women: Determination to make a good recovery; self-motivated; complying with advice; attempting to control the condition; feel confident (although require support); learning how to cope[488] MacInnes 2005: desire to	Tolmie 2009: older adults (over 65 years): "silly not to do it"; wanted "something to help me get back on my feet again"; essential part of recovery		

Facilitators	General population	Needs of ethnic minorities	Differences in gender	Differences in older /younger aged patients	Needs of those from low socioeconomic background	Employment issues Language-barriers
			return to level of independence and normality and regain control; "exercise programme would help me get back on my feet"; "I knew I would get an awful lot out of it"[352]			
Support from family and friends	Martin 2012: instrumental and social support from family and friends (i.e. encouragement that spurred participants on; giving a lift to the venue) Jones 2009: support from family members, some of whom also did the exercises and make lifestyle changes		Women: family support essential for returning to normal activities; positive endorsement form family or friends who had previously attended programme; practical support/ transport from partners [488] Jones 2007: partner, family and community supporting changes to lifestyle (e.g. smoking, diet)			
Programme appropriate	Madden 2011: home-based	Galdas 2012 (SR): Attendance higher			Beauchamp 2010: pre-arranged collection or	Galdas 2012 (SR): Participant

Facilitators	General population	Needs of ethnic minorities	Differences in gender	Differences in older /younger aged patients	Needs of those from low socioeconomic background	Employment issues Language-barriers
including language, timing, location, transport	programme avoids transport problems and being tied to fixed schedule, avoids problem when person does not want to join a group, avoids the problem that exercises done in a group (of mainly older people) not appropriate for a younger person[354] Jones 2007: time/ place convenient Jones 2009: exercises well planned; gradual build up helped to build confidence; education programme helped them learn more about what had	when programme "culturally competent"; participants valued opportunities for one-to-one discussions with Punjabi-speaking healthcare professionals; practical, culturally relevant dietary advice			home-based programmes	who had returned to work were able to attend programme because held in the evening Galdas 2012 (SR): participants valued opportunities for one-to-one discussions with Punjabi-speaking healthcare professionals

Facilitators	General population	Needs of ethnic minorities	Differences in gender	Differences in older /younger aged patients	Needs of those from low socioeconomic background	Employment issues Language-barriers
	happened to them and how to improve their lifestyle; sessions on medication particularly valued; "good balance between the walking and the lifting and the tread up and down...they give you a little bit of everything there"					
Support of health professionals	Martin 2012: instrumental support from health professionals (i.e. encouraged to progress from Phase III to Phase IV CRP; outlining location, time and enrolment procedures) and programme staff (i.e. making participants feel at ease; nice; made them feel	Galdas 2012 (SR): South Asians valued personal support, attention and caring environment provided by health professionals	Women: opportunity to receive expert advice[488]			

Facilitators	General population	Needs of ethnic minorities	Differences in gender	Differences in older /younger aged patients	Needs of those from low socioeconomic background	Employment issues Language-barriers
	welcome); maintaining support for newcomers to the programme Jones 2009: patients positive about nurse support; nurses very friendly, easy to talk to, helpful and knowledgeable; "If you've got any problems mental or physical they were there to help" Clark 2004: saw health professionals as experts and as useful sources of knowledge; seen as interested in safety and wellbeing of patients Clark 2005: atmosphere generated by					

Facilitators	General population	Needs of ethnic minorities	Differences in gender	Differences in older /younger aged patients	Needs of those from low socioeconomic background	Employment issues Language-barriers
	professionals (and other participants) friendly, encouraging and supportive; staff care and interest in the individual was valued and perceived as reassuring [374] Martin 2012: Safety benefits of exercising in the presence of specialist staff; feeling safe Jones 2009: Lack of confidence; little idea of what type or level of exercise was safe and appropriate; although positive about participating in CRP they felt that exercise could do harm as well as good; exercising					

Facilitators	General population	Needs of ethnic minorities	Differences in gender	Differences in older /younger aged patients	Needs of those from low socioeconomic background	Employment issues Language-barriers
	under supervision important to allay fears about possible risks of exercise Clark 2005: exercise sessions safe as supervised by well qualified health professionals					
Peer support	Martin 2012: social support from fellow participants (i.e. company and fun; opportunity to exercise with people who are in the same boat) Jones 2007: enjoyed the atmosphere of hospital programmes; found it friendly and fun; enjoyed the company; gained motivation	Galdas 2012 (SR): peer support identified as crucial by Punjabi Sikhs Radley 1998: having attended the CRP was a continuing source of support in the months after discharge	Women: being alone would have been a barrier to attending CRP; meeting others was important[488]			

Facilitators	General population	Needs of ethnic minorities	Differences in gender	Differences in older /younger aged patients	Needs of those from low socioeconomic background	Employment issues Language-barriers
	working in a group; "with some other fellows and you're having a laugh and a joke"; "liked the friendship of the group...You can see if he's doing better than you and that's what you want isn't it" Jones 2009: enjoyed exercising in a group and mixing with other people; gained motivation and support from other patients Clark 2004: gained encouragement from other patients that decreased embarrassment at first exercising with a group;					

Facilitators	General population	Needs of ethnic minorities	Differences in gender	Differences in older /younger aged patients	Needs of those from low socioeconomic background	Employment issues Language-barriers
	group increased confidence, motivation and fitness; camaraderie; others "in the same boat"; similar in age, circumstances and difficulties[374] Clark 2005: perceived similarity with others; being in the same boat; rapport between participants increased motivation to attend; mutual encouragement; atmosphere generated by other participants (and professionals) friendly, encouraging and supportive					

Facilitators	General population	Needs of ethnic minorities	Differences in gender	Differences in older /younger aged patients	Needs of those from low socioeconomic background	Employment issues Language-barriers
Opportunity to attend either a home based or hospital based CRP	Madden 2011: instructors could give more guidance and perform assessments, enough space and enough equipment[354] Jones 2007: difficulty with motivation on home programme and worried about doing too much or too little - preferred supervision Jones 2009: having regular appointments to attend sessions at hospital important motivation; would have been less likely to complete	Galdas 2012 (SR): some South Asian patients preferred to attend hospital-based CRP for motivation, feeling safer, being more closely monitored by staff and availability of equipment				

Facilitators	General population	Needs of ethnic minorities	Differences in gender	Differences in older /younger aged patients	Needs of those from low socioeconomic background	Employment issues Language-barriers
	exercises at home Jones 2009: some home-based patients would have found it difficult to attend hospital programmes because of transport difficulties or carer responsibilities; "don't like the idea of having to go to a gym, getting there, doing whatever you're doing, with a lot of other people"					
Design of the CRP	Martin 2012: exercises carried out in class were novel and stimulating; increasing challenge and variety of					

Facilitators	General population	Needs of ethnic minorities	Differences in gender	Differences in older /younger aged patients	Needs of those from low socioeconomic background	Employment issues Language-barriers
	exercises maintained motivation, as would goal setting, fitness tests and feedback Jones 2007: learnt new things about medication, diet, how the heart works; used relaxation tape; enjoyable; motivated participants "pushed you outside...to start getting about"; "a lot of information...if I get a bit worried about anything I can always refer to that [Heart Manual]" Jones 2009: Heart Manual well organised; covered a range					

Facilitators	General population	Needs of ethnic minorities	Differences in gender	Differences in older /younger aged patients	Needs of those from low socioeconomic background	Employment issues Language-barriers
	of topics in addition to exercise; helpful information and advice; positive and encouraging; advice relevant to patients' experience; read and followed dietary advice; relaxation tapes good; recording the exercises helped with motivation as patients knew nurse would be coming and encouraging to be able to look back and see the progress they had made Clark 2005: importance of health education sessions with new information or that reinforced what they already					

Facilitators	General population	Needs of ethnic minorities	Differences in gender	Differences in older /younger aged patients	Needs of those from low socioeconomic background	Employment issues Language-barriers
	knew or was reassuring					
Able to introduce components into their daily routine	Martin 2012: commitment to attend; sets targets for keep fit at set hours Jones 2009: home exercises became lifestyle change rather than a treatment; being able to fit exercise around normal routine rather than attending hospital at set times; continuing to exercise "addicted to them" Clark 2005: normalising exercise to be an integral part of everyday life					
Sense of	Martin 2012:					

Facilitators	General population	Needs of ethnic minorities	Differences in gender	Differences in older /younger aged patients	Needs of those from low socioeconomic background	Employment issues Language-barriers
purpose and identity	gives participants a sense of identity, a place in society; knowing where they are going today Jones 2009: being in a group like belonging to a community and being related to each other Clark 2005: sense of not being alone; similar challenges ahead; collective identity					
Provided a sense of control, that their future was in their own hands	Martin 2012: "I wanted to do it myself...You needed to get out there and start your life again." Task self-efficacy: ability to successfully perform exercises		Women: expected CRP to increase confidence and offer reassurance; feeling able to negotiate about exercise levels at CRP [488] MacInnes 2005: "when you live on your own you have to look after yourself"[352]			

Facilitators	General population	Needs of ethnic minorities	Differences in gender	Differences in older /younger aged patients	Needs of those from low socioeconomic background	Employment issues Language-barriers
	showed participants what they could do, built confidence. Barrier self-efficacy: distance from venue and traffic were inconvenient but did not lead to non-participation (i.e. people overcame these barriers). Recovery self-efficacy: lapses in adherence (e.g. due to holidays) but then returned to programme Jones 2009: home programme: more in control of own rehabilitation Clark 2004: saw themselves as active against					

Facilitators	General population	Needs of ethnic minorities	Differences in gender	Differences in older /younger aged patients	Needs of those from low socioeconomic background	Employment issues Language-barriers
	CHD and capable of managing it; realised they could safely put their bodies under pressure during exercise					
Method of recruitment (recommendation)	Martin 2012: existing participants could be used to encourage new people to join programme; information to health professionals to increase awareness of availability of CRP; Phase III staff visiting Phase IV CRP; patients in Phase III having a visit to Phase IV to reduce initial anxiety; need for quick transfer from Phase III to Phase IV					

Facilitators	General population	Needs of ethnic minorities	Differences in gender	Differences in older /younger aged patients	Needs of those from low socioeconomic background	Employment issues Language-barriers
Felt the benefit from the CRP	Jones 2009: Enjoyed and benefitted from CRP; feeling an improvement in health; regaining confidence to return to activities they enjoyed; learnt about heart; made lifestyle changes Clark 2004: gained a new sense of what it meant to be fit Clark 2005: Being with other former cardiac patients at different stages in rehabilitation demonstrated that progressively high levels of fitness could be achieved by people with cardiac disease					

G.1.2 Summary of healthcare professional barriers to the uptake of and adherence to cardiac rehabilitation

Facilitator	Summary
Unsure whose role it is to arrange CRP, referral issues	Madden 2011: gaps in individual patient pathways, especially for patients who moved between hospitals for treatment[354]
Problems of tailoring CRP to the individual	Halcox 2011: Underestimation of the importance of a menu-based approach, the fact that patients have variable expectations about rehabilitation and motivations O'Driscoll 2007: "people in the lower socioeconomic group don't do as well...they don't have the knowledge...their needs are very different"
Primary/secondary care interface	Halcox 2011: better integration between primary and secondary healthcare needed to improve provision of a consistent service
Lack of resources	Madden 2011: insufficient appropriately trained staff; lack of interpreters[354] O'Driscoll 2007: behind in milestones due to timing of receiving funding; "Cinderella service"; limited personnel resources; limited staff time for each patient leading to information overload; limited access to interpreters Proudfoot 2007: staffing levels: low levels of physiotherapists, dieticians and clinical psychologists; lack of funding; time constraints; lack of resources
Restricted choice of location	Madden 2011: Home based service only offered to patients who refused or could not participate in hospital or community based services, not offered as a positive choice (so tend to get unmotivated patients)[354]
Need to follow up patients who do not attend	O'Driscoll 2007: important that cardiac staff contact the patients to explore possible barriers and if possible provide assistance to facilitate attendance
Staff morale	O'Driscoll 2007: modernisation of NHS has increased workload and pressure and decreased inspiration and enthusiasm; "would be bored to tears if all I did was cardiac rehab"; "so much more we need to do"

G.1.3 Summary of healthcare professional facilitators to the uptake of and adherence to cardiac rehabilitation

Facilitator	Summary
Support from other health care professionals to aid uptake and adherence on CRP	Halcox 2011: GPs and cardiologists used regular consultations or involved other healthcare professionals to motivate patients to pursue a healthy lifestyle
Tailoring advice to individuals	Halcox 2011: Take ethnicity into account when delivering dietary advice; addressing health and social needs; tailoring advice to health beliefs or culture

Choice of location	Madden 2011: choice offered between hospital and community location[354]

G.2 Lifestyle

G.2.1 Omega-3 fatty acids

Table 1: Galan 2011[206]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Galan P, Kesse-Guyot E, Czernichow S, Briancon S, Blacher J, Hercberg S; SU.FOL.OM 3 Collaborative Group. **Title** Effects of B vitamins and omega 3 ethyl esters on cardiovascular diseases: a randomised	Multicentre RCT	**All patients:** N=2501 randomised N=2501 ITT Drop-outs (don't complete the study): N=279/2501 (11.1%) due to withdrew consent, lost to follow-up and died. Including N=53(2.1	**Inclusion criteria:** Participants with a history of cardiovascular disease were recruited via a network of 417 cardiologists, neurologists, and other physicians in 257 centres throughout France. Men and women aged 45–80 years who had had an acute coronary or cerebral ischaemic event within the 12 months before	**Group 1: vitamin B + omega-3** N=620 randomised N=620 (ITT/ACA) N=547 (PPA,completers) Intervention details 1xday Gelatin capsule containing 600mg of EPA and DHA at a 2:1 ratio and 5-methyletrahydrofolate (550µg), Vit B-G (3mg) and B-12 (20µg) **Group 2: Omega-3** N=633 randomised N=633 (ITT/ACA)	**Group 4: Placebo** N=626 randomised N=626 (ITT/ACA) N=561 (PPA, completers) Intervention details 1x day Placebo capsule	Follow-up Median 4.7 years	**Outcome 1:** Cardiovascular Death	Omega-3: 20/1253 Control: 20/1248	Funding: SU.FOL.OM3 French Ministry of Research/Ministry of health/Soexo, Candia, Unilever, Danone, Roche Lab, Merck Peirre Fabre Lab Limitations: Unclear if patients reported as died in Table 1 are included in total number of patients who died in Fig 4.
							Outcome 2: Myocardial infarction (non-fatal)	Omega-3: 32/1253 (2.6%) Control: 28/1248 (2.2%) HR: 1.15 (0.69 to 1.90)	
							Outcome 3: Stroke	Omega-3: 29/1253 (2.3%) Control: 28/1248 (2.2%) HR: 1.04 (0.62 to 1.75)	
							Outcome 4: All	Omega-3: 152/1253	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
placebo controlled trial. **Journal** BMJ. 2010 Nov 29;341:c6273. doi: 10.1136/bmj.c6273. Multicentre: Yes. Country:France Randomisation: Computerised block sequence stratified by 3 age groups (44-54, 55-64, 65-80), sex, prior disease at		%) stopped due to AE inhibitors 342 (54.6) Aspirin or antiplatelet agent 588 (93.9) ARB 70 (11.2) Calcium channel blockers 86 (13.7) Drop outs: N=65 (33 withdrew consent, 8 lost to follow-up, 24 died)	randomisation were eligible to participate. In 2003 the inclusion criteria were amended to include suspected acute coronary syndrome without characteristic electrocardiographic evidence of myocardial infarction provided there was angiographic evidence of coronary arterydisease. **Exclusion criteria:** Exclusion criteria included age (<45 years or>80 years), ill defined diagnosis of	N=572 (PPA,completers) Intervention details 1xday Gelatin capsule containing 600mg of EPA and DHA at a 2:1 ratio **Group 3: Vitamin B** N=622 randomised N=622 (ITT/ACA) N=542 (PPA,completers) Intervention details Intervention details 1x day Gelatin capsule containing 5-methyletrahydrofolate (550µg), Vit B-G (3mg) and B-12 (20µg) **Combined groups:** Vitamin B= ITT N=Vit B (VitB &			revascularisations	(12.2%) Control: 156/1248 (12.5%) HR: 0.97 (0.78 to 1.22)	Calculated CV death from outcome Major CV event. Additional outcomes: arrhythmia, Major CV events supraventricular arrhythmia, cardiac surgery of any kind, transient ischaemic attack, deep vein thrombosis, pulmonary embolism, carotid surgery or carotid artery angioplasty, peripheral arterial surgery or angioplasty, any vascular procedure, Resuscitation from sudden
							Outcome 5: All-cause mortality	Omega-3: 58/1253 (4.7%) Control: 59/1248 (4.7%) HR: 1.03 (0.72 to 1.48)	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
enrolment (myocardial infarction, acute coronary syndrome, or ischaemic stroke) and recruitment centre. Permuted block randomisation (with block size randomly selected as 8) was used. Blinding: Double blind Allocation concealment: Unclear Outcome			cardiovascular disease, inability or unwillingness to comply with study treatment, and disease or treatment that might interfere with metabolismof homocysteine or omega 3 ethyl esters, in particular methotrexate for treating cancer or rheumatoid arthritis and chronic renal failure (plasma creatinine concentration >200 µmol/l or creatinine clearance<40 ml/min). **Group 1: Vit B + Omega 3** (45.2%	VitB+Omega) vs. Controls (Omega & Placebo) **Omega=** ITT N=1253, Omega (Omega & VitB+Omega) vs. N=1248, Controls (VitB & Placebo) **Concomitant therapy:** BB Aspirin ACEi ARB CCB					death A coronary event = as either MI or acute coronary syndrome. Acute coronary syndrome without myocardial infarction Notes: Side effects: Chiefly gastrointestinal disturbances, nausea and cutaneous reaction accounted for 2.1% of patients withdrawing; 2.6% in omega 3, and 2% in controls

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
assessment: Major cardiovascular event—non-fatal myocardial infarction, ischaemic stroke, or death from cardiovascular disease (including fatal myocardial infarction, stroke, sudden death (within one hour of onset of acute symptoms in the absence of violence or accident), aortic dissection,			history MI) Mean age (range): 60.5 (53.9-68.9) No. of men: 493 (79.5) Current Smoking: 69 (11.4) No (%) with inclusion criteria MI 280 (45.2) Unstable angina 176 (28.4) Stroke 164 (26.4) No (%). using medication BB 409 (66) ACE inhibitors 340 (54.8) Aspirin or antiplatelet agent 569 (85.7) ARB 61 (9.8) Calcium channel blockers 86 (13.9) Drop outs: N=73 (31 withdrew consent, 5 lost to follow-up, 37 died).					

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
cardiac failure, or other fatal event defined by the medical committee as having a cardiovascular cause). Death from all causes Revascularisations: coronary and peripheral arteries revascularization, resuscitation from sudden death, CABG. Myocardial infarction was defined			**Group 2: Omega 3** (47.4% history MI) Mean age (range): 60.4 No. of men: 501 (79.2) Current Smoking: 70 (11.3) No (%) with inclusion criteria MI 300 (47.4) Unstable angina 185 (29.2) Stroke 148 (23.4) No. using medication BB 431 (68.1) ACE inhibitors 331 (52.3) Aspirin or antiplatelet agent 595 (94.0) ARB: 44 (7.0) Calcium channel blockers 103 (16.3) Drop outs: N=61 (30 withdrew						

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
on the basis of two or more of the criteria—typical chest pain, electrocardiographic changes consistent with myocardial infarction, and cardiac enzyme increase. Stroke an acute cerebral ischaemic event (stroke) = an ischaemic cerebrovascular accident based on clinical criteria confirmed			consent, 2 lost to follow-up, 29 died) **Group 3: Vitamin B46.**3% history MI) Mean age (range): 60.7 (54.7 -68.3) Current Smoking 67 (10.9) No (%) with inclusion criteria MI 288 (46.3) Unstable angina 168 (27) Stroke 166 (26.7) No. (%) using medication BB 422 (67.9) ACE inhibitors 584 (93.9) Aspirin or antiplatelet agent 584 (93.9) ARB 64 (10.3) Calcium channel blockers 79 (12.7)						

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
by computed tomography or magnetic resonance imaging and a Rankin score ≤3 at inclusion (ICD-10 codes I63.0–I63.9). Individuals with transient ischaemic attacks were not eligible for inclusion. Sample size calculation: The sample size was calculated for the estimated event rate of			Drop outs: N=80 (33 withdrew consent, 3 lost to follow-up, 44 died) **Group 4: Placebo** (45% history MI) Mean age (range): 60.9 (54.4-68.1) Current Smoking 63 (10.1) No (%) with inclusion criteria MI 282 (45) Unstable angina 184 (29.4) Stroke 160 (25.6) No (%). using medication BB 428 (68.4) ACE inhibitors 342 (54.6) Aspirin or antiplatelet agent 588 (93.9) ARB 70 (11.2) Calcium channel blockers 86 (13.7)						

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
0.087 in the placebo group, based on the event rates observed in previous trials in similar populations and in epidemiological studies.35-37 The planned enrolment of 2500 participants with an average follow-up of five years was expected to have more than 90% power to detect a 10% reduction			Drop outs: N=65 (33 withdrew consent, 8 lost to follow-up, 24 died)						

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
in the relative risk of major vascular events associated with B vitamins or omega 3 ethyl esters and a 19% reduction for the combination of omega 3 and B vitamins, given a two sided α value of 0.05.35 Type of analysis ITT Hazard ratios (adjusted for age and sex)									

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Compliance rates: Response rate for completed questionnaires was 99%, 96%, 94%, 95% at 6,12,24 and end of trial respectively 80% said they were compliant with the treatment (at least 80% of treatment) in both groups									

Table 2: GISSI 1999[228]

Reference	Study type	Number of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect sizes	Comments
Author [No authors listed]	RCT	**All patients:** N=11324	**Inclusion criteria:** Patients with	**Group 1: 3-PUFA** N=2836	**Comparison** **3-**PUFA (3PUFA±VitE)	**Follow-up**: 6, 12, 18, 30 and 42	**Outcome 1:** All-cause mortality	**3-PUFA:** 236/2836 **Control:**	**Funding**: Bristol-Myers Squibb,

Reference	Study type	Number of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect sizes	Comments
Title Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. **Journal** Lancet. 1999 Aug 7;354(9177):447-55. **Multicentre**: 172 **Country:**Italy **Randomisatio**		randomised N=11324 ITT Drop-outs (don't complete the study): N=3141 (28%)	recent ≤3 months MI. No contraindications to the dietary supplements, were able to provide written consent, and had no unfavourable short term outlook. No age limits. **Exclusion criteria**: None listed **Group 1: 3-PUFA** Mean age (SD): 59.4 (10.4) Male/Female: 2403 (84.7%):433 (15.3%) Time from MI to randomisation, days (SD): 25.4 (21) <10: 752	randomised N=2836 (ITT) N=2836 (completers) Intervention details 1 gelatin capsule containing 850-882 mg of EPA and DHA in average ratio of 1:2. **Group 2:Vitamin E** N=2830 randomised N=2830 (ITT) N=2830 (completers) Intervention details 300 mg Vit E in capsule **Group 3: 3-PUFA+Vitamin E** N=2830 randomised N=2830 (ITT) N=2830	vs. Control (VitE± Control)	months (or 3.5 yrs)		293/2828	Pharmacia-Uphon + Societa Prodotti Antibiotici (supplied 3-PUFA), and Pfizer, Bracco supplied Vit E. **Limitations:** Could not be certain on calculation of non-fatal MI. **Additional outcomes:** Event free survival Overall survival Cumulative: death, non-fatal MI, non-fatal stroke Cardiac death Coronary death Sudden death Other deaths Non-fatal CV events
							Outcome 2: Cardiovascular death	**3-PUFA:** 291/5666 **Control**:348/5668 Relative risk:0.83 95% CI: (0.71-0.97)	
							Outcome 3. Sudden death	**3-PUFA:** 122/5666 **Controls:** 164/5668	
							Outcome 4: Fatal and non-fatal stroke	**3-PUFA**: 424/5666 **Control**:485/5668 Relative risk:0.87 95% CI: (0.76-0.99)	
							Outcome 5: Non-fatal MI (CHD death and non-fatal MI) – (CHD death)	**3-PUFA:** 133/5666 **Control**:137/5668	
							Outcome 6: Adverse events –	**3-PUFA:** 3.8%=215/5666 **Control**: 2.1%	

Reference	Study type	Number of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect sizes	Comments
n: Over telephone and by computer network. Treatments were automatically assigned from a program based on the biased-coin algorithm, which allowed stratification by hospital. **Allocation concealment:** Yes. Central randomisation. Randomisation was kept at coordinating centre. **Blinding**: No. Open label **Outcome assessment**: Unclear.			(26.5%) 10-15: 641 (22.6%) 16-30: 613 (21.6%) ≥31: 830 (29.3%) Drop outs: 771 (3 lost to follow-up, 768 discontinued 3-PUFA) **Group 2: Vitamin E** Mean age (SD): 59.3 (10.5) Male/Female: 2398 (84.7%):432 (15.3%) Time from MI to randomisation: 25.4 (21) <10: 727 (25.7%) 10-15: 661 (23.4%) 16-30: 644 (22.8%) ≥31: 798 (28.2%)	(completers) Intervention details Combined above in one capsule. **Group 4: Control** N=2828 randomised N=2828 (ITT) N=2828 (completers) Intervention details No supplement. Unclear if given any capsules. **Concomitant therapy:** Patients were asked to adhere to recommended preventative treatments – aspirin, BB, ACEi. 92% were on antiplatelet therapy at baseline and 83% at 42 months.			reason fordiscontinuing.	119/5668 Gastrointestinal disturbances and nausea most common. 4.9% and 1.4% in n-3 PUFA and 2.9% and 0.4% in Vit E respectively.	Cumulative: Cardiovascular death+non-fatal MI+non-fatal stroke **Notes**: Side-effects: Gastrointestinal disturbances and nausea were the most frequently reported side-effects (4.9% and 1.4% in 3-PUFA respectively) and 2.9% and 0.4% in Vit E recipients respectively.
							Outcome 6: Revascularisation at 42 months	**3-PUFA:** 1369/5666 **Control:** 1321/5668	

Reference	Study type	Number of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect sizes	Comments
All-cause mortality: **Non-fatal MI**: at least 2 of the following: chest pain of typical intensity and duration: ST segment elevation or depression of 1mm or more in any limb lead of the ECG, of 2mm or more in precordial lead or both: or at least a doubling in necrosis enzymes Fatal MI: investigator identified this complication on a standard form or if a death certificate or hospital records			Drop outs: 691 (4 lost to follow-up, 687 discontinued Vit E) **Group 3: 3-PUFA and Vit E** Mean age (SD): 59.1 (10.5) Male/Female: 2451 (86.6%):379 (13.3%) Time from MI to randomisation: 25.4 (21) <10: 731 (25.8%) 10-15: 665 (23.5%) 16-30: 675 (23.9%) ≥31: 759 (26.8%) Drop outs: 1660 (4 lost to follow-up, 848 discontinued 3-PUFA, 808 discontinued Vit	46% were on ACEi at baseline, and 38% at 42 months. 45% were on BB at baseline and 39% at 42 months.						

Reference	Study type	Number of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect sizes	Comments
showed a fatal MI. Non-fatal stroke: unequivocal signs or symptoms of remaining neurological deficit, with sudden onset and a duration of more than 24 h. Diagnosis of fatal stroke also met these criteria, or hospital records or death certificate. **Sample size calculation:** Cumulative rate of death, non-fatal MI and stroke in control group was estimated at 20% over 3.5 yrs.			E) **Group 4: Control** Mean age (SD): 59.4 (10.5) Male/Female: 2407 (85.1%):421 (14.9%) Time from MI to randomisation: 25.2 (21.1) <10: 754 (26.7%) 10-15: 637 (22.5%) 16-30: 645 (22.8%) ≥31: 792 (28%) Drop outs: 19 (2 lost to follow-up, 15 received 3-PUFA, 2 Vit E)						

Reference	Study type	Number of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect sizes	Comments
Sample size was calculated to compare the main endpoint in each group to that of the control group (3000 /group, relative risk decrease of 20%) and to test combined treatment would decrease by a further 20% vs. PUFA and VitE alone. **Type of analysis** ITT HR: Kaplan-Meier survival curves **Compliance rates**: Information on vital status was available for 99.9% of									

Reference	Study type	Number of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect sizes	Comments
population.									

Table 3: Kromhout 2010[324]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Author Kromhout D, Giltay EJ, Geleijnse JM; Alpha Omega Trial Group **Title** n-3 fatty acids and cardiovascular events after myocardial infarction. **Journal** N Engl J Med. 2010 Nov 18;363(21):2015-26. Epub 2010 Aug 28. **Study design and quality**: Alpha OMEGA	RCT	**All patients:** N=4837 randomised N=4837 ITT Drop-outs (don't complete the study): N=1034 drop outs (21.4%) but data was included. N=370 died (7.6%)	**Inclusion criteria:** Previous MI up to 10 years before randomization, 60-80 years of age, **Exclusion criteria:** Daily consumption of less than 10g of margarine, use of n-3 fatty acid supplements, unintended weight loss of more than 5kg in previous year, and a diagnosis of cancer with life expectancy of less than 1 yr.	**Group 1: EPA-DHA** N=1192 randomised N=1192 (ITT/ACA) N=814 (completers, PPA) Intervention details Margarine supplemented with target of 400mg of EPA-DHA/day, ratio of 3:2 **Group 2: ALA** N=1197 randomised N=1197 (ITT/ACA) N=876 (completers, PPA) Intervention details Margarine	**Group 4: Placebo** N=1236 randomised N=1236 (ITT/ACA) N=919 (completers, PPA) Intervention details Placebo margarine	**Follow-up**: Median 40.8 months	**Outcome 1:** Death from cardiovascular disease	**Group1**: **EPA+DHA ±APA:** N= 80/2405 (3.3%) **Group 2: Placebo & AHA:** n= 82/2433 (3.4%) Unadjusted HR: 0.98 (0.72-1.33)	**Funding:** Margarine provided by Unilever **Limitations:** Unclear if those who died were included in the dropped out numbers **Additional outcomes:** Incidence of CV disease Ventricular-arrhythmia-related events (sudden death, fatal and non-fatal cardiac arrest, and placement of implantable cardiovascular-
							Outcome 2: All –cause mortality	**Group1: EPA+DHA ±APA:** N= 183/2405 (7.7%) **Group 2: Placebo & AHA:** n= 184/2433 (7.6%) Unadjusted HR: 1.01 (0.82-1.24)	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
2010 Multicentre **Country:** Netherlands **Randomisation:** Yes. Unclear. Patients will be randomized at a Randomization unit located at Wageningen University. **Allocation concealment:** Unclear. Patients will be randomized at a Randomization unit. **Blinding:**			**Group 1: EPA-DHA** (100% MI, av 4.3 yrs ago) Mean age (SD): 69.1 (5.6) Males: 931 (78.1%) Time since MI (yrs): 4.3 (3.2) Self-reported history of stroke, n (%): 83 (7.0) Diabetes mellitus : 262 (22) BB, n (%): 1090 (91.4) Antithrombotic agents, n (%): 1170 (98.2) Lipid lowering agents, n (%): 1017 (85.3) Smoker, n (%): 200 (16.8) Fish consumption >5g/wk, n (%): 971 (81.5) Intake of EPA-	supplemented with ALA, aim of 2g ALA/day **Group 3: EPA-DHA-ALA** N=1212 randomised N=1212 (ITT/ACA) N=824 (completers, PPA) Intervention details Placebo margarine supplemented with both Eight tubs of margarine, each of which contained 250g of margarine, provided every 12 weeks. **Concomitant therapy:**β blockers Antithrombotic agents					defibrillators) Major CV events Fatal and non-fatal CV events, + PCI+CABG
							Outcome 3: Death from coronary heart disease	**Group1: EPA+DHA ±APA** N= 67/2405 (2.8%) **Group 2: Placebo & AHA:** n= 71/2433 (2.9%) Unadjusted HR: 0.95 (0.68-1.32)	
							Adverse events Gastrointestinal problems, incidence of prostate cancer, cancer mortality + side effect reported to Data Safety Monitoring Board	**Group 1: EPA-DHA** n=18 n=11 n=33 n=0 Total = 62 **Group 2: ALA** n=9 n=8 n=32 n=1 Total = 50 **Group 3: EPA-**	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Yes, double-blind **Outcome assessment:** **Death** – from any cause Death – cardiovascular disease Death – coronary heart disease **Major cardiovascular events** – fatal and nonfatal CV disease and the cardiac interventions – PCI and CABG **Adverse events** **Sample size calculation**: Yes, in supplementary material. Sample size			DHA outside of study, mg/day (median) :120 Drop outs: 283/1192 **Group 2: 2 g of ALA**(100% MI, av 3.3 yrs ago) Mean age (SD): 69.0 (5.6) Males: 946 (78.1%) Time since MI (yrs): 4.4 (3.3)	Lipid lowering agents				**DHA-ALA** n=16 n=15 n=30 n=0 Total = 61 **Group 4: Placebo** n=10 n=8 n=27 n=3 Total = 48	
			Self-reported history of stroke, n (%): 89 (7.4) Diabetes mellitus, n (%): 258 (21.6) BB, n (%): 1058 (88.4) Antithrombotic agents, n (%):1172 (97.9) Lipid lowering agents, n (%): 1034 (86.4) Smoker, n (%): 208 (17.4)						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
required to detect an effect of EPA/DHA is 3408 patients, with 80% power and significance level of 5% **Type of analysis** ITT Time to event data **Compliance rates:** N=1034 dropout/ withdrawal due to drug related AEs. N=370 died Protocol violators will not be excluded once randomization has taken place.			Fish consumption, n (%): 996 (83.2) Intake of EPA-DHA outside of study mg/day (median): 130 Drop outs: 230/1197 **Group 3: EPA-DHA-ALA**(100% MI, av 4.2 yrs ago) Mean age (SD): 69.1 (5.5) Males: 946 (78.1%) Time since MI (yrs): 4.2 (3.1) Self-reported history of stroke, n (%): 92 (7.6) Diabetes mellitus, n (%): 245 (20.2) BB, n (%): 1088 (89.8) Antithrombotic agents, n (%): 1166 (96.2)						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
			Lipid lowering agents, n (%): 1058 (87.3) Smoker, n (%): 181 (14.9) Fish consumption, n (%): 996 (83.2) Intake of EPA-DHA outside of study mg/day (median): 130 Drop outs: 297/1212 **Group 4: Placebo** (100% MI, av 4.3 yrs ago) Mean age (SD): 68.9 (5.6) Males: 973 (78.7%) Time since MI (yrs): 4.3 (3.3) Self-reported history of stroke, n (%):81 (6.6) Diabetes mellitus, n (%): 259 (20.1)						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
			BB, n (%): 1104 (89.3) Antithrombotic agents, n (%):1210 (97.9) Lipid lowering agents, n (%): 1052 (85.1) Smoker, n (%): 223 (18) Fish consumption, n (%): 998 (80.7) Intake of EPA-DHA outside of study mg/day (median): 120 Drop outs: 224/1236						

Table 4: Matsuzaki 2009[371]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Author Matsuzaki M, Yokoyama M, Saito Y,	RCT	**All patients:** N=18,645 randomised N=14981	**Inclusion criteria:** People from the JELIS trial with	**Group 1: EPA+Statin** N=1823 randomised (ITT)	**Group 2: Statin** N=1841 randomised	**Follow-up:** 5 years, mean 4.6 yrs	**Outcome 1:** Coronary death	**EPA+Statin**:18/1808 **Statin:** 21/1826	**Funding:** Mochida Pharmaceutical Co.Ltd.

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Origasa H, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Itakura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shirato K, Matsuzawa Y; JELIS Investigators. **Title** Incremental effects of eicosapentaenoic acid on cardiovascular events in statin-treated patients with coronary artery disease. **Journal** Circ J. 2009 Jul;73(7):1283-90. Epub 2009 May 8.		primary prevention strata N=3664 secondary prevention strata Drop-outs (don't complete the study): N=270/3664 (7.4%) (30 lost to follow-up, 240 withdrew).	established CAD defined as previous MI, coronary intervention, or confirmed unstable angina (AP). **Exclusion criteria:** Acute MI in past 6 months, unstable AP, a history of complication by serious heart disease. Cardiovascular reconstruction within last 6 months, cerebrovascular disorder within last 6 months, serious hepatic or renal disease, malignant tumor, uncontrollable diabetes mellitus, hyperlipidemia,	N=1808 (ACA) N=1682 (completers, PPA) Intervention details Treatment began 4 to 8 weeks after washout period from antihyperlipidemic drugs. 1xday 1800 mg of EPA as 6 capsules containing 300 mg of pure (>98%) EPA ethyl-ester. **Concomitant therapy:** All patients received 10mg of pravastatin or 5mg of simvastatin once daily as first-line treatment and asked to follow National Cholesterol Education Program step1	(ITT) N=1826 (ACA) N=1712 (completers, PPA) Intervention details Unclear			HR: 0.79 (0.42-1.49) Relative risk: 95% CI:	**Additional outcomes:** Plasma fatty acids Unstable angina Sudden cardiac death Coronary death or MI
							Outcome 2: Reinfarction (Fatal or nonfatal MI)	**EPA+Statin**: 43/1808 **Statin**:58/1826 HR: 0.70 (0.44-1.12)	
							Outcome 3: Revascularisation	**EPA+Statin:** 88/1808 **Statin:**123/1826 HR: 0.83 (0.65-1.05)	
							Outcome 4: Nonfatal coronary events (Readmission)	**EPA+Statin**: 145/1808 **Statin:**178/1826 HR: 0.79 (0.63-0.98)	
							Outcome 5: Fatal MI	**EPA+Statin:** 5/1808 **Statin**:8/1826	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Country: Japan **Randomisation**: Yes, from Yokoyama paper, permuted-block randomisation with a block size of four was used. Patients were divided in two groups, primary and secondary prevention. Patients were then randomised to receive EPA or control treatment **Allocation concealment:** Unclear **Blinding:** No. Open label			hemorrhage, hemorrhagic diathesis, hypersensitivity to drugs, planned surgery, or other condition deemed inappropriate by physician in charge. **Group 1: EPA+Statin** (30% previous MI >6m) Mean age (SD): 63 (8) Male n(%): 844 (46) Clinical history, n (%) Old MI: 548 (30) Stable angina: 1419 (78) PTCA or CABG: 462 (25) Diabetes: 405 (22) Hypertension: 799 (44)	diet. Statin continued until trial termination in 1311/1652 cases in control and 1282/1620 cases in EPA group. All patients underwent 4-8 week of washout from antihyperlipidaemic drugs.				HR: 0.57 (0.19 to 1.74)	
							Outcome 6: Non fatal MI	**EPA+Statin:** 26/1808 **Statin:**38/1826 HR: 0.66 (0.4-1.08)	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Outcome assessment: Cumulative incidence of MCE; cardiac death, fatal and nonfatal MI, and other non-fatal events including unstable AP, angioplasty, stenting and CABG **Coronary death** **Fatal MI + Nonfatal MI** **Revascularization:** CABG or PTCA **Nonfatal coronary events** **Sample size**			Smoker): 492 (27) Concomitant drugs Antiplatelet:755 (41) Antiocoagulants : 192 (11) Ca antagonist: 899 (49) BB: 306 (17) Drop outs: 129 **Group 2: Statin** (27% previous MI >6m) Mean age (SD): 63 (8) Male, n(%): 822 (45) Clinical history n(%) Old MI: 502 (27) Stable angina: 1484 (81) PTCA or CABG: 433 (24) Diabetes: 420 (23) Hypertension:816 (44)						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
calculation: Unclear – ck Yoko paper **Type of analysis** ITT = all randomized Time to event ACA =randomised –lost to follow-up (but includes those who withdrew) **Compliance rates:** N=141 in EPA and N=129 in control group dropout/ lost to follow-up			Smoker:442 (24) Concomitant drugs Antiplatelet: 800 (23) Antiocoagulants : 177 (10) Ca antagonist: 930 (51) BB: 341 (19) Drop outs: 141						

Table 5: Nilsen 2001[427]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Author Nilsen DW,	RCT	**All patients:** N=300	rop-outs (don't complete the	**Group 1: Omega 3**	**Group 2: Placebo**	**Follow-up:** 5 years, mean	**Outcome 1:** All-cause	**Omega-3:** 11/150 **Placebo:** 11/150	**Funding:** None stated

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Albrektsen G, Landmark K, Moen S, Aarsland T, Woie L. **Title** Effects of a high-dose concentrate of n-3 fatty acids or corn oil introduced early after an acute myocardial infarction on serum triacylglycerol and HDL cholesterol. **Journal** Am J Clin Nutr. 2001 Jul;74(1):50-6. **Multicentre:** 1 hospital centre		randomised N=300 ITT N= unclear ACA (for descriptive analysis – only patients with complete information at all time points during 1st year were included)	study): Unclear **Inclusion criteria:** 1) Verified MI by World Health Organization criteria (29), 2) age > 18 y, 3) discontinuation of a regular supplementation of other fish-oil products, and 4) signed informed consent. **Exclusion criteria:** 1) assumed noncompliance to protocol; 2) expected survival < 2 y because of severe heart failure (New York Heart Association class IV), malignancy, or	N=150 randomised N=150 (ITT) N=unclear (completers) Intervention details 2 gelatin capsules of Omacor-R (Pronova AS, Oslo) 2x/day. Each capsule contained either 850–882 mg eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) as ethylesters in the average ratio of EPA to DHA of 1:2 or the same amount of corn oil. Tocopherol (4 mg) was added to all capsules. **Concomitant therapy:** β blockers Clopidogrel	N=150 randomised N=150 (ITT) N=unclear (completers) Intervention details Corn oil twice a day	4.6 yrs	mortality **Outcome 2:** Revascularization (CABG or PTCA) **Outcome 3:** Reinfarction **Outcome 4:** Cardiovascular death	HR: 1.02 (0.44, 2.36) **Omega-3:** 43/150 **Placebo**: 49/150 HR: 0.92 (0.61, 1.38) **Omega-3:** 21/150 **Placebo:** 15/150 HR: 1.43 (0.74,2.78) **Omega-3**=3:8/150 **Placebo**: 8/150 HR: 1.02 (0.38,2.71)	**Additional outcomes:** Resuscitation Unstable angina Cardiac event – for males and females Cardiac event or revascularization Fatal cardiac events and resuscitations Triglycerides HDL cholesterol Medical interventions

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Countries: Norway **Randomisation:** Parmacia randomised the patients and provided identical capsules containing Omaco or corn oil **Allocation concealment:** Unclear **Blinding:** Double-blind **Outcome assessment:** 6 wk, 6 mo, 1 y, 18 mo, and, for some patients, 2 y after the start of treatment			other reasons; 3) ongoing gastrointestinal bleeding or verified stomach ulcer; 4) thrombocytopenia or blood platelets < 100 - 109/L; 5) liver insufficiency; 6) participation in any other study; and 7) residence outside the recruitment area of this study. All patients were included between the fourth and the eighth day after an acute MI **Group 1: Omega 3** (100% MI) Mean age (SD): 64.4 (28.9-86.7)	ACEi Statins					

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Cardiac events Cardiac death, resuscitation, recurrent MI, and unstable angina **Recurrent MI**: unclear if fatal or non-fatal. **Revascularization** **Death from other causes** **Sample size calculation**: None **Type of analysis** ITT ACA for descriptive data: analysis was restricted to patients with complete			Sex M:F [n]: 115:35 Current smoker[n (%)]: 59 (39.3) Fish oil before inclusion [n (%)]: No 104 (69.8) Yes 45 (30.2) Clinical background [n (%)] Angina pectoris: 49 (32.9) Heart failure: 15 (10) Previous MI: 32 (323) Revascularizations 12 (8) Hypertension 40 (28.6) Hypertension treatment 29 (19.5) Family history CAD 98 (66.7) Diabetes 19 (12.0) Drop outs:						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
information at all time points during 1st year HR (unadjusted) **Compliance rates:** No details provided N=uncleardropout/ withdrawal due to drug related AEs. No details were provided			Unclear **Group 2: Placebo** (100% MI) Mean age (SD): 63.6 (29.3 -87.7) Sex M:F [n]: 123:27 Current smoker[n (%)]: 57 (38) Fish oil before inclusion [n (%)]: No 113 (75.3) Yes 37 (24.7) Clinical background [n (%)] Angina pectoris 57 (38.0) Heart failure 11 (7.4) Previous MI 38 (25.3) Revascularizations 15 (10.0) Hypertension 33 (22.8) Hypertension						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
			treatment 26 (17.3) Family history CAD 97 (65.5) Diabetes 13 (8.7) Drop outs: Unclear **Concomitant therapy** No significant differences were seen in drug use between the 2 groups.						

Table 6: Rauch 2010[492]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Author Rauch B, Schiele R, Schneider S, Diller F, Victor N, Gohlke H, Gottwik M, Steinbeck G, Del Castillo U, Sack R, Worth	RCT	**All patients**: N=3851 randomised Drop-outs (don't complete the study): N=5/3851	**Inclusion criteria:** Men and women with min age of 18 years, who were admitted to hospital for	**Group 1: Omega** N=1940 randomised (ITT) N=1937 (ITT) N=1919 (ACA for mortality) N=1686 (survivors)	**Group 2: Control** N=1911rand omised N=1909 (ITT) N=1885 (ACA for mortality)	**Follow-up**:12 months	**Outcome 1:** Sudden cardiac death	**Omega-3:** 28/1919 **Control:** 29/1885 Log rank p=0.84	**Funding:** Drugs were supplied by Pronova Biocare (Lysaker, Norway)
							Outcome 2: Total	**Omega-3:** 88/1919	**Additional**

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
H, Katus H, Spitzer W, Sabin G, Senges J; OMEGA Study Group. **Title** OMEGA, a randomized, placebo-controlled trial to test the effect of highly purified omega 3 fatty acids on top of modern guideline-adjusted therapy after myocardial infarction. **Journal** Circulation. 2010 Nov 23;122(21):2152-9. Epub 2010 Nov 8. **Multicentre:** Study centres,		withdrew before starting study N=47/3851 including 5 from above, and those lost after allocation to group due to withdrawal or lost to follow-up	acute STEMI or Non-STEMI and gave informed consent. Only patients without known adverse reactions to fish oil or olive oil were randomised. In April 2005, 75% of the patients had to have 1 or more of the following: no early revascularization, ejection fraction <40%, presence of diabetes mellitus, age >70 years. The inclusion period after MI was prolonged from 3-7 to 3-14 days. **Exclusion criteria:**	Intervention details Soft gelatine capsule containing 1g omega 3 acid ethyl esters-90 (460mg EPA, 380 mg DHA) **Compliance** N=561 (14.7%) discontinued medication (285 in Omega and 276 Control) **Concomitant therapy**: β blockers Clopidogrel ACEi Statins Aspirin VitK antagonist	N=1654 (survivors) Intervention details Soft gelatine capsule containing 1g of olive oil		mortality	**Control:** 70/1885 Log rank p = 0.18	**outcomes:** They did a sub-group analysis on: diabetes, age>70, no revascularization, ejection fraction <35%. Major adverse cerebrovascular + CV events **Notes:** Adverse events in more detail: Neoplams: Omega3 = 19 Controls = 8 Cardiac device therapeutic procedures Omega=16 Control = 2 Malignancies Omega = 32 Control =26 **Adverse events:** reported frequency of each event, not number
							Outcome 3: Revascularization in survivors:	**Omega-3:** 466/1919 **Control:** 482/1885	
							Outcome 4: Adverse events, number of events not the number of patients	**Omega-3:** n=1769 **Control:** n=1704	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
heart centre, university and community hospitals **Country:** Germany **Randomisation**: Yes, was performed in blocks of 8 (4 omega, 4 control). Randomization was stratified by centre **Allocation concealment:** Unclear. **Blinding:** Double blind **Outcome assessment:** within 365 days			None stated **Group 1: Omega** (n=1925) (100% recent MI) Mean age (range): 64 (54-72) Male: 1445/1925 (75.1%) Clinical presentation: STEMI, n (%): 1140 (59.2%) NSTEMI n (%): 785 (40.8%) Resuscitation n (%): 31 (1.6%) Left bundle-branch block: 70 (3.6%) Medical History Previous MI (>14 days) n (%): 294 (15.3%) Previous stroke n (%): 112 (5.8%) Previous PCI n							of patients.

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Sudden cardiac death (SCD)- unexpected death resulting from heart disease within 1 hr of onset of symptoms or unwitnessed overnight. Sudden cardiac arrest: occurring within 1 hour of symptoms with successful cardiopulmonary resuscitation and subsequent death in hospital within 3 weeks. **Total mortality:** **Major adverse cerebrovascul**			(%): 259 (13.5%) Previous CABG n (%): 127 (6.6%) At discharge: BB: 1796 (93.9%) Clopidogrel: 1683 (88%) ACEi: 1586 (82.9%) Statins: 1810 (94.6%) Drop outs: 26/1911 **Group 2: Control** n=1893(100% recent MI) Mean age (SD): 64 (54-72) Male %: 73.7% Clinical presentation: STEMI, n (%):1114 (58.8%) NSTEMI n (%) 779 (41.2%) Resuscitation n						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
ar and CV events: total mortality, reinfarction and stroke **Revascularization:** PCI and/orCABG **Adverse events** **Sample size calculation:** Using data from ANTIBIO and ACOS, the sample size calculation assumed a total mortality of 8% in 1 year for control group. Assuming a risk reduction of 45% by omega 3-acide ethyl esters-90, and a significance level of 2.5% (1 sided), a β			(%): 33 (1.7%) Left bundle-branch block: 49 (2.6%) Medical History Previous MI (>14 days) n (%): 255 (13.5%) Previous stroke n (%): 97 (5.1%) Previous PCI n (%): 222 (11.7%) Previous CABG n (%): 107 (5.7%) At discharge: BB: 1178 (94.3%) Clopidogrel: 1673 (88.8%) ACEi: 1578 (83.7%) Statins: 1768 (93.8%) Drop outs: 21/1940 Within 3 to 14 days after MI (STEMI and						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
error of 20% and drop out of 8.8%, 1900 patients in each arm are needed. **Type of analysis** PPA For the analysis of mortality, 14 patients (6 in omega, 8 in control) who were lost to follow-up were excluded bc determination of life status was not possible. ITT **Compliance rates:** N=47/3851 = 1.2% n=5 withdrew before starting study			NSTEMI)						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
N=42/3861 after allocation to group, lost due to withdrawal or lost to follow-up									

G.2.2 Oily fish consumption

Table 7: Burr 1989[86]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Author Burr ML, Fehily AM, Gilbert JF, Rogers S, Holliday RM, Sweetnam PM, Elwood PC, Deadman NM. Title Effects of changes in fat, fish, and fibre intakes on death and	RCT	**All patients:** N=2033 randomised N=2033 ITT Drop-outs (don't complete the study): N=0% for mortality (%) Unclear about how many dropped out.	**Inclusion criteria:** Men <70 yrs of age with MI (according to WHO definition) **Exclusion criteria:** Diabetics, men waiting for cardiac surgery, and intended to eat one of the diets.	**Group 1: Fish advice** N=1015 randomised N=1015 (ITT) N=1015 (completers) Intervention details Least two weekly portions (200-400 g) of fatty fish (mackerel, herring, kipper, pilchard, sardine, salmon or trout)	**Group 2: No fish advice** N=1018 randomised N=1018 (ITT) N=1018 (completers) Intervention details: No fish advice	Follow-up: 6 months and 2 years	**Outcome 1:** All-cause mortality	**Fish intake:** 94/1015 (9.3% **No fish advice:** 130/1018 (12.8%) RR Unadjusted: 0.71 (0.54-0.92) RR Adjusted: 0.71 (0.54-0.93)	Funding: Welsh Scheme, Welsh Heart Foundation, Flora Project, Health Promotion Research Trust. Limitations: Some in-balance at baseline Additional outcomes: Serum cholesterol Ischemic heart disease events

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
myocardial reinfarction: diet and reinfarction trial (DART). Journal Lancet. 1989 Sep 30;2(8666):757-61. Multicentre: 21 hospitals England (between 1983 and 1987) Randomisation: Yes, no details Allocation concealment: unclear Blinding: Participants – no. Investigators			Randomised average: 41 days after MI. Group1: Fish advice (N=1015) (100% post MI) Mean age (SD): 56.7 Smoking at time of MI (%): 61.7 History Previous MI: 19% Angina: 20.8% Hypertension: 22.7% Drug treatment BB: 26.2% Other hypertensive: 34.9% Antiangina: 46.5% Anticoagulant: 4.8% Aspirin/antiplatelet: 10.1%	Men who could not tolerate fish intake were given Maxepa capsules 3/day (0.5g) **Group 3: Fat advice** N=1018 randomised N=1018 (ITT) N=1018 (completers) Intervention details Reduce fat intake by 30% of total energy and increase polyunsaturated/saturated (P/S) ratio to 1:0 Group 4**: No fat advice** N=1015 randomised N=1015 (ITT) N=1015 (completers) Intervention					Fish advice RR Unadjusted: 0.84 (0.67- 1.07) RR Adjusted: 0.71 (0.54-0.93) Hazard ratios – no numbers were provided. Only that the difference in favour of the fish advice appeared early and persisted for 2 yrs. Notes: The same patients would fit into 3 groups. Fish advice group: 14% took Maxepa in place of fish at 6 months and 22% at 2 years. Only presented results on Fish advice diet vs no fish advice diet. Advice was reinforced 3-monthly.
							Outcome 2: Non-fatal MI	**Fish intake:** 49/1015 (4.8% **No fish advice:** 33/1018 (3.2%)	
							Outcome 3: Ischemic heart disease (IHD) death (cardiovascular death)	**Fish intake:** 78/1015 (7.7% **No fish advice:** 116/1018 (11.4%)	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
who collected medical history were blinded Outcome assessment: Questionnaire : Food intake 7-day diary: 25% weighed food intake for 7 days Reinfarction: confirmed by hospital notes or GP Total mortality: relatives providing death certificates. Or followed up with GP IHD events = ischemic heart disease			Digoxin/antiarrhythmic: 9.2% Group 2: No fish advice(100% post MI) Mean age (SD): Smoking at time of MI (%): 61.7 History Previous MI: 22.7% Angina: 23.9% Hypertension: 24.6% Drug treatment BB: 32.6% Other hypertensive: 32.5% Antiangina: 46.5% Anticoagulant: 4.8% Aspirin/antiplatelet: 10.1% Digoxin/antiarrhythmic: 9.8%	details: No fibre advice **Group 5: Fibre advice** N=1017 randomised N=1017 (ITT) N=1017 (completers) Intervention details: increase intake of cereal fibre to 18g /day **Group 6: No Fibre advice** N=1016 randomised N=1016 (ITT) N=1016 (completers) Intervention details: No fibre advice Concomitant therapy: Antiplatelet Anticoagulants					

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
deaths + non-fatal MI. Includes subjects who had a reinfarction, recovered and subsequently died of IHD IHD deaths Sample size calculation: Yes. 2000 subjects would be required to detect a 30% reduction in total mortality, reduction in IHD events at p<0.05 with a power of 90%. Type of analysis No details			Drop outs: there were no drop-outs for mortality.	Antiarrhythmic Antiangina					

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Relative risk – adjusted for confounders: history of MI, angina, hypertension; x-ray evidence of cardiomegaly, pulmonary congestion or oedema and treatments at entry. Compliance rates: N=Unclear dropout/ withdrawal due to drug related AEs.									

Table 8: Burr 2003[87]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Author Burr ML, Ashfield-Watt PA,	RCT	**All patients:** N=3114	**Inclusion criteria:** men with angina	**Group 1: Oily fish** N=764	**Group 2: Fruit** N=779 randomised	**Follow-up**: 36 to 108 months	**Outcome 1:** All death	**Dietary Fish:** 198/1109	**Funding:** British Heart foundation,

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Dunstan FD, Fehily AM, Breay P, Ashton T, Zotos PC, Haboubi NA, Elwood PC. **Title** Lack of benefit of dietary advice to men with angina: results of a controlled trial. **Journal**Eur J ClinNutr. 2003 Feb;57(2):193-200. **DART 2** **Multicentre**: General practitioners		randomised N=3114 ITT Drop-outs (don't complete the study): No details given N=0 unclear (%)	**Exclusion criteria:** men who denied ever having chest pain or discomfort; men awaiting coronary artery by-pass surgery; already ate oily fish 2x week; men who could not tolerate fish or fish oil; men who appeared unsuitable on other grounds (e.g. other serious illness, likelihood of moving out of the area). **Group 1: Oily Fish** (49.6% MI, 100% angina) Mean age (SD): 61.0 (6.5) Men: 100% Percentage with history of:	randomised N=764 (ITT) N=764 unclear (completers) Intervention details ≥2 portions of oily fish/wk, or up to 3g fish oil (0.54g/d EPA; 0.36g/d DHA)(Maxepa) as a partial or total substitute Dietary assessment suggested EPA intake increased by 2.4g/wk Note:For part of the trial, this group was subrandomized to receive either fish advice or capsules	N=779(ITT) N=779 unclear (completers) Intervention details 4-5 portions of fruit and vegetables, <orange juice daily, increase oats, Vit C, and 8g fibre **Group 3: Fruit+Fish** N=807 randomised N=807 (ITT) N=807unclear (completers) Intervention details Combination of above **Group 4: Sensible eating** N=764 randomised N=764 (ITT) N=764 unclear (completers) Intervention details Non-specific advice Dietary assessment suggested EPA intake increased by		Dietary fish vs. no fish advice	**Fruit:** 242/1543 HR: 1.13 (0.94, 1.37)	Seven Seas Ltd, NovexPharma Ltd, and Fish Foundation **Additional outcomes:** Dietary intake: EPA; VitC; total energy; fat Plasma β-carotene Effect of fish oil and individual four groups **Notes**: 462 participants randomised to the fish diet were sub-randomised to receive only fish oil capsules, not dietary advice. However for dietary fish, it included the patients in phase I who chose to take
							Outcome 2: Cardiac death Dietary fish vs. no fish advice	**Dietary Fish** :121/1109 **Fruit:**139/1543 HR: 1.20 (0.93, 1.53)	
							Outcome 3: Sudden death Dietary fish vs no fish advice	**Dietary fish**: 49/1109 **Fruit:** 47/1543 HR: 1.43 (0.95, 2.15)	
							Outcome 4: All-cause mortality HR: Fish advice vs. fruit advice	**Dietary Fish:** 283/1571 **Fruit:**242/1543 **Fruit+Fish**:275/1586 **Sensible:** 250/1528 **Fish:** 283/1571	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Country:UK **Randomisation:** Yes, but no details **Allocation concealment:** Unclear, used prepared envelopes **Blinding:** No. **Outcome assessment:** **All-cause death** **Cardiac death:** confirmation from hospital records, relatives or others as appropriate. **Sudden death** was			Heart attack: 49.6% Hypertension: 49% Diabetes: 11.3% % on BB: 42.5% Percentage of smokers:24.1 Drop outs: unclear **Group 2: Fruit** (48.3% MI, 100% angina) Mean age (SD): 61 (6.5) Men: 100% Percentage with history of: Heart attack: 48.3% Hypertension:45.8% Diabetes:11.6% % on BB: 41.6% Percentage of smokers: 21.6% Drop outs: unclear **Group 3:**	**Concomitant therapy:** β-blockers	0.2g/wk			**Fruit:** 242/1543 **Fish advice vs. none** HR: 1.15 (0.96, 1.36)	capsules instead of fish, but excluded those who were subrandomised to the fish oil group
							Outcome 5: Cardiac deaths HR: Fish advice vs. fruit advice	**Oily Fish:** 180/1571 **Fruit:**139/1543 **Fruit+Fish**:158/1586 **Sensible:** 161/1528 Fish: 180/1571 **No fish:** 139/1543 **Fish advice vs. None**: HR 1.26(1.0, 1.58) :	
							Outcome 6: Sudden death	**Dietary Fish:** 73/1571 **Fruit**:47/1543 **Fruit+Fish**:61/1586	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
defined as death within 1h of symptom onset. **Compliance**: dietary charts sent by post **Sample size calculation:** Estimate of 3000 subjects needed to detect a reduction in mortality from about 13% to just less than 10% over a period of 5 yrs, at power of 80% and p<0.05. **Type of analysis** ITT HR: adjusted			**Fruit+Fish** (49.8% MI, 100% angina) Mean age (SD): 61.1 (6.9) Men: 100% Percentage with history of: Heart attack: 49.8% Hypertension: 48.1% Diabetes:13.7% % on BB: 42.4% Percentage of smokers: 25.1% Drop outs: unclear **Group 4: Sensible eating** (52.2% MI, 100% angina) Mean age (SD): 61.2 (6.3) Men: 100% Percentage with history of: Heart attack:52.2% Hypertension:49				HR: Fish advice vs. fruit advice	**Sensible**: 59/1528 **Fish:** 73/1571 **No fish:** 47/1543 **Hazard Ratio:** **Fish**: 1.54 (1.06, 2.23)	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
for age, smoking, previous MI, history of high blood pressure, diabetes, BMI, serum cholesterol, medication, and fruit advice. **Compliance rates:** Measured in a subsample of subjects, measuring serum EPA levels. Post dietary questionnaire suggested dietary EPA intake increased to 2.4g/wk intervention; 0.2g control N=unclear			.1% Diabetes:13.1% % on BB: 39.5% Percentage of smokers:24.0% Drop outs: unclear Note: sensible eating were more likely than others to have a history of heart attack, less likely to take BB. Fruit group lower history of hypertension. Not clear if statistically significant differences.						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
dropout/ withdrawal due to drug related AEs. None for mortality.									

Table 9: Ness 2002[422]

Reference	Study type	Number of patients	Patients Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding
Author Ness AR; Hughes J; Elwood PC; Whitley E; Smith GD; Burr ML Title "The long-term effect of dietary advice in men with coronary disease: follow-up of the Diet and Reinfarction Diet (DART)" Journal:Euro	RCT	**All patients**: N=2033 randomised N=2033 ITT Drop-outs (don't complete the study): N=1083 died by Feb 2000 N = 879/1030 surviving men completed survey in 2000. By the end of	**Inclusion criteria:** Men <79 yrs who had survived a MI. **Exclusion criteria:** Diabetics, men waiting for cardiac surgery, and intended to eat one of the diets. Group 1: Fish advice N = 447 Mean age (SD): NA	**Group 1: Fish advice** N=1015 randomised in 1989 N=447 completers of survey in 2000 Intervention details Eat 2 portions of fatty fish/week and as much as can manage. Those unable to eat this amount of fish were offered fish oil capsules (MAXEPA)	**Group 2: No fish advice** N=1018 randomised in 1989 N=432 completers of survey in 2000 Intervention details Fibre advice Eat at least 6 slices of wholemeal bread/day or an equivalent amount of cereal fibre from a mixture of wholemeal bread, high-fibre breakfast cereals **Sensible eating;** No specific advice on any interventions	Follow-up: 2 yrs (follow-up every 3 months)	**Outcome 1:** All-cause mortality Fish advice vs. no fish advice **Outcome 2:** Mortality coronary	**Fish advice vs. no fish advice**: Deaths =530/1015 vs. 553/1018 Hazard ratio: Unadjusted: 0.94 (0.84, 1.06) Adjusted: 0.95 (0.85, 1.07) Fish advice vs. no fish advice: Deaths =	**Funding:** British Heart Foundation and Wales Office of R&D Additional outcomes: Effects of Fibre and Fat.

Reference	Study type	Number of patients	Patients Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding
pean J of ClinNutr 2002 (56; 512-18 Follow-up of DART, Diet and Reinfarction Trial See Burr1989 Study design and quality: Min. 10 year follow-up after a trial of dietary advice was completed (1989). Questionnaires sent out 1999-2000 Original study Multicentre: 21 hospitals England (between		2000, 972 patients were still alive.	Other variables: Fish intake (g/day): 43.6 (37.8) Fatty fish intake (g/day): 20.7 (26.2) Cereal fibre intake (g/day): 5.6 (4.8) Body weight (kg): 77.8 (12.1) Current smokers: 76 (17.0) Fish oil supplement takers: 120 (26.9) Maxepa takers (fish oil): 10 (2.3) Aspirin: 265 (59.3) Regular medication: 412 (92.2) At follow-up 1999-2000:	**Concomitant therapy:** Aspirin + other medication. No detail			disease Fish advice vs. no fish advice	354/1015 vs. 384/1018 Hazard ratio: Unadjusted: 0.91 (0.79, 1.05) Adjusted: 0.92 (0.80, 1.07)	
							Outcome 3: Stroke (Fatal) Fish advice vs. no fish advice	Fish advice vs. no fish advice: Stroke = 29/1015 vs. 23/1018. Hazard ratio: Unadjusted: 1.24 (0.72, 2.15) Adjusted: 1.23 (0.71, 2.14)	

Reference	Study type	Number of patients	Patients Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding
1983 and 1987). Completed 1989 and participants were recommended to continue with their allocated diet and advising all men to eat more fish. Randomisation: Yes, unclear Allocation concealment: Unclear Blinding: No Outcome assessment: Questionnaire: Dietary intake, current health			Fatty fish intake: 35g/day Group 2: No fish advice n=432 Mean age (SD): NA Other variables: Fish intake (g/day): 36.9 (33.7) Fatty fish intake (g/day): 13.2 (20.6) Cereal fibre intake (g/day): 5.6 (5.1) Body weight (g/day): 78.7 (13.2) Current smokers: 83 (19.3) Fish oil supplement takers: 83 (19.3) Maxepa takers (fish oil): 2 (0.5) Aspirin: 248						

Reference	Study type	Number of patients	Patients Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding
All-cause mortality: Identified from questionnaire and confirmation from NHS central register. Numbers are from 1983/2000 Coronary heart disease mortality =as above Stroke mortality=as above Sample size calculation: Estimate of 3000 subjects needed to detect a reduction in			(57.3) Regular medication: 408 (94.2) At follow-up 1999-2000: Fatty fish intake: 9g/day						

Reference	Study type	Number of patients	Patients Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding
mortality from about 13% to just less than 10% over a period of 5 yrs, at power of 80% and p<0.05. Type of analysis Hazard ratios, adjusted for history of MI, angina, hypertension at baseline; x-ray evidence of cariomegaly, pulmonary congestion or pulmonary oedema at baseline; and BB, other hypertensive treatment, or									

Reference	Study type	Number of patients	Patients Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding
anticoagulants Calculated HR at different time points: 0-2, 2-5, 5-10, 10+, overall. Presented overall. Compliance rates: Completed questionnaires were obtained from 879/1030 men (85%). N= Unclear about how many dropped out.									

G.3 Cardiac rehabilitation

G.3.1 Barriers to the uptake of and adherence to cardiac rehabilitation

Table 10: Blake 2009[67]

Study	Blake 2009	
Aim	To compare patient and staff perceptions of phase III cardiac rehabilitation delivered in a hospital versus community setting.	
Population	5 patients who had attended a phase III hospital programme; 4 patients who had attended a community programme; 4 hospital and community staff members.	
Methods	Semi-structured interviews; content analysis.	
Themes with findings: barriers	**Uncomfortable exercising in a public gym/in a group**	Never been in a gym before.
		Other content duplicating previous data (data saturation).
Limitations	All patients were attenders at phase IV programme; views from patients who did not progress to phase IV because of negative experiences of phase III were not obtained; patients interviewed 6-12 months after programme so prone to retrospective reinterpretation.	

Table 11: Beauchamp 2010[48]

Study	Beauchamp 2010	
Aim	To determine whether key interventions for CVD prevention and treatment are effective among lower socioeconomic groups, to describe barriers to their effectiveness and the potential or actual impact of these interventions on the socioeconomic gradient in CVD	
Population	Four studies of effectiveness of cardiac rehabilitation after MI by socioeconomic groups	
Methods	Systematic review	
Themes with findings: barriers	**Too costly**	Neighbourhood deprivation and unemployment; programme cost.
	Transport	Lack of transport.
	Comorbidities	Depression.
	Attitude of professionals	Strength of recommendation from professionals; scepticism from professionals about ability of lower SES patients to make lifestyle change.
Themes with findings:	**Programme appropriate including language, timing, location, transport**	Pre-arranged collection or home-based programmes.

Study	Beauchamp 2010	
facilitators		
Limitations	Data not "rich".	

Table 12: Clark 2004[109]

Study	Clark 2004	
Aim	To examine patients' beliefs and decision-making about CRP attendance.	
Population	Purposive sample of patients eligible for CRP (post-MI or CABG; unclear how many patients had MI) from a mixed urban-rural region: high-attendance (>60%, n=27), high attrition (<60% attendance, n=9) and non-attendance (0%; n=8); range of ages.	
Methods	8 focus groups; audiotaped; themes identified.	
Themes with findings: barriers	**Lack of understanding that lifestyle factors contributed to MI**	Stress identified as cause rather than smoking, diet, sedentary lifestyle or obesity.
	Belief that MI due to factors outside person's control rather than lifestyle factors; fatalistic	Saw themselves as relatively helpless in combating CHD.
	Ambience at CRP	Saw attenders as old, illness-focused and "needy".
	Ambience at CRP	Thought programme was too narrow, too short, insufficiently taxing and unlikely to benefit them.
	Lack of appropriately trained staff	Saw professionals as providing inconsistent information that was inappropriately timed, as coercive, overly negative or too intense.
	Not seen as beneficial	Saw service as poorly organised and did not meet expectations.
Themes with findings: facilitators	**Health in the participant's own hands; self-efficacy**	Saw themselves as active against CHD and capable of managing it; realised they could safely put their bodies under pressure during exercise.
	MI seen as a warning/ motivator for change	Saw their CHD event as a warning that they should change their behaviour.
	Peer support	Gained encouragement from other patients that decreased embarrassment at first exercising with a group; group increased confidence, motivation and fitness; camaraderie; others "in the same boat"; similar in age, circumstances and difficulties.
	Felt the benefit from CRP	Gained a new sense of what it meant to be fit.
	Positive attitude of health professionals	Saw health professionals as experts and as useful sources of knowledge; seen as interested in safety and wellbeing of patients.

Study	Clark 2004	
	Desire to reduce risk of secondary MI	Saw attendance as rational choice.
Limitations	None.	

Table 13: Clark 2005[112]

Study	Clark 2005	
Aim	To report patients' experiences of CRP and perceptions of the mechanisms and contexts influencing its long-term effectiveness	
Population	47 patients with coronary heart disease who had attended CRP 3 years previously	
Methods	focus groups; realist approach focusing on explaining why programmes do and do not work for people by exploring choices and capacities (mechanisms) they offer in different circumstances (contexts); audiotaped; transcribed; analysed separately by two researchers; theme compared	
Themes with findings: barriers	**Lack of understanding on the importance of CRP on recovery or what CRP entails**	Surprise that CRP was principally group-based.
	Uncomfortable exercising in a public gym/in a group	Initially uncomfortable exercising in group "concerned about doing exercises in front of other people in case I make a fool of myself"; "stayed at the back ... so nobody would watch us"; concerned that programme would be tailored to the needs of others to the neglect of their own needs.
Themes with findings: facilitators	**Part of routine**	Normalising exercise to be an integral part of everyday life.
	Peer support	Perceived similarity with others; being in the same boat; rapport between participants increased motivation to attend; mutual encouragement.
	Sense of purpose and identity	Sense of not being alone; similar challenges ahead; collective identity.
	Felt the benefit from CRP	Being with other former cardiac patients at different stages in rehabilitation demonstrated that progressively high levels of fitness could be achieved by people with cardiac disease and by them personally; increased confidence and reduced fear of exercise; fitness increased as a result of participation; equipping person with a personal realisation of what levels of physical activity could and should be undertaken safely.
	Aspects and components of CRP	Importance of health education sessions with new information or that reinforced what they already knew or was reassuring.
	Availability of specialist staff	Exercise sessions safe as supervised by well qualified health professionals.
	Positive attitude of health professionals	Atmosphere generated by professionals and other participants friendly, encouraging and supportive;

Study	Clark 2005	
		staff care and interest in the individual was valued and perceived as reassuring.
Limitations	Study examined views of CRP retrospectively (3 years later) among attenders only; accounts may be prone to retrospective re-interpretation.	

Table 14: Galdas 2012[210]

Study	Galdas 2012	
Aim	To review the empirical literature relating to South Asians patients' experiences of cardiac rehabilitation	
Population	Individuals of South Asian origin (originating from India, Pakistan, Bangladesh or Sri Lanka) in 11 primary studies	
Methods	Systematic review. Key findings from each included study extracted into review matrix; discussed by team and distilled into themes; consensus between all reviewers	
Themes with findings: barriers	**Lack of understanding of CRP**	Not sure what CRP entails.
	Location/ transport/ mobility/ distance difficulties	Transport difficulties, mobility, distance to travel. lack of access to a car; women fearful of racial abuse when waiting outdoors for a taxi provided by CRP; being in the presence of young male taxi drivers unacceptable for younger females; anxious about attending sessions held in high crime areas.
	Referral issues	Lack of referral, did not know CRP available, waiting to be formally invited.
	Time constraints	Lack of time.
	Reluctant to exercise	Women had never been in a formal exercise environment/ joined a gym/ used sports equipment before.
	Unsure about safety (location)	Women reluctant to exercise outdoors and unaccompanied: found it difficult to identify safe and suitable walking routes in inner-city areas or to arrange for a family member to accompany them.
	Unmotivated	Female South Asian participants lacked motivation to exercise on their own.
	Religious reasons	Gujarati Hindus and South Asian Muslims felt that MI and recovery were tied to fate or the will of God (external locus of control); low perceived control of patients towards rehabilitation and therefore low adherence to CR advice. Mixed gender classes problematic for Muslim women due to need to wear appropriate clothing in mixed groups and embarrassment about exercising in front of others. Early afternoon or Friday CRP sessions conflicted with call to prayer for Muslim women.
	Uncomfortable exercising in a public gym/in a group	Preference for private home-based CR programme. Female South Asian participants lacked confidence to take part in group exercise activities.
	Lack of support at home	South Asian families less inclined to encourage family members to participate in regular exercise as

Study	Galdas 2012	
		recommended by CRP providers; male patients received more family support during rehabilitation while female patients attempted to modify their lifestyle with limited help, some South Asian women reported they would need their husband's agreement to attend CRP.
	Clothing	Clothing requirements for exercise incompatible with traditional South Asian dress including long headscarves; reluctance to adapt to Western norms for exercise attire.
	Belief that exercise is harmful	South Asian women had long-standing beliefs that exercise brings on chest pain.
	Exercise not helpful/ inappropriate/ excessive/ unnecessary	South Asians feeling no immediate benefit from exercise; belief that they were too old to exercise; having more exercise forced on them than they were prepared to do.
	Programme culturally insensitive	Dietary advice inappropriate to South Asians (e.g. recommending dhal which was perceived to be food for poor people); embarrassment about advice about sexual relations, assumptions made by health professionals on basis of person's appearance.
	Language/interpreters	Inability to speak English, lack of audio- or video-taped information in preferred language or use of interpreter, lack of direct communication with patients so lack of opportunity to emphasis importance of family involvement in rehabilitation. Reliance on family members to interpret could go against usual family roles and privacy; children tended to avoid conveying negative aspects and seriousness of parents' cardiac condition to reduce distress.
Themes with findings: facilitators	**Programme appropriate including language, timing, location**	Attendance higher when programme "culturally competent"; participants valued opportunities for one-to-one discussions with Punjabi-speaking healthcare professionals; practical, culturally relevant dietary advice.
	Timing	Participant who had returned to work were able to attend programme because held in the evening.
	Religious reasons	Some South Asians (e.g. Sikhs) felt that MI was an indication from God that they had not looked after their health, so willing to make lifestyle changes to take personal responsibility and guard against future problems.
	Positive attitude of health professionals	South Asians valued personal support, attention and caring environment provided by health professionals.
	Peer support	Peer support identified as crucial by Punjabi Sikhs.
	Preference for hospital-based CRP	Some South Asian patients preferred to attend hospital-based CRP for motivation, feeling safer, being more closely monitored by staff and availability of equipment.
Limitations	None.	

Table 15: Grace 2007[241]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect sizes	Source of funding
Author: Grace SL, Scholey P, Suskin N, Arthur HM, Brooks D, Jaglal S, Abramson BL, Stewart DE. **Title**: A prospective comparison of cardiac rehabilitation enrollment following automatic vs usual referral. **Journal**: J Rehabil Med. 2007 Apr;39(3):239-45.	Observational – Prospective.	**All patients:** N=661 Consecutive patients with ACS were recruited on relevant cardiovascular units by a research assistant when medically stable.	**Inclusion criteria**: were diagnosis with a confirmed myocardial infarction (MI), unstable angina (UA), ischemic congestive heart failure (CHF), percutaneous coronary intervention (PCI), or acute coronary bypass (ACB), and at least 18 years of age. Exclusion criteria: included being medically unstable, too confused to participate, previous participation	**Group 1:** The automatic referral model implemented at this centre uses hospital electronic patient records to prompt the standard order for a CR referral for all eligible patients with cardiac diseases. This discharge order is initiated on the inpatient ward and printed on a hospital network printer in the CR center and again screened. An information package, including a personalized letter stating the name of the	**Group 2:** This involves referral to CR at the discretion of the cardiologist, cardiovascular surgeon, general practitioner, or other healthcare provider through paper-based means.	9 month follow up.	**Outcome 1:** Reasons for withdrawal or non-participation.	**Lack of referral :** n=59; too distant or inconvenient n=13; health or mobility issues n=13; did not know about CR n=11; conflicts with employment n=7. Others: Not knowing why, not being interested, indirect costs, not capacity for new patients; physicians saying they did not need CR.	**Funding:** Canadian Health Services Research Foundation and Ontario Ministry of Health and Long-Term Care, and administered by the Canadian Institutes of Health Research FRN # 73996. Dr Grace is supported by the Ontario Ministry of Health and Long-Term Care.

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect sizes	Source of funding
Country Canada			in CR, being ineligible for CR based on CACR guidelines due to musculoskeletal, vision, psychiatric, or other co-morbidities, or being unable to read or speak English. Those who met study criteria and agreed to participate signed a consent form and were provided with a self-report questionnaire. Consent was also obtained to link participant's self-report questionnaire data with their clinical data. Characteristics:	referring physician, a program brochure, a schedule of classes, and a request that the patient telephone to book an appointment, is mailed to the patient's home. Patients who live outside of the geographic area are also sent a similar package, but they are provided with the contact information of the site closest to their home. This alternate site is also sent the patient's contact information.					

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect sizes	Source of funding
			UHN Usual (n = 330) THC Automatic (n = 331) In order as above PCI, n (%) 251 (76.1) 154 (46.5) Males, n (%) 251 (76.1) 253 (76.4) Ethnocultural background: white, n (%) 247 (82.6) 262 (81.1) Marital status: married, n (%) 246 (74.5) 257 (77.6) Retired 118 (35.8) 140 (42.6) Education: some postgraduate, n (%) 177 (53.6) 163 (50.6) Family income: ≥					

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect sizes	Source of funding
			$50 000 CADa, n (%) 142 (56.3) 157 (53.2) NYHA Class 1, n (%) 258 (86.9) 298 (90.9) Age, mean (SD) (years) 60.65 (10.6) 61.78 (11.91)						

Table 16: Halcox 2011[251]

Study	Halcox 2011	
Aim	Survey of current practice assessing views on and adherence to NICE guidance on secondary prevention of MI.	
Population	GPs (n=250) and cardiologists (n=53).	
Methods	Questionnaire survey.	
Themes with findings: barriers	**Problems of tailoring CRP to the individual**	Underestimation of the importance of a menu-based approach, the fact that patients have variable expectations about rehabilitation and motivations.
	Primary/secondary care interface	Better integration between primary and secondary healthcare needed to improve provision of a consistent service.
Themes with findings: facilitators	**Support from other health care professionals to aid uptake and adherence on CRP**	GPs and cardiologists used regular consultations or involved other healthcare professionals to motivate patients to pursue a healthy lifestyle.
	Tailoring advice to individuals	Take ethnicity into account when delivering dietary advice; addressing health and social needs; tailoring advice to health beliefs or culture.
Limitations	Qualitative part only a small part of overall study.	

Study	Halcox 2011
	Questionnaire not interview. Not "rich" data.

Table 17: Hansen 2009[256]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect sizes	Comments
Author: D Hansen, J Berger, P Dendale, R De Rybel, and R Meeusen. Title: Training adherence in early cardiac rehabilitation: effect of exercise session duration. **Journal:** J Cardiopulm Rehabil Prev. 2009 May-Jun;29(3):179-82.	RCT	**All patients:** N=417 CAD patients referred to the coronary revascularisation unit Drop outs: 7 weeks: n=83 (19.9%)	Men n=156 Age = mean 63 yrs BMI 26.7 NS difference between baseline characteristics	**Group 1:** 40-min exercise sessions (40) N=198 ITT = 198 ACA = 68 Exercise training intervention included only endurance training (no strength training exercises were performed). Exercise was under close supervision 3 days/ week for 7 weeks, at 65% of the maximal oxygen uptake capacity. Exercise sessions had equal time distribution in each session on the different exercise	**Group 2:** 60-min exercise sessions (60) N=219 ITT = 219 ACA = 81	7 weeks	**Outcome 1:** Reasons for drop-out.	Medical reasons: 40 =15.4% 60=20.2% Non-medical reasons- main reason lack of motivation: 40 Lack of motivation = 41% Return to work=20.5% Transport difficulties = 17.9% Undefined = 2.6% Continuation at home = 2.6% Intervention was too heavy =0% Negative advice from physician=0%	**Funding:** Research grant from Hartcentrum Hasselt. No details given of randomisation, blinding, power or other Risk of bias elements.

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect sizes	Comments
Country: Belgium Methods: Training adherence evaluated at the end of the 6th week of exercise training (≥18 exercise sessions). Dropouts definition: Pts who did not complete 7 wks of training because of nonmedical or medical reasons, or exercised on average less than 2 sessions/w				modalities: 42% treadmill, 33% bike, and 25% arm cranking device). In both groups: when musculoskeletal discomfort or pain appeared throughout the intervention, the type of exercise was changed so that these exercises could be executed without symptoms. However, exercise intensity, frequency and duration of the exercise sessions remained constant.				60 Lack of motivation = 38.6% Return to work=11.7% Transport difficulties = 6.8% Undefined = 6.8% Continuation at home = 6.8% Intervention was too heavy =2.3% Negative advice from physician=2.3%	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect sizes	Comments
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Table 18: Jackson 2012[287]

Study	Jackson	
Aim	Understand the non-participation in CR and CHD self-help groups from the perspective of the non-participants and to provide insight into their experience and that of their significant others in rehabilitating in the absence of these resources.	
Population	Twenty-seven people who had not participated in either hospital based CR or CHD group, 6-14 months post MI and 17 significant others in Lothian, Scotland.	
Methods	In depth interviews.	
Themes with findings	**Referral issues**	Not being informed or invited and non-availability. Inadequate information on whether to attend cardiac rehabilitation or coronary heart disease groups.
	Uncomfortable asking for support	Reticence about highlighting health service difficulties and reluctance to ask for support. Deterred by perceived judgement, staff attitudes regarding issues, for example smoking or their motivation.
	Uncomfortable exercising in a public gym/in a group	Do not like the group.
	Location/ transport/ mobility/ distance difficulties	Transport difficulties (data saturation).
	Comorbidities	Physical discomfort and disability.
	Time constraints	Mostly because of work.
	Lack of appropriately trained staff	Expressed frustration at the lack of CRP support.
	Lack of understanding on the importance of CRP on recovery or what CRP entails	Believe that CRP will have little benefit on their recovery and that only medical or surgical intervention could improve health. Low expectations. Uncertainty about future health, risk of further MI and the extent they could regain their former way of life. Belief that CRP would make little difference to their health or co-morbidities. Struggled to understand the Heart Manual, causing misunderstandings, anxiety and misjudgements and maladjustment.

Study	Jackson	
	Lack of support	Follow-up support was too late, too brief or did not addressed key needs particularly regarding mental, emotional, and for some cognitive issues. Lack of long-term support.
Limitations	The views of responders may not be typical. Although the responses were not dissimilar to average health questionnaire response rates, suggesting that not all non-participants were 'hard to reach'. Interviewing patients 8-15 months post MI may be late, since their experiences and expectations may change over time.	

Table 19: Jolly et al 2009[296]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect sizes	Source of funding
Author: K. Jolly, G. Y. H. Lip, R. S. Taylor, J. Raftery, J. Mant, D. Lane, S. Greenfield, and Stevens. **Title:** The Birmingham rehabilitation uptake maximisation study (BRUM): a randomised controlled trial	RCT	**All patients:** N=525	Men n=402 Age = mean 61 yrs Education mean= 14 years Race: n=418 White, n=89 Asian, n=17 other In paid employment n=220 Current smoker n=179 SBP mean = 124 mmHg BMI mean = 28 NS difference between groups for baseline	**Group 1: Home-based rehab (H)** N=263 ITT = 263 ACA (6 mths)=246 ACA (12 mths)=239 In both groups: programs included exercise, relaxation, education and lifestyle counselling. Home-based program consisted of a manual, 3 home visits (at 10	**Group 2: Centre-based rehab (C)** N=262 ITT = 262 ACA (6 mths)=239 ACA (12 mths)=236	Clinical outcomes assessed by blinded nurse at a hospital site at 6 and 12 months.	**Outcome 1:** Reasons for drop-out	6 months: Died: H=3, C=2 Withdrew: H=3, C=3 Not attend follow-up: H=11, C=18 12 months (not cumulative): Died: H=0, C=1 Withdrew: H=4, C=0 Not attend follow-up: H=14, C=20	**Funding:** Grant from NHS and DoH, UK COMMENT: ITT analysis performed (missing data substituted with a predicated outcome value) Randomisation: individual pt randomisation by an

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect sizes	Source of funding
comparing home-based with centre-based cardiac rehabilitation. **Journal:** Heart 95 (1):36-42, 2009. Country: UK Methods: Adherence to cardiac rehab was confined to the physical activity component; data collected by questionnaires at 6, 9 and 12 weeks after recruitment asking about			characteristics Drop outs: 6 months n=17 (H), n=23 (C) 12 months (cumulative) n=24 (H), n=26 (C) Patients who were referred to the cardiac rehab program (CRP) in 1 of 4 hospitals, following an MI, PTCA or CABG within the previous 12 weeks and not considered to be high risk for a home-based exercise program.	days, 6 weeks and 12 weeks) and telephone contact at 3 weeks. Pts who had MI or revascularisation were discharged with the Heart manual or an adapted version (manual encourages gradual exercise to achieve minimum 15 mins of moderately intense exercise). Additional visits were made as deemed necessary by the rehab nurse (nurses delivering home program were trained for 2 days). Centre-based programs varied in length including 9 sessions at weekly intervals, 12 sessions over 8 weeks and 24					independent CTU using computerised program and minimising for age, ethnicity, initial diagnosis and hospital of recruitment. Blinding: single blind (nurse/data collector) Powered study

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect sizes	Source of funding
intensity and duration of physical activity undertaken the previous 7 days. Nurse blinded to randomised groups.				individualised sessions over 12 weeks. Programs commenced between 4 and 8 weeks following the cardiac event. Pts exercised to 65-75% of their predicted maximal heart rate and the exercise element of the program lasted from 25-40 mins plus warm-up and cool-down times.					

Table 20: Jolly et al 1999 [295]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding
Author: Jolly K, Bradley F, Sharp S, Smith H, Thompson S, Kinmonth AL, Mant D.	RCT - stratified	N=597 Analysis = ITT but excluded deaths. Inclusion	Control (n=320) Intervention (n=277) Age (years) C= 64 (10) I = 63 (10) No (%) of men C = 237 (74)	N=321 MI = 191 Angina =71 Follow up care for patients, particularly the transfer of responsibility for care between	N=277 MI = 198 Angina=99	1 month, 4 months, and 1 year after recruitment.	**Outcome 1** Reasons for withdrawal	Total population. No details /gp Five patients were too ill or dying, 23 refused, and 29 were uncontactable.	**Funding:** The study was funded by a research and development national program grant from the NHS Executive, with

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding
Title: Randomised controlled trial of follow up care in general practice of patients with myocardial infarction and angina: final results of the Southampton heart integrated care project (SHIP). The SHIP Collaborative Group. **Journal:** BMJ. 1999 Mar 13;318(7185) :706-11. Group. Country: UK		criteria All 723 patients admitted to hospitals in the district who had survived a first or subsequent myocardial infarction and all patients with angina of recent onset (less than 3 months) who had been seen in a direct access chest pain clinic or admitted were systematically identified over a period of 18 months and considered	I = 189 (68) No (%) of smokers* C = 87 (27) I =89 (32) Serum total cholesterol (mmol/l) C = 6.1 (1.3) I =6.1 (1.3) Systolic blood pressure (mm Hg) C = 129 (21) I = 128 (19) Diastolic blood pressure (mm Hg) I =81 (14) C = 81 (13) Body mass index (kg/m2) I= 28 (3.7) C =27 (4.2)	hospital and general practice at the time of discharge and the support of practice nurses. A liaison nurse telephoned the practice (speaking to the practice nurse if possible) shortly before patients were to be discharged to discuss the care of each patient and to book the first follow up visit to the practice. Practice nurses were encouraged to telephone back to discuss problems or to seek advice on clinical or organisational issues. Evidence based guidance on clinical management was attached to each					service support from Southampton and South West Hampshire Health Authority. Rose Wiles was in receipt of a NHS South and West Region research and development research training fellowship

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding
Methods Randomised controlled trial; stratified random allocation of practices to intervention and control groups. Randomisation: 597 adult patients (422 with myocardial infarction and 175 with a new diagnosis of angina) were recruited during hospital admission or attendance at a chest pain clinic		for inclusion in the trial. The baseline characteristics of the 95 subjects who died or who were lost to follow up at 1 year were similar at baseline to those of the subjects who were followed up.		discharge communication, which was given to each patient (or relative) to give to the general practitioner. Each patient was also given a patient held record, which prompted and guided follow up at standard intervals. The liaison nurses did not provide individual clinical care after discharge but provided support to practice staff both by telephone and by visiting each practice every 3–6 months. They also encouraged practice nurses to attend both initial training on behavioural change and an					

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding
between April 1995 and September 1996. Power The power of the study to detect clinically important differences at a 5% significance level was anticipated to be reasonably high for continuous variables (about 95% for a difference of 0.35 mmol/l in blood total cholesterol concentration and of 40 m in the distance				ongoing support group to tackle their information needs as they arose.					

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding
walked); it was less for dichotomous									

Table 21: Jones 2009[297]

Study	Jones 2009	
Aim	To compare the views of patients who had completed a home- or hospital-based CRP and explore the benefits and problems of each programme	
Population	16 patients from 4 hospital programmes and 10 home programme patients	
Methods	3 hospital focus groups and 2 home focus groups; tape recorded and transcribed; analysed for themes	
Themes with findings: barriers	**Location/ transport/ mobility/ distance difficulties**	Difficulty parking.
	Reluctant to exercise	Patients worried about exercising on their own in home programme and reluctant to push themselves.
Themes with findings: facilitators	**Support at home**	Support from family members, some of whom also did the exercises and make lifestyle changes.
	Programme appropriate including language, timing, location, transport	Exercises well planned; gradual build up helped to build confidence; education programme helped them learn more about what had happened to them and how to improve their lifestyle; sessions on medication particularly valued; "good balance between the walking and the lifting and the tread up and down...they give you a little bit of everything there".
	Positive attitude of health professionals	Patients positive about nurse support; nurses very friendly, easy to talk to, helpful and knowledgeable; "If you've got any problems mental or physical they were there to help".
	Peer support	Enjoyed exercising in a group and mixing with other people; gained motivation and support from other patients.
	Preference for hospital-based CRP	Having regular appointments to attend sessions at hospital important motivation; would have been less likely to complete exercises at home.
	Aspects and components of CRP	Heart Manual well organised; covered a range of topics in addition to exercise; helpful information and advice; positive and encouraging; advice relevant to patients' experience; read and followed dietary advice; relaxation tapes good; recording the exercises helped with motivation as patients knew nurse would be coming and encouraging to be able to look back and see the progress they had made.

Study	Jones 2009	
	Availability of specialist staff	Lack of confidence; little idea of what type or level of exercise was safe and appropriate; although positive about participating in CRP they felt that exercise could do harm as well as good; exercising under supervision important to allay fears about possible risks of exercise.
	Part of routine	Home exercises became lifestyle change rather than a treatment; being able to fit exercise around normal routine rather than attending hospital at set times; continuing to exercise "addicted to them".
	Sense of purpose and identity	Being in a group like belonging to a community and being related to each other.
	Health in the participant's own hands; self-efficacy	Home programme: more in control of own rehabilitation.
	Felt the benefit from CRP	Enjoyed and benefitted from CRP; feeling an improvement in health; regaining confidence to return to activities they enjoyed; learnt about heart; made lifestyle changes.
	Preference for home-based programme	Some home-based patients would have found it difficult to attend hospital programmes because of transport difficulties or carer responsibilities; "don't like the idea of having to go to a gym, getting there, doing whatever you're doing, with a lot of other people".
Limitations	None	

Table 22: Jones 2007[298]

Study	Jones 2007	
Aim	To explore patients' reasons for non-participation in or non-adherence to a home- or hospital-based CRP	
Population	49 patients in an RCT of home vs. hospital based CRP who did not complete their CRP (purposive sampling; patients invited until at least 10 interviewed from each category: female; elderly (aged 70 or over); ethnic minority; and middle-aged males)	
Methods	Semi-structured interview; tapes transcribed; themes identified	
Themes with findings: barriers	**Lack of understanding on the importance of CRP on recovery or what CRP entails**	In denial about heart attack.
	Location/ transport/ mobility/ distance difficulties	Heavy traffic, lack of parking, irregular bus services, location inconvenient.
	Lack of information on where and when CRP is available/ referral issues	Patients had not been invited; misunderstanding (having been given information on times of programmes but had not got an appointment with a specific start date).
	Time constraints	Carer: unable to leave partner for extended periods required for hospital programme; return to

Study	Jones 2007	
		work made attendance difficult; unwilling to go out in the evening; only able to attend in the evening as relied on working daughter for transport; time unsuitable as cannot exercise after meals due to indigestion; wife having to take too much time off work to take patient to hospital.
	Reluctant to exercise	Has never done any exercise so does not know what to expect or how to do it.
	Unmotivated	Lack of motivation; would not have been motivated on home programme.
	Not seen as beneficial	Doing alternative types of exercise instead; had made a good recovery and did not see need for, or potential benefits from, programme.
	Comorbidities	Health problems affecting ability to do exercise (e.g. emphysema, arthritis, back pain, angina, waiting for hip replacement).
	Exercise not helpful/ inappropriate/ excessive/ unnecessary	Patients aged between 52 and 60 thought that the other patients were all old people and did not feel comfortable with this. Home exercises too easy.
	Ambience at CRP	Overcrowded; did not enjoy it.
Themes with findings: facilitators	**Desire to achieve goals**	Did exercises so he could return to work; "hope to improve by...doing it".
	Support at home	Partner, family and community supporting changes to lifestyle (e.g. smoking, diet).
	Peer support	Enjoyed the atmosphere of hospital programmes; found it friendly and fun; enjoyed the company; gained motivation working in a group; "with some other fellows and you're having a laugh and a joke"; "liked the friendship of the group...You can see if he's doing better than you and that's what you want isn't it".
	Preference for hospital-based CRP	Difficulty with motivation on home programme and worried about doing too much or too little - preferred supervision.
	Aspects and components of CRP	Learnt new things about medication, diet, how the heart works; used relaxation tape; enjoyable; motive participants "pushed you outside...to start getting about"; "a lot of information...if I get a bit worried about anything I can always refer to that [Heart Manual]".
Limitations	None.	

Table 23: MacInnes 2005[352]

Study	MacInnes 2005
Aim	To explore the illness perceptions of women following MI

Study	MacInnes 2005	
Population	Purposive sample of 10 women from a range of age groups (30-59; 60-79; 80 and over); clinically stable; English as first language	
Methods	Semi-structured interview; field notes; tapes transcribed and returned to participants for checking; framework method of analysis	
Themes with findings: barriers	**Not seen as beneficial**	Belief that illness was inevitable: " I don't think heart attacks can be prevented".
Themes with findings: facilitators	**Desire to achieve goals**	Desire to return to level of independence and normality and regain control; "exercise programme would help me get back on my feet"; "I knew I would get an awful lot out of it".
	Health in the participant's own hands; self-efficacy	"When you live on your own you have to look after yourself".
Limitations	Qualitative part only a small part of overall study. Purposive sample cannot be considered representative of the population of women following MI.	

Table 24: Madden 2011[354]

Study	Madden 2011	
Aim	To study the choices patients make when offered home-based or hospital-based cardiac rehabilitation.	
Population	35 patients and 12 staff members delivering a pilot programme in five rehabilitation services.	
Methods	Semi-structured interviews.	
Themes with findings: barriers	**Lack of understanding on the importance of CRP on recovery or what CRP entails**	Patients did not know what a CR service was or why it was important; lack of perceived status of service (suggested by nurses rather than prescribed by cardiologists).
	Location/ transport/ mobility/ distance difficulties	Lack of access to transport; geographical location of services.
	Lack of information on where and when CRP is available/ referral issues	Lack of information on which to base a choice between hospital and home-based programme (e.g. different course content); lack of referral; patients who had to find rehab programme rather than being offered it lost motivation.
	Time constraints	Inflexible working hours; restricted choice of times to attend hospital programme; clash with family commitments

Study	Madden 2011	
	Lack of appropriately trained staff	staff running home-based service not medical and unable o answer the patient's questions; problems of staff leave, retention, sickness, lack of like-for-like maternity cover, NHS restructuring and short-term financial crisis.
	Unmotivated	Work constraints meant that some patients could not join group, but found it hard to do exercises on their own and said that group would have helped motivation; others thought home-based programme more suitable for those not working and hard to fit exercises into tiring work day. Bored/ depressed doing exercises alone at home.
Themes with findings: facilitators	**Programme appropriate including language, timing, location**	Home-based programme avoids transport problems and being tied to fixed schedule, avoids problem when person does not want to join a group, avoids the problem that exercises done in a group (of mainly older people) not appropriate for a younger person.
	Preference for hospital-based CRP	Instructors could give more guidance and perform assessments, enough space and enough equipment.
Limitations	None.	

Table 25: Martin 2012[369]

Study	Martin 2012	
Aim	To investigate the motivations and supports necessary to adhere to a community-based CRP.	
Population	Individuals with established coronary heart disease (single to multiple cardiac events; unclear if all had MI); 24 long-term adherers to CRP (at least 6 months attendance with lapse no greater than 1 month).	
Methods	Focus group discussions (three for men, two for women; 4-7 participants in each); notes from focus groups recorded; participant verification; constant comparative analysis; theme identification.	
Themes with findings: facilitators	**Desire to reduce risk of secondary MI**	Understanding among participants of health benefits of continuing to adhere to physical activity – this should be reinforced by staff; continued participation as an insurance policy against being in stage they had just left; keeping on the straight and narrow.
	Support at home	Instrumental and social support from family and friends (i.e. encouragement that spurred participants on; giving a lift to the venue).
	Positive attitude of health professionals	Instrumental support from health professionals (i.e. encouraged to progress from Phase III to Phase IV CRP; outlining location, time and enrolment procedures) and programme staff (i.e. making participants feel at ease; nice; made them feel welcome); maintaining support for newcomers to the programme.
	Peer support	Social support from fellow participants (i.e. company and fun; opportunity to exercise with people who are in the same boat).
	Aspects and	Exercises carried out in class were novel and stimulating; increasing challenge and variety of exercises maintained

Study	Martin 2012	
	components of CRP	motivation, as would goal setting, fitness tests and feedback.
	Availability of specialist staff	Safety benefits of exercising in the presence of specialist staff; feeling safe.
	Part of routine	Commitment to attend; sets targets for keep fit at set hours.
	Sense of purpose and identity	Gives participants a sense of identity, a place in society; knowing here they are going today.
	Health in the participant's own hands; self-efficacy	I wanted to do it myself...You needed to get out there and start your life again." Task self-efficacy: ability to successfully perform exercises showed participants what they could do, built confidence. Barrier self-efficacy: distance from venue and traffic were inconvenient but did not lead to non-participation (i.e. people overcame these barriers). Recovery self-efficacy: lapses in adherence (e.g. due to holidays) but then returned to programme.
	Method of recruitment	Existing participants could be used to encourage new people to join programme; information to health professionals to increase awareness of availability of CRP; Phase III staff visiting Phase IV CRP; patients in Phase III having a visit to Phase IV to reduce initial anxiety; need for quick transfer from Phase III to Phase IV.
Limitations	Unclear if all patients had MI.	

Table 26: McCorry 2009[374]

Study	McCorry 2009	
Aim	To explore patients' beliefs about exercise for promoting recovery form an MI within the context of cardiac rehabilitation among men and women who did not attend a formal CR programme	
Population	8 men and 6 women post-MI who did not attend a formal CR programme; age range 34-82 years	
Methods	Semi-structured interviews; taped and transcribed verbatim; units of meaning funnelled into themes; themes organised and inter-related; later themes tested against earlier transcripts; recruitment until data saturation	
Themes with findings: barriers	**Lack of understanding on the importance of CRP on recovery or what CRP entails**	Manner of invitation did not indicate it was important to attend: "you had the option to go...If they had pushed it... I would probably have gone ...at least once".
	Time constraints	"Didn't want to be running to places where I hadn't time to go...".
	Not seen as beneficial	Didn't feel I needed the support...just to reassure you... wouldn't do anything for you medically...if you are feeling OK you can do without it". Adherence to medication perceived to give greater control of health ; CRP no additional value feeling that heart problem had cleared up (i.e. did not see MI as a symptom of underlying heart

Study	McCorry 2009	
		disease).
	Comorbidities	"With the pain, with the arthritis you can't do an awful lot...you get tired and then you get weak" symptoms put down to other comorbidites (e.g. asthma).
	Belief that exercise is harmful	Concerns about straining heart or becoming breathless; "don't know whether I'm doing myself any harm or whether I'm doing myself any good". Activity that caused participants to breather more heavily was not thought to be appropriate: "I'm afraid really to overdo things , cause I don't want to put a strain on my heart obviously".
	Exercise not helpful/ inappropriate/ excessive/ unnecessary	Some younger participants thought CRP not appropriate for them because attendees perceived to be elderly and exercises not appropriate for younger people. Belief that keeping active through everyday activities was sufficient. Feeling that existing management sufficient: "I survived for 12 years... I didn't think it was worth my while going in [to CR]".
	Perceived as only to get people back to normal, not long-term behaviour change	CR exercises perceived as a course to get back to normal.
	Attitude/ remarks of health professionals	If heart attack was described as "mild" (and person perceived they were back to normal).
	Lack of understanding that lifestyle factors contributed to MI	Only 2 (younger) patients identified lifestyle factors as contributing to the MI.
	Belief that MI due to factors outside person's control rather than lifestyle factors; fatalistic	Participants attributed MI to factors outside their control (e.g. fate, familial disposition) or stressful/ emotional circumstances; "If it's your time, it's your time. When you've got to go, you've got to go".
Limitations	None.	

Table 27: Miller 1988[390]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes (at 2 months post-discharge)	Source of funding Comments

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes (at 2 months post-discharge)	Source of funding Comments
Author: P. Miller, R. Wikoff, M. McMahon, M. J. Garrett, and K. Ringel. **Title:** Influence of a nursing intervention on regimen adherence and societal adjustments postmyocardial infarction. **Journal:** Nurs.Res. 37 (5):297-302, 1988. Country; USA, 3 hospitals with comparable rehab programs Methods: All patients while in hospital completed a	RCT	N=115 initial Drop outs: 30 days: C = 4, E = 2 60 days (cumulative includes 30 days count): C = 10, E = 2 Analysis Inclusion Data analysis was based on the N=103 people who completed all follow-up measurements (ie. ACA)	In N=103 (ACA population) All= first MI patients who underwent a 10-15 day inpatient based cardiac rehab program Men n=83 Women n=20 Age = 30-65 yrs Race: white n=96, Black n=7 SBP mean 123 mmHg Current smokers n=59 Non-smokers n=44 Occupation: unknown n=3, retired n=12, labour and service n=25, proprietor and skilled craftsman n=37, professional n=21, top management n=5	**Experimental: CV nursing intervention (E)** N=58 ITT = 58 ACA = 30 and 60 days n=56 E: Baseline 30 day data obtained and used for problem identification by CV nurse visits to pts and spouses, discussing the cognitive and attitudinal info with the pt and spouse. Specific societal adjustments and coping methods were examined for their effectiveness. Unclear or missing info from the rehab program was also discussed. Problems identified and pts perception were	**Control (C)** N=57 ITT = 57 ACA = 30 days n=53, 60 days n=47 Completed the same measurement scales as experimental group just prior to dismissal from hospital, and at 30 and 60 day visits to home. Received no nurse intervention and no discussion of medical regimen or problems experienced.	30 and 60 days after hospital discharge	**Outcome 1** Reasons for withdrawal	Death n=2 (E=1, C=1) Lost to follow-up n=5 Not want to continue n=4	**Funding:** Partial grant from NIH COMMENT: Randomisation: says pts were alternately assigned to experimental or control groups. No other details given of randomisation, blinding, power or other Risk of bias elements.

Table 28: O'Driscoll 2007[432]

Study	O'Driscoll 2007	
Aim	To examine the effectiveness of a London National Health Service Trust Hospital's CRP	
Population	3 post-MI patients and 11 healthcare professionals	
Methods	Patients: individual case studies; participant observation; in-depth semi-structured interviews	
Themes with findings: barriers	**Location/ transport/ mobility/ distance difficulties**	Staff unclear if hospital could provide transport.
	Time constraints	Twice a week is quite a tall order really.
	Lack of appropriately trained staff	Lack of staff leading to information overload, un-interactive and didactic teaching with rapid pace and sometimes vague and too general with limited clarifications; contradicting or omitted advice; lack of psychologist to provide support (e.g. for depression, stress management).
	Lack of support at home	Not all patients informed that family members welcome to attend rehab programme; constraints if room not big enough for patients and relatives.
	Comorbidities	Limited level of concentration.
	Poor communication between departments	Failure in transferring information between departments (e.g. exercise test results) so staff unable to set accurate training intensities or tailored goals; patients not being set challenging targets.
	Problems of tailoring CRP to the individual	"People in the lower socioeconomic group don't do as well...they don't have the knowledge...their needs are very different".
	Lack of resources	Behind in milestones due to timing of receiving funding; "Cinderella service"; limited personnel resources; limited staff time for each patient leading to information overload; limited access to interpreters.
	Need to follow up patients who do not attend	Important that cardiac staff contact the patients to explore possible barriers and if possible provide assistance to facilitate attendance.
	Staff morale	Modernisation of NHS has increased workload and pressure and decreased inspiration and enthusiasm; "would be bored to tears if all I did was cardiac rehab"; "so much more we need to do".
Limitations	None.	

Table 29: Pell 1998[463]

Study	Pell 1998
Aim	To determine the factors associated with patients failing to attend rehabilitation.
Population	208 patients who had been invited to CRP after MI.

Study	Pell 1998	
Methods	Questionnaires.	
Themes with findings: barriers	**Location/ transport/ mobility/ distance difficulties**	Parking/ lack of access to suitable transport/ cost of transport; community venue easier to attend.
	Time constraints	Conflicting work commitments; conflicting domestic commitments (dependent family member); dislike of class times.
	Reluctant to exercise	Dislike of exercise.
	Uncomfortable exercising in a public gym/in a group	Dislike of large mixed-sex classes.
	Not seen as beneficial	Perception that attendance would result in little benefit; felt better/fine.
	Comorbidities	Clinical problems (e.g. worsening cardiac symptoms or other health problems).
	Belief that exercise is harmful	Perception that attendance would result in increased risk/advised against.
	Exercise not helpful/ inappropriate/ excessive/ unnecessary	Dislike of exercise level.
Limitations	Qualitative data only a small part of questionnaire study. Role of researcher not clearly described. Not "rich" data.	

Table 30: Proudfood 2007[486]

Study	Proudfoot 2007	
Aim	To investigate the UK and any national (within UK) differences in the provision, staffing, content of phase I cardiac rehabilitation (P1CR), national guidelines achieved and any identified barriers.	
Population	Patients with acute coronary syndromes .	
Methods	Questionnaire to 247 cardiac rehabilitation centres with qualitative free text.	
Themes with findings: barriers	**Lack of resources**	staffing levels: low levels of physiotherapists, dieticians and clinical psychologists; lack of funding; time constraints; lack of resources
Limitations	Qualitative part only a small part of overall study.	

Study	Proudfoot 2007
	Data not "rich".

Table 31: Pullen 2009[488]

Study	Pullen 2009	
Aim	To provide an analysis of how women think about their illness and cardiac rehabilitation and examine how this relates to decisions about whether or not to attend a CRP	
Population	Female cardiac patients who had accepted (n=5) or declined (n=3) a CRP (all except 1 had MI)	
Methods	Semi-structured face-to-face interviews; interpretative phenomenological analysis	
Themes with findings: barriers	**Lack of understanding on the importance of CRP on recovery or what CRP entails**	Dismissing doctors' advice (e.g. to give up smoking); tended to ascribe condition to stress or family tendency not alterable factors; being independent, having to cope alone , dislike of asking for external help , frustration at loss of independence leading to lack of perceived need for CRP; poor understanding of programme (e.g. thinking it was for other people, not for them); thinking it was not needed if had family support.
	transport	Transport barriers.
	Comorbidities	Previous cardiac problems (felt they had sufficient knowledge on condition already) and/or comorbidities (e.g. prioritised spondylitis over cardiac condition).
Themes with findings: facilitators	**Desire to reduce risk of secondary MI**	Being able to do something to control the condition; able to identify causes of condition and appreciate importance of appropriate lifestyle control (smoking, diet, exercise).
	Desire to achieve goals	Determination to make a good recovery; self-motivated; complying with advice; attempting to control the condition; feel confident (although require support); learning how to cope.
	Support at home	Family support essential for returning to normal activities; positive endorsement form family or friends who had previously attended programme; practical support/transport from partners.
	Peer support	Being alone would have been a barrier to attending CRP; meeting others was important.
	Availability of specialist staff	Opportunity to receive expert advice.
	Health in the participant's own hands; self-efficacy	Expected CRP to increase confidence and offer reassurance; feeling able to negotiate about exercise levels at CRP.
Limitations	Examines decision to attend CRP but not all participants had actually attended.	

Table 32: Radley 1998[489]

Study	Radley 1998	
Aim	To compare the problems reported by women and men six months after MI.	
Population	60 women and 60 men six months after MI.	
Methods	Interview.	
Themes with findings: barriers	**Location/ transport/ mobility/ distance difficulties**	Public transport arrangements not suitable.
	Lack of information on where and when CRP is available/ referral issues	Women not offered the opportunity to attend.
	Uncomfortable exercising in a public gym/in a group	Woman did not like group arrangement (would have preferred one-to-one sessions); being the only woman in a group of mostly younger men made women self-conscious and hindered involvement
	Unhelpful comments from health professionals	doctor told one woman that attendance "wasn't necessary"
Themes with findings: facilitators	**Peer support**	having attended the CRP was a continuing source of support in the months after discharge
Limitations	Role of researcher not clearly described. Not "rich" data.	

Table 33: Rivett 2009[500]

Study	Rivett 2009	
Aim	to identify the reasons for withdrawal and stage of physical activity (PA) readiness in patients previously engaged in CRP.	
Population	101 withdrawn patients from community based CRP (Heart Watch).	
Methods	Telephone interviews (10 minutes each).	
Themes with findings: main reasons for withdrawal	**Lack of support at home**	Lack of female support.
	Ambience at CRP	Too crowded.

Study	Rivett 2009	
	Too costly	Too expensive.
	Time constraints	Lack of time.
	Location/ transport/ mobility/ distance difficulties	Lack of transport.
	Ambience at CRP	Lack of enjoyment.
	Unmotivated	Lack of motivation.
	Time constraints	Work demands.
	Time constraints	Family demands.
	Comorbidities	Injury or illness.
	Exercise not helpful/ inappropriate/ excessive/ unnecessary	Joined other facilities.
	Location/ transport/ mobility/ distance difficulties	Unhappy with city centre location.
Limitations	Significant proportion of potential participants (187/288) not contactable by telephone following introductory letter after 2 attempts, so results may not be representative of all patients who withdrew from programme.	

Table 34: Tolmie 2009[584]

Study	Tolmie 2009	
Aim	To examine the needs of older people in relation to cardiac rehabilitation and to determine if these were currently being met	
Population	31 older men and women (≥65 years) with MI in last 6 months with full, partial or non-attendance at CRP	
Methods	Mixed-methods: structured questionnaire; brief clinical assessment; in-depth interviews .	
Themes with findings: barriers	**Time constraints**	Desire to reduce time already being spent attending clinics/ appointments.
	Unmotivated	Classes had little time for social interaction; the leader turned on the music and left participants to it so little motivation to continue attendance.
	Lack of support at home	Comments from a family member who believed the person wasn't "at that stage" and "wouldn't gain anything".
	Not seen as beneficial	"I've only got one life and I...intend to use it as it suits me".
	Comorbidities	Physically restricting or socially embarrassing problems (e.g. arthritis, incontinence).
	Exercise not helpful/ inappropriate/	Belief that exercise regime was too strenuous / outwith the person's capabilities; day to day activities enough; severe pain or exhaustion during or after exercise session so too frightened to try again; low-level exercise programmes felt not

Study	Tolmie 2009	
	excessive/ unnecessary	to provide any more benefit than routine everyday activities; negative beliefs about ageing process and extent to which health/ quality of life could be improved; belief that surgery/drugs/ radiological interventions more effective than lifestyle change, and beyond these interventions, little could be done.
	Discontinued when participant felt no further benefit	Continued only until felt back to normal or no longer challenged by programme.
	Unhelpful comments from health professionals	Consultant who made the person feel "worthless"; member of CRP who told them they didn't think there was much they could do for the patient.
	No desire to extend lifespan	"Not really keen on staying too long...rather live a natural life than to ... linger on and become a burden to people...when it's done, it's done".
Themes with findings: facilitators	**Desire to achieve goals**	"Silly not to do it"; wanted "something to help me get back on my feet again"; essential part of recovery.
Limitations	Role of researcher not clearly described.	

G.3.2 Interventions to increase the uptake of and adherence to cardiac rehabilitation

Table 35: Beckie 2010 [49]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding
Author: Beckie TM, Beckstead JW **Journal:** Cardiopulm Rehabil Prev.	RCT	N=252	The inclusion criteria were: 1) women >21 years 2) diagnosed with a AMI, angina, or having undergone coronary artery	The gender-tailored exercise protocol was identical to that of the traditional CR program except that participants	The traditional CR program, nationally certified by the American Association of	12wk CRP	**Outcome 1:** Adherence >80% to exercise	**Intervention =** 123/141 **Control =** 74/111	**Funding: t**his study was sponsored by the National Institutes of Health grant 5 RO1 NR007678.

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding
2010 May-Jun;30(3):147-56. **Title:** Predicting cardiac rehabilitation attendance in a gender-tailored randomized clinical trial. Outpatient CR program in Southeastern United States between January 2004 and March 2008. .			bypass graft (CABG) surgery or percutaneous coronary intervention (PCI) within the last year; and 3) able to read, write, and speak English. The exclusion criteria were: 1) health insurance coverage for less than 36 ECG-monitored exercise sessions, 2) cognitive impairment, 3)inability to ambulate 4) insertion of an automatic internal cardiac defibrillator (AICD) in the last year.	exercised exclusively with women in their cohort and the time of the intervention was restricted to 1 time slot when the traditional CR facility was closed. The intervention, guided by the Transtheoretical Model (TTM) of behaviour change and delivered with a motivational interviewing (MI) counselling style was administered by female research nurses and EPs (Figure 2).	Cardiovascular and Pulmonary Rehabilitation (AACVPR), was delivered by female nurses and exercise physiologists (EP) using a case management model.				

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding
			With a mean age of 63 years (SD=12, range, 31-87 years) most women were Caucasian (82%), married (53%), retired (47%) with ≥high school education (92%). Seventeen percent were African American and 16% of Caucasians considered themselves Hispanic. The groups were not different at baseline on marital status, education, previous CR attendance, work status, race, risk factors or co-morbidities. Urine						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding
			cotinine levels ranged from 25-2500 ng/mL with a median of 25 ng/mL. The groups did not differ in baseline psychosocial variables (all with acceptable reliabilities; Table 1). All participants reported poor health perceptions on all SF-36 subscales compared to national norms for women experiencing a myocardial infarction within the past year60 particularly on the physical functioning, the role functioning-physical, and the vitality subscales.						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding
			Fifty one percent of the sample had CES-D scores of ≥16.						

Table 36: Carroll 2007 [94]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes (at 2 months post-discharge)	Source of funding
Author: Carroll DL, Rankin SH, Cooper BA. **Title:**The effects of a collaborative peer advisor/advanced practice nurse intervention: cardiac rehabilitation participation	RCT	N=247 N=195 final Drop out n=52 N=12 died N=34 withdrew 18.6% attrition rate	**Inclusion criteria** 5 academic centres of the USA. Diagnosis of MI or CABS; older than 65 yrs, unpartnered, were able to speak and read English, and had access to telephone.	**Community based collaborative peer advisor/advanced practice-nurse interevention** within 48 hours of discharge. Home visit within 72 hours and telephone calls at 2, 6 and 10 weeks from an advanced practice nurse and 12 weekly telephone calls	Pamphlet with information on the benefits and drawbacks of exercise	12 weeks intervention with 12 month follow-up	**Outcome 1:** Uptake 12 month	**Intervention:** 92/121 **Usual care:**46/126	They included a 12 month follow-up but only included the 12 week or 3 month data since this covered the duration of the CRP.

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes (at 2 months post-discharge)	Source of funding
and rehospitalization in older adults after a cardiac event. **Journal:** J Cardiovasc Nurs. 2007 Jul-Aug;22(4):313-9. Randomised: yes, but no details Allocation concealment: unclear Blinding: Unclear Power calculation: Based on previous study.				from a peer advisor.					

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes (at 2 months post-discharge)	Source of funding
Mending Hearts together 1 (R15 NR04255). A sample of 186 subjects was needed to detect a moderate effect size with p<0.05. An attrition rate of 25% was projected. Therefore a total of 232 subjects were estimated for recruitment of this study.									

Table 37: Cossette 2012 [125]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes (at 2 months post-discharge)	Source of funding Comments
TRANSIT-CCU trial **Author:** Sylvie Cossette, Nancy Frasure-Smith, Jocelyn Dupuis, Martin Juneau, and Marie Claude Guertin. **Title:** Randomized controlled trial of tailored nursing interventions to improve cardiac rehabilitation enrollment. **Journal:** Nurs.Res. 61 (2):111-120,	RCT	N=242 Lost to follow-up at the 3rd follow-up phone call (for secondary outcomes): C = 17 N=5 Analysis Inclusion All pts were included in analysis in the intervention group (N) and 85% of both groups participated in all 3 steps. primary outcome	In N=242 All= ACS pts admitted to a tertiary cardiac centre for suspected ACS Men n=207 Age = mean 59 yrs Smokers n=93 Hypertension n=149 Diabetes n=57 BMI ≥30) n=90/206 Education ≤high school n=115 Employed n=150	**Nursing intervention (N)** N=121 ITT = 121 ACA = 121 (for primary outcome) ACA = 116 (for secondary outcome) N: intervention had 3 parts – 1. face-to-face meeting before discharge; 2. Telephone call three days post-discharge; 3. final contact of telephone call or a hospital meeting 10 days post-discharge. A family member was invited to participate at any	**Usual care Control (C)** N=121 ITT = 121 ACA = 121 (for primary outcome) ACA = 104 (for secondary outcome) The regular nurse continued to provide their care until hospital discharge, researcher contact them 6 weeks after discharge for the end-of-study questionnaire. For questions after	6 weeks after hospital discharge	**Outcome 1** Adherence to medications (score ≥1) Did not include. They didn't measure adherence to CR	N= 13/91 C= 14/82	FRSQ, GRIISIQ and Montreal Heart Institute Foundation and Research Center. Canada. COMMENT: Powered study Single blind (nurses) Randomised by statistician at co-ordinating centre Allocation concealment: nurses given sealed opaque envelopes opened after each pt completed baseline questionnaire Pts informed of randomisation assignment
							Outcome 2 (primary) Enrollment in rehab program (attended at least 1 rehab session within 6 weeks of discharge)	N=45% =55/121 C= 25% = 29/121 Unadjusted OR 2.56 (95% CI 1.48, 4.43), p<0.001 Adjusted OR still p<0.01	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes (at 2 months post-discharge)	Source of funding Comments
2012. Country Canada Methods Baseline questionnaire completed in person before discharge by a researcher who was blinded to Tx assignment. Questionnaires used: Illness perceptions questionnaire; Pts perceptions of support by family (14-item Family care climate questionnaire – pt		(enrollment in rehab) all pts data included as had data showing who enrolled for rehab programs Baseline differences: C group had more men, fewer pts who lived alone, more obese pts and physically inactive. N group had more HT pts		time (but not mandatory). Goal of step 1 was to address pts and family's management of symptoms and physical activity after discharge, their understanding of the illness episode, and their concerns and worries. Focus of second step was patient's clinical condition and ability to manage the disease after discharge, and any other worries or concerns including risk factor modification. Focus of 3rd step was also clinical and treatment issues, as well as addressing risk factor and	discharged they were encouraged to contact regular healthcare resources (eg. telephone health hotline, their family physician or cardiologist, or emergency services). BOTH GROUPS: After hospital discharge, all pts in both groups were referred to rehab centre with a program including multifactorial and multidisciplinary				

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes (at 2 months post-discharge)	Source of funding Comments
version); anxiety; medication adherence (4-item Self-reported Medication-taking Scale – higher scores = better adherence); several other questionnaires				lifestyle modification, including rehabilitation enrollment. This meeting occurred mean of 10 days after discharge. Nurse also discussed patients' anticipated difficulties with risk factor modification to improve the perceived benefits and lower the barriers to entering rehabilitation.	interventions. Staff (blinded to group assignment) phoned all study pts to invite them to enroll and pts who accepted were scheduled for first appointment within 6 weeks after discharge. Pts in both groups were encouraged to call rehab centre themselves at any time to schedule an appointment.				

Table 38: DALAL[130]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author: Dalal HM, Evans PH, Campbell JL, Taylor RS, Watt A, Read KL, Mourant AJ, Wingham J, Thompson DR, Pereira Gray DJ. **Title:** Home-based versus hospital-based rehabilitation after myocardial infarction: A randomized trial with preference arms--Cornwall Heart Attack Rehabilitation Management Study (CHARMS).	RCT	N=91 Drop outs/early discontinuation. Hospital based = n=10 (4 died, 6 lost to follow-up) Home-based n=10 (1 died, 9 lost to follow-up)	Inclusion criteria: confirmed acute MI; ability to read English; registered GP in one of the two primary care centres Exclusion criteria Severe heart failure; unstable angina; uncontrolled arrhythmia; history of major psychiatric illness (including dementia); other significant comorbidity; patients readmitted with acute Mi who had already received an intervention in the study Baseline characteristics	Hospital based rehabilitation: classes once a week for 8-10 weeks. Patients were also encouraged to exercise at home	Home based rehabilitation: Patients were seen during their hospital admission by a CR nurse and issued with the Heart Manual to use over 6 consecutive weeks. A CR nurse made a home visit in the first week and followed up by a telephone call over 6 weeks.	8-10 weeks	Outcome 1 Adherence (author defined satisfactory adherence)	Hospital = 38/51 (75%) Home based = 29/40 (73%)	**Source of funding:** NHS Executive South West Project grant. Limitations: no details of what is satisfactory adherence. No details on uptake

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Journal: Int J Cardiol. 2007 Jul 10;119(2):202-11 . **Country:** UK **Randomisation:** Yes, simple randomistaion Allocation Concealment: Unclear **Blinding:** No Power Calculations: Based on hospital Anxiety Depression scale score used in pilot			Hospital based Age 64.3 (11.2) Men 80% In employment 26% HAD Score Anxiety 3.83% HAD Score Depression 2.25% Previous MI 15% Angina 21% Diabetes 11% Home-based Age 60.6 (10.1) Men 82% In employment 51% HAD Score Anxiety 4.39% HAD Score Depression 3.41% Previous MI 12% Angina 15% Diabetes 18%						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
study. They estimated they need 104 patients in each arm. This would provide 95% power with two-sided significance of 0.05 to detect a difference of 0.5 SD. With the numbers achieved, they were able to detect a difference of over 2 points (0.56SD) with 80% power and p=0.05 which is still clinically significant.									

Table 39: Daltroy 1985[132]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes (at 2 months post-discharge)	Source of funding Comments
Authors: L. H. Daltroy. **Title:** Improving cardiac patient adherence to exercise regimens: a clinical trial of health education. **Journal:**J.Card.Rehab. 5:40-49, 1985. Country USA – 6 sites Methods Drop-out defined as: person who misses 18 sessions regardless of	RCT	N=174 Drop outs: Half the patients had stopped coming to the exercise programs by the 12week.	In N=174 All= patients with CHD (history of MI, angina, CABG) who joined a site supervised cardiac exercise program and had not been in one previously. Men 88% Age = mean 54 yrs Education at least 1 year college= 59% Race: 95% White Employed 71% White collar (current/previous) 75% Current smoker 14%	**Educational intervention (E)** N=84 ITT = 84 ACA Aim to improve pts attendance at 6 cardiac exercise programs during 1st 3 months by supplementing the existing educational efforts for pts and family members. Pts filled out a baseline questionnaire and the received a telephone persuasive communication in	**Pamphlet alone (P)** N=90 ITT = 90 ACA Pts received the mailed pamphlet after the baseline questionnaire was returned (same pamphlet as for the educational group). Spouse of pts received only the written persuasive communication (as per the	1 year	**Outcome 1** Attendance	**3 months:** NS diff between groups for % of sessions attendance (p=0.7; E=63.8%, SD 27.24 sessions, P=62.2%, SD 28.17 sessions) After controlling for baseline variables, exposure to educational intervention accounted for 11.7% increase in attendance. Experimental intervention more effective for pts with high school education or less than for pts with at least 1 year of college (regression	**Funding:** Grant from NIH or and Maryland Affiliate of the American Heart Association, USA. COMMENT: Randomisation: stratified by site and current cigarette smoking status Blinding: single blind (nurse/data collector for attendance outcomes) Powered study No other details of RoB elements mentioned

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes (at 2 months post-discharge)	Source of funding Comments
subsequent attendance Attendance recorded, and questionnaires sent to collect data on home exercise Primary outcome: % of sessions attended over 3 months in the program (ie. the first 36 sessions offered for the patient regardless of calendar time.			Weight = 178 lbs NS difference between groups for baseline characteristics	a scripted counselling format designed to convince them of benefits of regular exercise in the program, warn them of likely drawbacks so their experience was more realistic, acquaint them with methods used by other pts to cope with the drawbacks so that they might be able to use the methods themselves, and elicit an oral commitment to the interviewer that they would attend at least 2 classes/wk in the 1st 6 wks. In addition, each received a mailed, written persuasive	education group)			analysis).	
							Outcome 2: Drop-outs	Varied over time; exact numbers not given (but data in a graph) Study site was the only variable SS associated with time until drop-out. Half the pts had stopped coming to exercise programs by the 12th week There was NS difference between the 2 groups for the length of time pts exercised at the sites before they dropped out (p=0.05)	
							Outcome 3 Spousal support	77% pts had spouses who participated (75.6% E, 78.6% P)	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes (at 2 months post-discharge)	Source of funding Comments
				communication that reinforced these points. Telephone counselling for the pts spouses was similar to that of the pts, and they also received a written persuasive communication.				Pts with spouses (n=134) attended SS better than pts without spouses (n=31); mean attendance 66.4% vs 41.8%. Pt spousal support was most important to pt attendance than pt perceived spousal support) However there was NS difference between the E and P groups in behavioural support given by spouses (despite spouses having more education in the E group – E=36% vs P=35% spouses accompanied pts to exercise classes; and	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes (at 2 months post-discharge)	Source of funding Comments
								E=60% vs P=59% spouses gave oral encouragement)	
							Outcome 4 Attendance in relation to baseline variables	Spouse oral encouragement was only factor (other factors were spouse came to sessions and group or staff influence) that made a SS difference in good attendance vs poor attendance	
							Outcome 5 Exercise performed at home (during 11th month of study)	Most had dropped out of supervised programs by this time N=160 responded; 78% reported doing at least some exercise on their own; Of all pts who started in months 1-5, only 31% were exercising at least 15 mins 3 or	data from 1 site suggested that a planned graduation of exercise (every 3 months) may encourage higher initial attendance while not lessening the amount of exercise achieved at home, compared with pts from sites without a planned

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes (at 2 months post-discharge)	Source of funding Comments
								more times/week with heart rate in the training zone.	graduation policy.

Table 40: Grace 2011[240]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding/Comments
Authors: Sherry L. Grace, PhD; Kelly L. Russell, MSc; Robert D. Reid, PhD, MBA; Paul Oh, MD, FRCPC; Sonia Anand, MD, PhD, FRCPC; James Rush, PhD; Karen Williamson, PhD; Milan Gupta, MD; David A. Alter, MD,	Prospective cohort	N=1809	**Inclusion criteria** A total of 2635 stable cardiac inpatients were recruited. Inclusion criteria were a confirmed diagnosis of acute coronary syndrome diagnosis, having undergone percutaneous coronary intervention (PCI) or CABG, having a concomitant diagnosis of	Referral strategy Liaison only = 490 Automatic only =551 Combined n=471 Liaison = the referral is facilitated through a personal discussion with a health care professional (i.e. nurse or physiotherapist) and or/peer graduate (at the bedside or in some cases by	**Usual** N=297 Usual referral =at the discretion of health care providers.	1 yr	**Outcome 1** Uptake	Usual = 83/297 (29%) Liaison = 239/490 (51%) Automatic = 321 /551 (61%) Combined = 335/471 (74%)	The CRCARE study was funded by the Canadian Institutes of Health Research (CIHR) Institute of Gender and Health and the Heart and Stroke Foundation of Canada grant HOA-80676. Dr Grace is supported by the CIHR Institute of Health Services and Policy Research New
							Outcome 2 Mean attendance of those referred	Usual =247/297 83.4% Liaison =408/490 83.2% Automatic =460/551 83.6% Combined = 385/471 81.9%	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding/Comments
PhD, FRCPC; Donna E. Stewart, MD, FRCPC; for the Cardiac Rehabilitation Care Continuity Through Automatic Referral Evaluation (CRCARE) Investigators **Title:** A Prospective, Controlled Study **Journal:** ARCH INTERN MED/VOL 171 (NO. 3), FEB 14, 2011 Country Canada			heart failure or arrhythmia, eligibility for CR based on guidelines of the Canadian Association of Cardiac Rehabilitation,20 and proficiency in English, French, or Punjabi Exclusion criteria had participated in CR within the past 2 years or had a clinically significant orthopedic (ie, total joint replacement), neuromuscular (ie, Parkinson disease), visual (ie, blindness), cognitive (eg, debilitating stroke,	telephone shortly after discharge) Automatic only referral using electronic patient records or standard discharge orders as a systematic prompt before hospital discharge					Investigator Award, MSH-80489. Role of the Sponsors: The funding sources played no role in the design and conduct of the study; in the collection, management, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript. The researchers were independent from the funders.

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding/Comments
			dementia), or nondysphoric psychiatric condition (eg, schizophrenia) documented in their medical chart that precluded CR participation. Usual,16.4%(n=297) Liaison Only,27.1%(n=490) Automatic Only,30.5%(n=551) Combined Automatic and Liaison, 26.0%(n=471) Same order as above Sociodemographic Age, mean (SD), y 64.0 (10.9) 66.7 (11.0)						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding/Comments
			65.6 (10.1) 64.7 (9.7) Female sex 88 (29.6) 148 (30.2) 119 (21.6) 97 (20.6) White ethnocultural background 237 (83.5) 362 (76.1) 453 (86.0) 394 (88.3) Married 223 (75.9) 354 (74.1) 443 (80.7) 372 (79.3) Some postsecondary education 227 (76.9) 349 (76.5) 405 (74.4) 331 (72.3) Retired 133 (46.8)						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding/Comments
			264 (55.8) 280 (53.0) 228 (50.1) Family income _CaD $50 000 125 (49.6) 184 (45.8) 216 (49.1) 205 (56.2) Rural living 58 (19.5) 91 (18.6) 85 (15.4) 79 (16.8) Clinical Cardiac condition/procedured PCI 270 (90.9) 80 (16.6) 180 (32.8) 72 (15.3) CABG 8 (2.7) 194 (40.3) 199 (36.2) 342 (72.6)					

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding/Comments
			Heart failure 15 (5.1) 72 (15.0) 81 (14.8) 26 (5.5) Arrhythmia 14 (4.7) 81 (16.8) 71 (12.9) 57 (12.1) Valve repair/replacement 7 (2.4) 30 (6.3) 58 (10.6) 58 (12.3) Diabetes mellitus 82 (31.3) 151 (37.0) 154 (29.8) 130 (28.4) BMI, mean (SD) 28.9 (4.9) 28.2 (5.3) 29.9 (6.5) 29.2 (5.0) Hypertension						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding/Comments
			218 (79.3) 329 (76.3) 353 (69.6) 339 (73.9) Smoker 24 (8.4) 28 (5.9) 39 (7.4) 20 (4.4) Comorbidities present 184 (65.9) 290 (67.3) 317 (66.6) 323 (70.8)						

Table 41: Grace 2007 [241]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding
Author: Grace SL, Scholey P, Suskin N, Arthur HM, Brooks D, Jaglal S,	Observational - Prospective	N=661	Consecutive patients with ACS were recruited on relevant cardiovascular units by a	The automatic referral model implemented at this centre uses hospital electronic	This involves referral to CR at the discretion of the cardiologist,	9 months	**Outcome 1** Uptake	Int = 118/241 C =96/265	This study was funded by Canadian Health Services Research Foundation
							Outcome 2 Adherence	Int = 109/241 C =90/265	
							Outcome 3	Lack of referral n=59; too distant	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding
Abramson BL, Stewart DE. **Title:** A prospective comparison of cardiac rehabilitation enrollment following automatic vs usual referral. **Journal:** J Rehabil Med. 2007 Apr;39(3):239-45. Country CANADA			research assistant when medically stable. Inclusion criteria were diagnosis with a confirmed myocardial infarction (MI), unstable angina (UA), ischemic congestive heart failure (CHF), percutaneous coronary intervention (PCI), or acute coronary bypass (ACB), and at least 18 years of age. Exclusion criteria included being medically unstable, too confused to participate, previous participation	patient records to prompt the standard order for a CR referral for all eligible patients with cardiac diseases This discharge order is initiated on the inpatient ward and printed on a hospital network printer in the CR center and again screened for eligibility. An information package, including a personalized letter stating the name of the referring physician, a program brochure, a	cardiovascular surgeon, general practitioner, or other healthcare provider through paper-based means.		Reasons for withdrawal or non-participation	or inconvenient n=13; health or mobility issues n=13; did not know about CR n=11; conflicts with employment n=7. Others: not knowing why, not being interested, indirect costs, not capacity for new patients; physicians saying they did not need CR.	and Ontario Ministry of Health and Long-Term Care, and administered by the Canadian Institutes of Health Research FRN# 73996. Dr Grace is supported by the Ontario Ministry of Health and Long-Term Care.

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding
			in CR, being ineligible for CR based on CACR guidelines due to musculoskeletal, vision, psychiatric, or other co-morbidities, or being unable to read or speak English. Those who met study criteria and agreed to participate signed a consent form and were provided with a self-report questionnaire. Consent was also obtained to link participant's self-report questionnaire data with their clinical data.	schedule of classes, and a request that the patient telephone to book an appointment, is mailed to the patient's home. Patients who live outside of the geographic area are also sent a similar package, but they are provided with the contact information of the site closest to their home. This alternate site is also sent the patient's contact information.					

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding
			Characteristic UHN Usual (n = 330) THC Automatic (n = 331) In order as above PCI, n (%) 251 (76.1) 154 (46.5) Males, n (%) 251 (76.1) 253 (76.4) Ethnocultural background: white, n (%) 247 (82.6) 262 (81.1) Marital status: married, n (%) 246 (74.5) 257 (77.6) Retired 118 (35.8) 140 (42.6) Education: some postgraduate, n (%) 177 (53.6)						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding
			163 (50.6) Family income: ≥ $50 000 CADa, n (%) 142 (56.3) 157 (53.2) NYHA Class 1, n (%) 258 (86.9) 298 (90.9) Age, mean (SD) (years) 60.65 (10.6) 61.78 (11.91)						

Table 42: Grace 2012[242]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes (at 2 months post-discharge)	Source of funding Comments
Author: Grace SL, Angevaare KL, Reid RD, Oh P, Anand S, Gupta M, Brister S, Stewart DE;	Observational study - prospective	N=2635 Follow-up: N=1809 Drop outs: 826 (31%)	**Inclusion** confirmed acute coronary syndrome diagnosis, patients who had undergone percutaneous	Pre-approved clinical practice guidelines promote CR referral as the standard of care, some cardiac wards have	Control Each strategy was tested individually in comparison to patients who were not exposed to	One year	**Outcome 1** Uptake	Pre-approved =735/1172 (62.7%) Control = 243/637 (38.1%) Pre-booked = 324/478 (67.8%)	The CRCARE study was funded by the Canadian Institutes of Health Research (IGH and ICRH) and The Heart and Stroke Foundation

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes (at 2 months post-discharge)	Source of funding Comments
CRCARE Investigators **Title:** Effectiveness of inpatient and outpatient strategies in increasing referral and utilization of cardiac rehabilitation: a prospective, multi-site study. **Journal** Implement Sci. 2012 Dec 13;7:120 Country CANADA		Analysis ACA	coronary intervention (PCI) or coronary artery bypass graft surgery (CABG), patients with a concomitant diagnosis of heart failure, eligibility for CR based on guidelines of the Canadian Association of Cardiac Rehabilitation, and proficiency in English, French, or Punjabi (surveys were translated into each of these languages). Diagnosis of acute coronary syndrome was confirmed through patient chart review of detailed history, focused physical examination,	standing orders in place so that nurses, allied healthcare professionals, and ward clerks can facilitate referral form completion and submission for indicated patients as pre-approved by the cardiac program leadership. The forms would be specific to the CR program to which patients are referred. There is no requirement for patients for this process to occur, however it is assumed that verbal consent is secured. This process is perceived to overcome referral failure because there is no time demand for	that specific strategy, because they were not mutually exclusive735.			Control = 654/1331 (49.1%) Pre-education = 159/198 (80.3%) Control = 819/1611 (50.8%)	of Canada Grant # HOA-80676. Dr. Grace is supported by CIHR New Investigator Award #MSH-80489. COMMENT: This is a re-analysis of a previous group of patients presented in study by GRACE et al 2007
							Outcome 2 Attendance (mean)	Pre-approved =82.7% Control = 84.3% Pre-booked = 80.6% Control = 84.4% Pre-education = 80.4% Control = 83.6%	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes (at 2 months post-discharge)	Source of funding Comments
			diagnostic ECG changes, and/or troponin levels above the 99th percentile of normal. Excluded if they had participated in CR within the past two years, or had a significant orthopedic, neuromuscular, visual, cognitive, or non-dysphoric psychiatric condition that precluded CR participation. Patient characteristics Total Sample n=1809 Age: 65.4 (10.9) Gender: F25% White: 83% Married: 77.8%	physicians Pre-booked inpatients are provided with a CR intake appointment prior to discharge. This would be done routinely for all patients providing verbal consent. Early education: outpatient strategy, here CR programs arranged interprofessional education sessions for outpatients shortly after referral, but before commencing the CR program. These patient education sessions generally					

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes (at 2 months post-discharge)	Source of funding Comments
			Secondary education or greater: 74.8% Retired: 52% Family income>$50K CAD = 50% Rural living = 17.3% Cardiac condition/clinical procedure: MI 28% PCI 33.5% CABG 41.3% HF 10.8% Arrhythmia: 12.4% Valve repair/replacement: 8.5% Comorbidities: 67.8%	conveyed information regarding cardiac risk factors and their reduction, cardiac medications, the nature of the CR program, and answering any questions patients may have. While this is not a referral strategy per se, more patients may ultimately enrol in CR if they learned about the CR program at a time when they are more motivated from their recent cardiac episode and discharge.					

Table 43: Hansen 2009[256]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes (at 2 months post-discharge)	Source of funding Comments
Author:D Hansen, J Berger, P Dendale, R De Rybel, and R Meeusen. **Title:**Training adherence in early cardiac rehabilitation: EFFECT OF EXERCISE SESSION DURATION. **Journal:** J Cardiopulm Rehabil Prev. 2009 May-Jun;29(3):179-82. Country Belgium Methods Training adherence evaluated at	RCT	N=417 Drop outs: 7 weeks: n=83 (19.9%)	In N=417 All= CAD patients referred to the coronary revascularisation unit Men n=156 Age = mean 63 yrs BMI 26.7 NS difference between baseline characteristics	40-min exercise sessions (40) N=198 ITT = 198 ACA = 68 Aerobic exercise intervention: exercise training intervention included only endurance training (no strength training exercises were performed). Exercise was under close supervision 3 days/ week for 7 weeks, at 65% of the maximal oxygen uptake capacity. Exercise sessions had equal time distribution in	60-min exercise sessions (60) N=219 ITT = 219 ACA = 81 In both groups: when musculoskeletal discomfort or pain appeared throughout the intervention, the type of exercise was changed so that these exercises could be executed without symptoms. However, exercise	7 weeks of exercise	**Outcome 1** Adherence reasons	CABG pts adhered significantly more to exercise than PCI pts (91.4% vs 80.7%, OR4.7, 95% CI 1.6-14.4, p<0.01) Acute MI pts adhered significantly more to exercise than chronic CAD pts (86.8% vs 81.0%, OR2.1, 95% CI -1.1 to -3.8, p<0.5) Short: 160/198 Long: 185/219	Research grant from Hartcentrum Hasselt vzw COMMENT: No details given of randomisation, blinding, power or other Risk of bias elements.
							Outcome 2: Drop-outs/adherence	Medical reasons: 40 =3% 60=14.4% p>0.05 Non-medical reasons: 40=16.6% 60=16.0% p>0.05	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes (at 2 months post-discharge)	Source of funding Comments
the end of the 6th week of exercise training (≥18 exercise sessions). Dropouts definition: Pts who did not complete 7 wks of training because of nonmedical or medical reasons, or exercised on average less than 2 sessions/week				each session on the different exercise modalities: 42% treadmill, 33% bike, and 25% arm cranking device).	intensity, frequency and duration of the exercise sessions remained constant.		**Outcome 3** Reasons for drop-out	Medical reasons: 40 =15.4% 60=20.2% Non-medical reasons- main reason lack of motivation: 40=41% 60=38.6%	

Table 44: Jolly 2009 [296]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes (at 2 months post-discharge)	Source of funding Comments
Author:K. Jolly, G. Y. H.	RCT	N=525	In N=525	**Home-based rehab (H)**	**Centre-based rehab (C)**	6 months	**Outcome 1** Reasons for	6 months: Died: H=3, C=2	Grant from NHS and DoH, UK

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes (at 2 months post-discharge)	Source of funding Comments
Lip, R. S. Taylor, J. Raftery, J. Mant, D. Lane, S. Greenfield, and Stevens. **Title:**The Birmingham rehabilitation uptake maximisation study (BRUM): a randomised controlled trial comparing home-based with centre-based cardiac rehabilitation. **Journal:**Heart 95 (1):36-42, 2009. Country UK		Drop outs: 6 months n=17 (H), n=23 (C) 12 months (cumulative) n=24 (H), n=26 (C)	All= patients who were referred to the cardiac rehab program (CRP) in 1 of 4 hospitals, following an MI, PTCA or CABG within the previous 12 weeks and not considered to be high risk for a home-based exercise program. Men n=402 Age = mean 61 yrs Education mean= 14 years Race: n=418 White, n=89 Asian, n=17 other In paid employment n=220 Current smoker n=179 SBP mean = 124	N=263 ITT = 263 ACA (6 mths)=246 ACA (12 mths)=239 In both groups: programs included exercise, relaxation, education and lifestyle counselling. Home-based program consisted of a manual, 3 home visits (at 10 days, 6 weeks and 12 weeks) and telephone contact at 3 weeks. Pts who had MI or revascularisation were discharged with the Heart manual or an	N=262 ITT = 262 ACA (6 mths)=239 ACA (12 mths)=236 Centre-based programs varied in length including 9 sessions at weekly intervals, 12 sessions over 8 weeks and 24 individualised sessions over 12 weeks. Programs commenced between 4 and 8 weeks following the cardiac event. Pts exercised	and 1 year	drop-out	Withdrew: H=3, C=3 Not attend follow-up: H=11, C=18 12 months (not cumulative): Died: H=0, C=1 Withdrew: H=4, C=0 Not attend follow-up: H=14, C=20	COMMENT: ITT analysis performed (missing data substituted with a predicated outcome value) Randomisation: individual pt randomisation by an independent CTU using computerised program and minimising for age, ethnicity, initial diagnosis and hospital of recruitment. Blinding: single blind (nurse/data collector) Powered study
							Outcome 2: Adherence to rehab program (≥ 3 sessions of ≥15mins physical activity in previous 7 days)	6 weeks H: 95.2% C: 85.1% p=0.01 12 weeks H: 90.1% 236/263 C: 93.4% 245/262 p=0.3 (NS)	
							Outcome 3 Adherence to rehab program (attendance at rehab sessions)	C: 66% of sessions attended; n=73 (28%) did not attend any sessions H: mean 4.8 (SD 1.5) home	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes (at 2 months post-discharge)	Source of funding Comments
Methods Adherence to cardiac rehab was confined to the physical activity component; data collected by questionnaires at 6, 9 and 12 weeks after recruitment asking about intensity and duration of physical activity undertaken the previous 7 days. Nurse blinded to randomised groups. Clinical outcomes			mmHg BMI mean = 28 NS difference between groups for baseline characteristics	adapted version (manual encourages gradual exercise to achieve minimum 15 mins of moderately intense exercise). Additional visits were made as deemed necessary by the rehab nurse (nurses delivering home program were trained for 2 days).	to 65-75% of their predicted maximal heart rate and the exercise element of the program lasted from 25-40 mins plus warm-up and cool-down times.			contacts. Contacts with rehab nurse (visit or telephone) n=241 (96.1%) received 5 contacts; in C group, only n=147 (56.1%) attended this number of classes	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes (at 2 months post-discharge)	Source of funding Comments
assessed by blinded nurse at a hospital site at 6 and 12 months.									

Table 45: Jolly 1999 [295]

Reference	Study quality	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding/ Comments
Author: Jolly K, Bradley F, Sharp S, Smith H, Thompson S, Kinmonth AL, Mant D. **Title:**Randomised controlled	RCT - stratified	N=597 Analysis = ITT but excluded deaths. Inclusion criteria All 723 patients admitted to	**Characteristics** Control (n=320) Intervention (n=277) Age (years) C= 64 (10) I = 63 (10) No (%) of men C = 237 (74) I = 189 (68) No (%) of	N=321 MI = 191 Angina =71 Follow up care for patients, particularly the transfer of responsibility for care between hospital and general practice at the time of	N=277 MI = 198 Angina=99	1 month, 4 months, and 1 year after recruitment.	**Outcome 1** Uptake	**Total** Int= 109/262 (42%) C = 70 /297 (24%) MI Int = 79/191 (41%) C = 60/198 (30%)	The study was funded by a research and development national program grant from the NHS Executive, with service support from Southampton and South West Hampshire
							Outcome 2 Lost to follow-	**Total** Int= 27/277	

Reference	Study quality	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding/ Comments
trial of follow up care in general practice of patients with myocardial infarction and angina: final results of the Southampto n heart integrated care project (SHIP). The SHIP Collaborative Group. **Journal:**BMJ. 1999 Mar 13;318(7185) :706-11. Country: UK Methods Randomised controlled		hospitals in the district who had survived a first or subsequent myocardial infarction and all patients with angina of recent onset (less than 3 months) who had been seen in a direct access chest pain clinic or admitted were systematical ly identified over a period of 18 months and considered for inclusion in the trial.	smokers* C = 87 (27) I =89 (32) Serum total cholesterol (mmol/l) C = 6.1 (1.3) I =6.1 (1.3) Systolic blood pressure (mm Hg) C = 129 (21) I = 128 (19) Diastolic blood pressure (mm Hg) I =81 (14) C = 81 (13) Body mass index (kg/m2) I= 28 (3.7) C =27 (4.2)	discharge and the support of practice nurses. A liaison nurse telephoned the practice (speaking to the practice nurse if possible) shortly before patients were to be discharged to discuss the care of each patient and to book the first follow up visit to the practice. Practice nurses were encouraged to telephone back to discuss problems or to seek advice on clinical or organisational issues. Evidence based guidance on clinical management was attached to each discharge communication, which was given			up (excluding deaths Int=15, C=23)	(10%) C = 30 /320 (9%) MI Int = 21/204 (10%) C = 20/218 (9%)	Health Authority. Rose Wiles was in receipt of a NHS South and West Region research and development research training fellowship
							Outcome 3 Reasons for withdrawal	Total population. No details /gp Five patients were too ill or dying, 23 refused, and 29 were uncontactable.	
							Mean number of sessions attended by tvs. usual referral effect as usual referral by hosptial n was at increaeing adherence. 264264264264		

Reference	Study quality	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding/ Comments
trial; stratified random allocation of practices to intervention and control groups. Randomisation: 597 adult patients (422 with myocardial infarction and 175 with a new diagnosis of angina) were recruited during hospital admission or attendance at a chest pain clinic between April 1995 and September		The baseline characteristics of the 95 subjects who died or who were lost to follow up at 1 year were similar at baseline to those of the subjects who were followed up.		to each patient (or relative) to give to the general practitioner. Each patient was also given a patient held record, which prompted and guided follow up at standard intervals. The liaison nurses did not provide individual clinical care after discharge but provided support to practice staff both by telephone and by visiting each practice every 3–6 months. They also encouraged practice nurses to attend both initial training on behavioural change and an ongoing support group to tackle their information					

Reference	Study quality	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding/ Comments
1996. Power The power of the study to detect clinically important differences at a 5% significance level was anticipated to be reasonably high for continuous variables (about 95% for a difference of 0.35 mmol/l in blood total cholesterol concentratio n and of 40 m in the distance walked); it was less for dichotomous				needs as they arose.					

Table 46: Miller 1988[390]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes (at 2 months post-discharge)	Source of funding Comments
Author: Shirley M. Moore, Jacqueline M. Charvat, Nahida H. Gordon, Fredric Pashkow, Paul Ribisl, Beverly L. Roberts, and Michael Rocco. **Title:**Effects of a CHANGE intervention to increase exercise maintenance following cardiac events. **Journal:**Ann. Behav.Med. 31 (1):53-62, 2006. Country	RCT	N=259 (actually randomised) Drop outs: End of CRP: n=9 End of 1 year (cumulative): n=39 (the extra n=30 dropouts were included in the analysis because sufficient data was available for the analysis) NS differences between groups for number of	In N=250 (final sample) All= patients who recently had a cardiac event (MI, CABG and/or angioplasty) recruited at the end of their cardiac rehabilitation program Men n=155 Age = mean 63 yrs Education mean 14 years Race: n=203 Caucasian, n=42 African American, n=5 other NS difference between baseline characteristics	CHANGE intervention – exercise + usual care (Ex) N=?? ITT = ?? ACA =119 Usual care + CHANGE intervention. CHANGE was 5 small-group (6-8 people) counselling and behaviour modification sessions for pts attending a CRP in which they are taught self-efficacy enhancement, problem solving skills, and relapse prevention strategies to	Usual care only (C) ACA =131 Usual care: routine care provided at the CRP. In both groups: all pts received the usual CRP-prescribed structured exercise and individual group classes (4) on diet modification and stress reduction that are part of routine care at the CRPs. At the end of the CRP, all individuals	1 year exercise data collection	**Outcome 1** Discontinue exercise in 1 year post CRP	HR 1.76 (95% CI 1.07-2.86), p=0.02 – usual care group most likely to discontinue Men, non-hispanic caucasians, those with higher motivation were less likely to discontinue exercise. Higher comorbidity scores and more muscle and joint pain were more likely to discontinue exercise	Research grant from National Institute of Nursing Research at the NIH, USA LIMITATIONS Full randomised population unclear in both groups COMMENT: Pts recruited by research nurse during the 6th-8th weeks of the CRP. ITT analysis performed Randomisation using computerised randomisation stratification program managed by the project director in which pts were stratified
							Outcome 2: Adherence/compliance (met the exercise guideline)	1month Met the number of hours required: Ex:52/119 43.8% C: 45/131 34.4% 12 months Met	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes (at 2 months post-discharge)	Source of funding Comments
USA Methods Missing data defined as: pts who failed to return the exercise monitor recording or diary after repeated reminder calls. Data collected by telephoen calls at month 2 and month 12 as well as using wristwatch monitors for exercise intensity, activity diary, adherence and self-efficacy		dropouts		address their identified exercise maintenance problems. CHANGE base on cognitive-behavioural theoretical frameworks. Once a week pts were given 3 half-hour sessions during the last 3 weeks of the CRP and 2 sessions held at 1 and 2 months following completion of the CRP. Sessions taught by an experienced cardiac nurse. During the 10th – 12th weeks of the CRP and at 1 and 2 months after CRP, pts received the CHANGE intervention in	were given an exercise prescription that included their THR and counselled to exercise at least 5 times/week for 30 mins			the number of hours required: Ex: 28.8% C: 26.7% Met the number of sessions required: Ex: 7.5% C: 8.1%	on gender and site of recruitment. Allocation: randomisation sequence was concealed until the intervention was assigned Blinding: single blind (data collectors) Powered study (for regression analysis)
							Outcome 2 Reasons for drop-out	Withdrawals from study were older, less fit, had greater muscle and joint pain that limited movement, and reported less self-efficacy for overcoming barriers to exercise at baseline than those who did not withdraw from the study.	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes (at 2 months post-discharge)	Source of funding Comments
questionnaire (8 items assessing pts confidence to continue participating in exercise 3/week for 40 mins or more at moderate intensity for increasingly greater numbers of weeks) and other questionnaires/tests.				addition to the routine education program offered at the CRP.					

Table 47: Oldridge 1983[440]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes (at 2 months post-discharge)	Source of funding Comments
Authors:N. B. Oldridge and N. L. Jones. **Title:**	RCT	N=120 Drop outs: 6 months	In N=120 All= CHD patients	**Experimental(Ex)** N=63 ITT = 63	**Control (C)** N=57 ITT = 57	6 months	**Outcome 1** Compliance (see definition)	C= 42% (/n=63) Ex= 54% (/n=63) NS difference	Not mentioned COMMENT: No

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes (at 2 months post-discharge)	Source of funding Comments
Improving patient compliance in cardiac exercise rehabilitation. **Journal:** J.Card.Rehab. 3:257-262, 1983. Country Canada Methods Tests given and analysis of diaries		n=62 (51.7%) Analysis / definitions Compliance: had to attend >60% of the 48 scheduled supervised sessions. Drop-out: non-attendance at 8 consecutive sessions	Men and women: not given Age = mean 50.8 years Weight mean 81.3 kg SBP mean 129 mmHg Smokers n=27% Non-smokers n=73% Country of origin: Canada 50%, 17% not specified. Education post-high school: 49%, 17% not specified Employed 62% 17% not specified White collar 58% Blue collar 42%	ACA: unclear – only % given of drop-outs As for control group with additional self-management techniques for 6 months: diary for heart rates, recall questionnaires of daily activities (6 questionnaires given over the time period), weight loss diary for those agreed to lose weight, smoking diary for those wanting to stop smoking.	ACA: unclear - only % given of drop-outs Regular 6 month rehab service program with reassessment at 3 and 6 months. Twice/week attendance at supervised exercise sessions, and participants also had to exercise at least 3 additional times/week. Group discussions frequently held also, educational lecture series given every 2 weeks and additional			(p>0.10 and <0.20)	details given f randomisation, blinding, power or other Risk of bias elements. COMMENT: high drop-out rate (see definition of drop-outs)
							Outcome 2 Reasons for withdrawal	In experimental group 15/63 would not sign agreement to comply for the 6 month program. More likely to drop-out were: blue collar work, smoking at entry and inactive leisure habits. Age was signif lower in drop-outs than compliers	
							Outcome 3 Attendance of compliers	C= 74% Ex= 76%	
							Outcome 4 Attendance of dropouts	C= 21% Ex= 16%	
							Outcome 5 Compliance of those agreed to participate in Ex group vs control group	Ex= 65% total n=48 (63-15) since 15 would not sign the agreement form to comply for the 6m period.	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes (at 2 months post-discharge)	Source of funding Comments
					counselling given as needed.			C= 42% p<0.01	
							Outcome 6 Compliance with self-monitoring / recording submaximal heart rate response	31/48 (65%) 24/31 (77%) completed 5 of 6 possible tests.	
							Outcome 7 Compliance with daily physical activity logs (5 or 6)	16/31 (52%)	
							Outcome 8 Compliance with weight loss and smoking cessation diariesty logs	Weight: 2/5 Smoking: 1/10	

Table 48: Pack 2013[447]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding
Author: Pack QR, Mansour M, Barboza JS, Hibner BA, Mahan MG, Ehrman JK, Vanzant MA, Schairer JR, Keteyian SJ. **Title:**An early appointment to outpatient cardiac rehabilitation at hospital discharge improves attendance at orientation: a randomized, single-blind, controlled trial.	RCT	148	**Inclusion criteria** Inpatients at Henry Ford Hospital in Detroit, MI, were recruited to participate between February and November 2011, with follow-up occurring through May 2012. Patients were eligible to participate if they had a qualifying diagnosis for referral to CR, were >18 years of age, granted access to their medical record for research, and gave written informed consent.	Early, within 10 days, appointment for the CR orientation class	Standard-of-care, 35 days, appointment for the CR orientation class. Patients in the standard care were not forbidden from attending an earlier orientation class. Although they were given an official 5-week appointment.	End of CRP.	**Outcome 1** Uptake (to orientation class)	Early: 55/74 (77%) Standard: 44/74 (59%)	Dept of Graduate medical Education at Henry Ford Hospital
							Outcome 2 Completion to CRP (meeting pre-specified number or ≥12 sessions)	Early: 27/74 (36%) Standard: 22/74 (30%)	
							Outcome 3 Actual time from discharge to orientation	Early: 8.5 days (7-13) Standard: 42 days (35 to NA)	
							Outcome 4 Reasons for withdrawal	Reasons for not attending orientation: Early n=17, Standard n=30 Lost contact/unknown: E=11 S=19. Financial/insurance barrier: E=0 S=1. Need to return to work: E=0. S=2. Transportation obstacles:E=2 S=3.	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding
Author: Circulation. 2013 Jan 22;127(3):349-55 **Randomisation:** Yes, but no details **Allocation concealment: Unclear** **Blinding:** Yes. Patients were told a survey was the purpose of the study. **Power calculations:** On the basis of an estimated absolute effect size of			Qualifying diagnoses included having an MI, PCI, or angina with an ischemic stress ECG, stress echocardiogram, or stress myocardial perfusion imaging study. **Exclusion criteria** For this trial, although eligible for CR, patients who had undergone recent coronary artery bypass grafting, valve surgery, or cardiac transplantation were excluded. Additional exclusion criteria included patient refusal to attend					Other E=4,S=5. Reasons for not exercising>1session	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding
20%,15 a control group attendance of 50% (baseline enrollment rates at our institution were 44% [unpublished data]), an intervention attendance of 70%,19 α=0.05, and β=0.80, we estimated that 206 patients (103 per group) would be needed			CR, plans to attend CR outside of the Henry Ford Health System, current or previous enrollment into CR within the prior 6 months, the presence of moderate or severe dementia, unstable psychiatric condition, severe peripheral vascular disease that precluded exercise, uncorrected severe aortic stenosis, uncorrected severe mitral stenosis, presence of a left ventricular assist device, discharge to a nursing home						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding
			or rehabilitation center, planned future medical care outside of the Henry Ford Health System, or safety concerns that precluded exercise per the discretion of the treating/referring physician. We did not exclude underinsured or uninsured patients because these patients could attend CR orientation without cost, and a self-pay option was available for those who might choose to participate in CR exercise sessions.						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding
			Baseline characteristics Early Appointment (n=74) Age: 61 ±12 Male: 61% Index event: STEMI: 7 NSTEMI: 36 Angina with ischemic stress test:4 PCI without MI:27 PCI as part of index event:64 Left ventricular EF: 53 ±12 Distance to rehab: 8.4 ± 5.4 miles Standard appointment (N=74) Age: 59±12 Male:50% Index event:						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding
			STEMI:18 NSTEMI:33 Angina with ischemic stress test:5 PCI without MI:18 PCI as part of index event:56 Left ventricular EF: 54±12 Distance to rehab:8.7±5.9 miles						

Table 49: Parker 2011[452]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding
Author: Karen Parker et al. **Title:**An early cardiac access clinic	Prospective cohort (but control group identif	N=469 (intervention N=245; comparison N=224)	Patients admitted to tertiary care hospital, with acute STEMI and low risk. Inclusion criteria (1) STEMI identified as low	ECAC (early cardiac access clinic) model. Dedicated clinic nurses screened and subsequently enrolled all eligible STEMI	Traditional models (access to CR service weeks to months of discharge)	12 weeks for intervention. Not specified for	**Outcome 1** CR referral	Int = 245/245 C =125/224	Alberta Cardiac Access Collaboration, Alberta Health Services-Ministry of Health and Wellness,
							Outcome 2 Attendance (Uptake)	Int = 237/245 C =83/224	
							Outcome 3	Int = 215/245	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding
significantly improves cardiac rehabilitation participation and completion rates in low-risk ST-elevation myocardial infarction patients. **Journal:** Canadian Journal of Cardiology 27 (2011) 619-627. Country CANADA	ied retros pectiv ely)		risk based on either Cardillac Risk Score (30-day mortality <1%) if treated using primary PCI or TIMI Risk Score if initially treated with thrombolysis; (2) angiographic evidence of revascularization of the infarct-related artery (IRA), further defined as ≥80% patency; (3)residing within 100km of the city limits if Calgary, Canada; (4) willing and able to participate in the ECAC model; (5) able to read and speak English; (6) referral to CR approved by the attending physician.	patients admitted at the participating hospital. At time of ECAC visit, a dedicated interdisciplinary clinic team composed of exercise specialists, clinic nurses, CR physicians, cardiologist, and administration staff provided ECAC participants with CAD-specific education and on-site CR orientation. Dedicated clinic nurses delivered standardises discharge planning activities, including a pre-scheduled ECAC visit booked within 4-14 days of the expected hospital discharge		control.	Participation (Adherence) **Outcome 4** Completion (actively received regular support from affiliated CR staff over the course of a 12-week multidisciplinary lifestyle program)	C =75/224 Int = 175/245 C =67/224	Government of Alberta

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding
			Exclusion criteria (1) any physical, neurological or mental illness that would preclude graded exercise testing; (2) hospitalization period >10 days from STEMI admission; (3)coronary artery bypass grafting; (4) patient treated with thrombolytic therapy without subsequent angiography (5) delay in treatment of >6 hours to revascularization of IRA; (6) incomplete revascularization of IRA. Characteristic Sex (male): int=80.4%; C=79.5%	date, and emergency telephone contact support between the time of discharge and the ECAC visit.					

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding
			Age (y) Int=56.14; C=56.65 STEMI inferior: int=67.8%; C=68.8 STEMI anterior: int=15.7%; C=25.5% STEMI posterior/lateral: int=16.5%; C=5.8%						

Table 50: Parry 2009 [453]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Result	Source of funding Comments
Author:M Parry, J Watt-Watson, E Hodnett, J Tranmer, C-L Dennis, D Brooks. **Title:**Cardiac Home Education and Support	RCT	N=101 Follow-up N=95	Men and women who were having first-time non-emergency CABG surgery, ready for discharge home and able to communicate via telephone.	N=49 N=45 Telephone calls = In addition to usual care, patients received peer-generated telephone calls for eight weeks following hospital	N=52 N=50 Received preoperative and postoperative education, and visits from in-hospital peer	8 weeks	**Outcome 1** Cardiac Rehabilitation uptake	Peer support program = 11/45 Usual program =6/50	Canadian Institutes of Health Research FUTURE Program for Cardiovascular Nurse Scientists, Cardiac Science Medtronic Research Grant/Kingston General Hospital,

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Result	Source of funding Comments
Trial (CHEST): A pilot study. **Journal:**Can J Cardiol 2009;25(12): e393-e398. Randomisation Random assignment was centrally controlled using an Internet-based randomization service (www.randomize.net) with stratification based on sex, using variable block sizes of four and eight. Patients and peer				discharge. Peer volunteers used usual care material to focus their telephone conversations on pain management, exercise and encouragement to attend CRP.	volunteers				CCCN Research Grant, Nurse Practitioner Association of Ontario Cardiovascular Acute Care Nurse Practitioner Pfizer Award and a Canadian Pain Society Nursing Research Award.

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Result	Source of funding Comments
volunteers were matched by sex and as closely by age as possible. Allocation concealment : Unclear Blinding: Patients – unclear if blinded. RA was blinded. Power calculation: 50 patients per group allowed them to estimate continuous variables, but unclear about									

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Result	Source of funding Comments
dichotomous variables.									

Table 51: Peterson 2011 [467]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding
Author Peterson GM, Thompson A, Pulver LK, Robertson MB, Brieger D, Wai A, Tett SE; for the DMACS Project Group. **Title:**Management of	Registry	N=1545 N=45 hospitals Follow-up N=41 hospitals (8% loss)	Australian hospitals, public and private, were eligible to participate. Patient demographics Baseline n=1545 Median age = 66 Female = 450 Discharge diagnosis:	Quality improvement approach to optimize prescription of medications, education regarding lifestyle modifications including CR; and communication between hospital staff, patients and GPs. Educational	Baseline measurements of referrals to CRP	8-9months	**Outcome 1** Inpatient medical record referral	Baseline = 878/1545 Post =1078/1589	-
							Outcome 2 GP survey, referral to CRP	Baseline = 288/731 Post = 281/636	
							Outcome 3 Patient survey, Referral to CRP	Baseline = 880/1319 Post = 944/1285	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding
Acute Coronary Syndromes at Hospital Discharge: Do Targeted Educational Interventions Improve Practice Quality? **Journal** J Healthc Qual. 2011 Mar 1.			STEMI=342 NSTEMI=590 Unstable angina = 305 Unspecified ACS=308 Postintervention, n=1589 Median age = 66 Female = 460 Discharge diagnosis: STEMI=375 NSTEMI=621 Unstable angina = 342 Unspecified ACS=251	meetings (aimed at changing practice and enhancing patient outcomes), academic detailing (involves training staff in techniques to behaviour change designed to influence how clinical staff use evidence-based information in their practice) and point of care reminders and feedback of baseline audit results.					

Table 52: Pinto 2011[475]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding
Author:	RCT	N=130	Patients who had	N=64	N=66	6	**Outcome 1**	Int = 15	National heart,

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding
Pinto et Al. **Title:** Maintenance of exercise after phase II cardiac rehabilitation . A randomized control trial. **Journal:** Am J Prev Med 2011;41(3):274-283. . . Country USA			completed a phase II cardiac rehabilitation program. **Inclusion criteria** Men and women aged ≥40 years (1) participating in supervised phase II cardiac rehab (2) scheduled to complete phase II cardiac rehab in the next 4 weeks; (3) able to read and speak English; (4) providing consent for medical chard review to extract disease and treatment variables; (5) able to walk unassisted; (6) having access to a telephone. Exclusion criteria Not stated **Characteristic**	Maintenance Counselling (MC). 6-month program of exercise counselling (based on transtheoretical model and social cognitive theory) delivered via telephone, as well as print materials and feedback report.	This group received tip-sheet on cardiovascular health. After the 12-month assessment, they received the exercise tip-sheet.	months and 12 months	Attrition at 6 months	C =8	Lung and Blood Institute.

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding
			MC (n = 64) Control (n = 66) In order as above n(%) Male 50(78.1) 53(80.3) Age(y, M(DS)) 62.9(9.3) 64.3(10.0) Non-Hispanic white 61(95.3) 61(92.4) Non-Hispanic black 2(3.1) 3(3.0) Other race 1(1.6) 3(4.6) Employed full-time 28(43.8) 25(37.9) Employed part-time 5(7.8) 7(10.6) Unemployed 2(3.1) 0(0.0) Homemaker/medical leave 5(7.8) 7(10.6) Retired 24(37.5) 27(40.9) Household						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding
			income($) <39,999 18(31.0) 18(29.5) 40,000-79,999 14(24.2) 23(37.7) >80,000 26(44.8) 20(32.8)						

Table 53: Scott 2000 [530]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding
Author: Scott IA, Eyeson-Annan ML, Huxley SL, West MJ. **Title:** Optimising care of acute myocardial infarction: results of a regional quality improvement project.	Cohort study	Before and after study, 245 patients	Post MI. **Inclusion criteria:** admitted to one of the study hospitals bw 1995 -1998 with acute MI and residents of West Moreton. Discharged alive and not transferred. **Exclusion criteria**: >85yrs, marked physical frailty, terminal illness,	Dissemination of clinical guidelines to hospital staff and GPs. Guidelines were adapted from the American College of Cardiology and the American Heart Association. For CR: assessment of all AMI patients by the CR co-	Baseline period relates to start of implementation of new guidelines	1 yr	**Outcome 1** Uptake to CR	Intervention increased over time from 24% to 54%	Limitations: no baseline data, only measured changes over time.

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding
Journal J Qual Clin Pract. 2000 Mar;20(1):12-9. AUSTRALIA Methods Questionnaires at 3 months post discharge determined the numbers of patients participating in CR following hospital.			and uncontrolled heart failure or unstable angina. Post population: n=245 M/F = 63/37 Age = 66.4 ± 13.1 Previous MI=31% Previous revas =6.8% Hypertension=44.4% STEMI = 29.2%	ordinator as to eligibility of enrolment in CR.					

Table 54: Sniehotta 2006[548]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding Comments
Author F. F. Sniehotta, U. Scholz, and R. Schwarzer. **Title** Action plans and coping plans for physical exercise: A longitudinal intervention study in cardiac rehabilitation. **Journal** British Journal of Health Psychology 11 (Pt 1):23-37, 2006. Country Germany Methods All patients	RCT and before-after study combined: prospective before-after study for initial intervention (longitudinal observational) – with randomisation later	N=246 Drop outs: 2 months post-discharge: C = 13 AP = 13 CP = 9 Analysis **Inclusion** All those who completed questionnaires at 2 month follow-up No differences in baseline characteristics between completers and drop-outs	In N=211 (completers) All= CHD patients who underwent a 3-week residentially based cardiac rehab program Men n=165 Women n=46 Age = 31-82 yrs Current smokers n=25 Non-smokers n=182 Education post-secondary n=75 (n=3 did not respond) Employed n=96	**Action planning (AP)** N=81 ITT = 81 ACA = 68 Combined Action planning (CP) N=71 ITT = 71 ACA = 62 AP: participants formed up to 3 action plans about when, where, and how they intended to exercise and/or intended to implement extra everyday physical activities after	**Control (C)** N=94 ITT = 94 ACA = 81 Received no additional intervention (planning sessions)	10 weeks (follow-up at 2 weeks into rehab and 2 months post-discharge)	**Outcome 1** Adherence (achievers)	C= 34/81 AP= 30/68 CAP=44/62	Not mentioned COMMENT: Cell sizes of the 3 experimental groups turned out to be unequal due to the randomisation procedure, and ended up being unequally sized groups. COMMENT: No details given f randomisation, blinding, power or other Risk of bias elements.
							Outcome 2 Reasons for withdrawal	Did not complete questionnaires or not send them back in time or not enough time in the rehab centre to meet with some pts to give them the planning intervention (n=35)	
							Outcome 3 Intention score	C= 3.30 (SE 0.05) AP= 3.39 (SE 0.06) CAP= 3.43 (SE 0.06)	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding Comments
initially received a 3-week residentially based cardiac rehab program were then encouraged to continue exercising after the program (vigorous exercise for 30 min sessions at least 3 times/week) and increase their everyday physical activities. Psychoeducational classes were given to increase compliance to these recommenda	in the trial to 3 groups aimed at increasing adherence to regular exercises post-discharge from rehabilitation 2 weeks into rehab program			discharge CP: participants additionally formed up to 3 coping plans about strategies to overcome anticipated barriers All treatments were conducted by trained consultants in a 1:1 setting and lasted up to 30 mins. Consultants trained to guide the planning session in a non-directive manner					

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding Comments
tions. Questionnaire was sent 2 months after the rehab program (discharge). Intention score = behavioural intentions: reply to 6 statements regarding exercise and other physical activities. Statements started with 'I intend to...' and all items had a response range from 1-4 (not at all true – exactly true)	pts were randomised.								

Table 55: Sniehotta 2005 [549]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding Comments
Author Sniehotta FF, Scholz U, Schwarzer R, Fuhrmann B, Kiwus U, Völler H. **Title** Long-term effects of two psychological interventions on physical exercise and self-regulation following coronary rehabilitation. **Journal** Int J Behav Med. 2005;12(4):244-55. Country	RCT and before-after study combined: prospective before-after study for initial intervention (longitudinal observational) – with randomisation later	N=240 Drop outs: 2 months post-discharge: n=23 4 months post-discharge: n=41	In N=240 All= CHD patients who underwent a 3-4 week residentially based cardiac rehab program Men n=195 Age = 31-80 yrs Education post-secondary n=84 (35%) Employed n=114	**Planning (P)** N=not given ITT = 81 ACA = 68 Planning+diary (PD) N=not given ITT = 71 ACA = 62 P: participants formed up to 3 action plans about when, where, and how they intended to exercise and/or intended to implement extra everyday physical activities after discharge, as well	**Control – standard care (C)** N=not given ITT = 94 ACA = 81 Received no additional intervention (planning sessions)	4 months post-rehab	**Outcome 1** Adherence (attenders at cardiac training group within 4 months post-discharge)	C= 23/79 P= 16/56 PD=28/65	Not mentioned COMMENT: Few baseline details given, or numbers of pts randomised into each of the 3 groups. COMMENT: No details given f randomisation, blinding, power or other Risk of bias elements.

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding Comments
Germany Methods All patients initially received a 3-4 week residentially based cardiac rehab program were then encouraged to continue exercising after the program (regular strenuous exercise, increase exercise in general, participate in cardiac sports group). Psychoeducational classes were given	in the trial to 3 groups aimed at increasing adherence to regular exercises post-discharge from rehabilitation During the last week of the rehab			as how to cope. PD: participants additionally received in the mail 6 weekly diaries after discharge, which contained their plan and was to record how often they adhered to their plan and how they felt. Plans could also be modified.					

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding Comments
to increase compliance to these recommendations. Questionnaire was sent to all 3 groups 2 weeks into rehab, 2 months after the rehab program (discharge) and one more 4 months later. Intention score = behavioural intentions: reply to 6 statements regarding exercise and other physical activities.	program pts were randomised.								

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding Comments
Statements started with 'I intend to...' and all items had a response range from 1-4 (not at all true – exactly true)									

Table 56: Wyer 2011 [622]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding
Author Wyer SJ; Earll J; Joseph S; Harrison J; Giles M; Johnston M **Title** "Increasing attendance at a cardiac rehabilitation program: an	RCT	N=87	All had acute MI and referred to the CRP. Recruited 3 days post MI at a district hospital. Experimental group Age = 62.16	Theory of Planned behaviour. Two letters given to patients 3 weeks post MI N=43 The letters intended to influence the person's: attitude towards attending CR	Nominal letters including course dates N=44	Unclear	**Outcome 1** Uptake	Int = 37/43 (86%) C = 26/44 (59%)	None mentioned. Comments The numbers don't add up for the control group and adherence. 26 accepted the offer to attend CRP, yet they give the

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding
intervention study using the theory of planned behaviour" **Journal** Coronary Heart Care (2001) 593) 154-59 Country UK Methods Randomisation = yes, only details were that they randomly numbered and given to patients in numerical order Allocation concealment =Only that			Male = 37 Female =6 Mean distance from program (miles) = 61.9 Mean number of sessions attended =5.89 Control group Age =63.35 Male = 39 Female =5 Mean distance from program (miles) = 7.67 Mean number of sessions attended =5.82	highlight how they are following medical recommendations , they will be supported and there is a point of contact					attendance numbers out of 31.

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding
patients were handed a sealed envelope Power calculations None given									

G.4 Drug therapy

G.4.1 ACE inhibitors vs. placebo and optimal duration of treatment

Table 57: AIRE 1993[12]

Reference	Study type	No. of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Author Aire study investigators **Journal** Lancet 1993; 342: 821-828. Country: Multinationa	RCT (Acute Infarction Ramipril Efficacy [AIRE] trial)	N= 1986 Drop outs 1 lost to follow up Analysis: ITT	**Inclusion criteria** Definite acute MI and clinical evidence of heart failure or LV dysfunction (at least one of: pulmonary venous congestion with interstitial or alveolar oedema; pulmonary oedema with bilateral post-tussive crackles at least one third up lung fields; third heart sound	2.5mg ramipril twice daily started between day 3 and day 10 after MI; for 2 days if	Placebo (n=982)	Mean 15 months (minimum 6 months)	**Outcome 1** Death in hospital	34/1004 ramipril vs. 46/982 placebo	Source of funding Hoechst Limitations Randomisation and allocation concealment not stated
							Outcome 2 Death by 15 months	170/1004 ramipril vs. 222/982 placebo, p=0.002	
							Outcome 3	81/1004 ramipril vs. 88/982	

Reference	Study type	No. of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
l Randomisation: Not stated Allocation Concealment: Not stated Blinding: Double blind Power Calculations: Around 2000 patients required for average follow up 15 months; predicted placebo mortality 20%; clinically relevant improvement of 25% reduction in all-cause mortality;			and persistent tachycardia); aged at least 18 years **Exclusion criteria** Severe heart failure (usually NYHA grade IV); heart failure of primary valvular or congenital aetiology; unstable angina; contraindications to ACE inhibitor **Baseline characteristics** Age: mean 65 (SD 10.8) years Gender: 1461/1986 (74%) male MI: 100% Hypertension 554/1986 (28%) Treatment thrombolysis 591 (59%) ramipril and 551 (56%) placebo Concomitant medications: aspirin:773 (77%) ramipril and 770 (78%) placebo; beta-blockers: 236 (24%) and 207 (21%); calcium-channel blockers: 159 (16%) and 158 (16%); digoxin: 124 (12%) and 119 (12%);	tolerated; then 5mg twice daily; 1.25mg twice daily for those who did not tolerate 2.5mg twice daily (n=1004)			Reinfarction	placebo	
							Outcome 4 Stroke	25/1004 ramipril vs. 17/982 placebo	
							Outcome 5 Serious adverse events	581/1004 ramipril vs. 625/982 placebo	
							Outcome 6 Hypotension	42/1004 ramipril vs. 23/982 placebo	
							Outcome 7 Renal failure	15/1004 ramipril vs. 12/982 placebo	

Reference	Study type	No. of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
power 80%; p=0.05			diuretics: 586 (58%) and 602 (61%); nitrates: 565 (56%) and 544 (55%)						

Table 58: Kingma 1994[313]

Reference	Study type	No. of pts	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Authors: Kingma et al for CATS investigators **Journal** Eur Heart J 1994; 15: 898-907. **Country:** Netherlands **Randomisation:** Not stated **Allocation Concealment:** Not stated **Blinding:**	RCT (Captopril and Thrombolysis Study [CATS])	N= 298 **Drop outs** 15 pts (5%) died and 1 was lost to follow up **Analysis:** ITT	**Inclusion criteria** First anterior wall MI within 6 hours of onset of symptoms (MI acute) treated with thrombolysis with IV streptokinase; consent; LV function – unselected (mixture of dysfunction or normal) **Exclusion criteria** Intolerance to ACE inhibitors; renal insufficiency; systolic BP >200mmHg or <100mmHg; diastolic >120mmHg or <55mmHg; severe valvular heart disease; arrhythmias requiring antiarrhythmic therapy; serious systemic or metabolic disease except diabetes mellitus; AV conduction disturbance (PR interval ≥0.24 s); left bundle branch block; history of TIAs or CVA within 6 weeks **Baseline characteristics**	Captopril 6.25mg, repeated after 4 and 8 hours; 12.5mg at 16 hours and 25mg at 24 hours; target maintenance dose 25mg three times daily (reached by 95% of patients) to 3 months	Placebo (n=149)	3 months	**Outcome 1** Hypotension: titration phase Hypotension: during 3 months follow up	33 captopril and 22 placebo 40 (26.8%) captopril and 27 (18.1%) placebo	**Source of funding** Bristol-Myers Squibb **Limitations** Randomisation and allocation concealment not stated
							Outcome 2 Death	9/149 captopril and 6/149 placebo	
							Outcome 3 Revascularisation (PTCA and/or CABG)	33 captopril and 35 placebo	

Reference	Study type	No. of pts	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Double blind **Power Calculations:** 280 patients sufficient to detect a mean difference in end diastolic volume index between groups of 8ml/m^2 with 80% power			Age: mean 59 (10) years captopril and 60 (9) years placebo Gender: 70% male captoril and 80% male placebo MI: 100% Hypertension: 27.5% captoril and 16.1% placebo Treatment thrombolysis 100% Concomitant medications: aspirin: 32.9% captoril and 31.5% placebo; beta-blockers: 14.1% and 11.4%; calcium-channel blockers: none in either group; diuretics: 12.1% and 5.4%; nitrates: 10.7% and 9.4%	(n=149)			**Outcome 4** Reinfarction	10 captopril and 4 placebo	

Table 59: CCS 1995[7]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Reference Chinese Cardiac Study Collaborative Group. Lancet 1995; 345: 686-687.	RCT (Chinese Cardiac Study)	N=13634 **Drop outs** 88% captopril and 91% placebo patients completed 4 weeks (or	**Inclusion criteria** Within 36 hours of onset of symptoms of suspected acute MI (MI acute); no contraindications to ACE inhibitors (persistent hypotension: systolic BP <90mmHg; chronic use of large doses of diuretics) or indications for ACE inhibitors.	Captopril 6.25mg initial dose, 12.5mg 2 hours later if BP did not fall profoundly; 12.5mg	Placebo (n=6820)	4 weeks	**Outcome 1** Hypotension requiring study treatment to be stopped **Outcome 2** Persistent hypotension (SBP <90mmHg for over	575 (8.4%) captopril vs. 335 (4.9%) placebo 1113 (16.3%) captopril vs. 738 (10.8%) placebo,	**Source of funding** Cardiovascular Institute and Fu Wai Hospital, Beijing; Clinical Trials Service Unit, University of

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Country: China **Randomisation:** Not stated **Allocation Concealment:** Not stated **Blinding:** Not stated **Power Calculations:** Not stated		died earlier) **Analysis:** not stated	LV function – unselected (mixture of dysfunction or normal) **Exclusion criteria** Not stated **Baseline characteristics** Age: Not stated Gender: Not stated MI: 100% Treatment not stated Concomitant medications: aspirin: 73%; fibrinolytic therapy: 27%; IV nitrates: 39%; diuretics: 20%	three times daily to 4 weeks (n=6814)			2 hours)	p<0.0001	Oxford; Sino-American Shanghai Squibb Pharmaceuticals **Limitations** Randomisation, allocation concealment, blinding, power calculations, baseline characteristic and ITT not stated
							Outcome 3 Death	617 (9.05%) captopril and 654 (9.59%) placebo	
							Outcome 4 Proteinuria	54 (0.79%) captopril and 65 (0.95%) placebo	

Table 60: Dipasquale 1994[155]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Authors Di Pasquale P, Paterna S, Cannizzaro S, Bucca V.	RCT	N=371 randomised 51 dropped out as no enzymatic variations so	Patients with acute myocardial infarction **Inclusion criteria:** Had a first episode	Captopril pre-treatment (6.25mg orally as first dose at least 15 minutes before thrombolysis and	Late-treatment group: 6.25mg captopril per os as first dose	Minimum 6 months follow-up	**Outcome 1** All-cause mortality	Captopril:3/42 Placebo:8/45	**Source of funding:** No details. **Limitations:** Unclear
							Outcome 2 Revascularisati	Captopril:16/42 Placebo:18/45	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Title Does captopril treatment before thrombolysis in acute myocardial infarction attenuate reperfusion damage? Short-term and long-term effects. **Journal** International Journal of Cardiology, 1994, 43; 43-50. **Country**: Italy **Randomisation:** Unclear, no details. **Allocation**		classified as unstable angina; 61 were excluded as they did not fulfil the reperfusion criteria. Number studied: N=259 total; N= 131 in pre-treatment group; N= 128 late-treatment group. 23 died (11 in the pre-treatment group and 14 in the late-treatment group). Analysis: not stated but	of acute MI; Killip class I-II; acceptable echocardiographic window; admitted within 4 hours of onset of symptoms (pain); ST elevation of at least 1mm in the peripheral leads and 2mm in the precordial leads, involving more than one lead with concomitant alterations of the segmentary kinetic in the mono-2-dimensional echocardiograph (M-2D echo) (Aloka 720; Sonos HP); blood concentrations of CK, CK-MB at the basal sample before thrombolysis had to be within normal range.	then every 8 hours for the first 2 days, from the third to the sixth day 12.5mg ever 8 hours). The captopril dose was subsequently increased depending on blood pressure change, to a maximum of 25mg every 8 hours.	3 days after thrombolysis; the captopril dose was subsequently increased as pre-treatment group.		on **Outcome 3** Reinfarction - fatal	 Captopril:1/42 Placebo:2/45	randomisation and allocation concealment; no power calculation; single-blinded This was a 4 arm study design, only using 2 of the group's results

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Concealment: Unclear, no details. **Blinding:** Single blinded. **Power Calculations:** No power calculations reported.		analysis included all patients who were left after exclusions for not meeting reperfusion and those classified as unstable angina.	**Exclusion criteria:** Patients not suitable for thrombolysis; left branch block (LBB) on admission ECG, cardiomyopathy, or previous episodes of heart failure; not satisfying the reperfusion criteria; already receiving ACE-inhibitors. **Baseline characteristics:** Pre-treatment group: Sex (M/F): 106/25 Age (years): 61+/-2 Early VHA: 16 (12.2%) Lown's Class >2: 19 (14.5%) Associated						

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			therapy (BB): 58 (44.3%) Late-treatment: Sex (M/F): 102/26 Age (years): 59+/-2 Early VHA: 50 (39%) Lown's Class >2: 34 (26.5%) Associated therapy (BB): 49 (38.3%)						

Table 61: Dipasquale 1997[156]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
AuthorDi Pasquale P,	RCT	N=33	Acute MI (<4 hours of symptoms) Unselected LV function	Captopril	Placebo	10 d	**Outcome 1**	Captopril:2/16 Placebo:2/17	**Source of funding**

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Valdes L, Albano V, Bucca V, Scalzo S, Pieri D, Maringhini G, Paterna S **Title** Early captopril treatment reduces plasma endothelin concentrations in the acute and subacute phases of myocardial infarction: a pilot study. **Journal** J Cardiovasc Pharmacol. 1997 Feb;29(2):202-8. **Country:**		**Drop outs** Unclear **Analysis:**	**Inclusion criteria** First episode of anterior acute MI, Killip class I – II, acceptable echocardiographic window, and admission to hospital within 4 h of onset of symptoms (pain). ST elevation of > 1mm in periperhal leads, 2mm in precordial leads, with concomitant alterations of the segmentary kinetics in the ECG at entry. Basal creatinine kinase had to be normal. All had to have successful reperfusion. **Exclusion criteria** Not suitable for thrombolysis, left bundle branch block on ECG, history of cardiomyopathy, or HF. Who did not satisfy reperfusion criteria, receiving ACEi and BB. **Baseline characteristics** Captopril: F/M: 7/16 Age (yr):60±10 Ventricular tachycardia:18 BB:9 CK peak (U/L): 1,875±1,797 CK peak normalization time: 56.4±17.8	3x25d/mg			All-cause mortality 0-10days		Unclear **Limitations** Placebo group received Captopril 72hr after thrombolysis

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
ITALY **Randomisation:** Yes, sequence numbered boxes **Allocation Concealment:** Unclear, no details **Blinding:** Double blind **Power Calculations:** unclear			EF (41) %:56.8±11.9 PTCA/CABG:10 Hypertension:10 Diabetes:1 Hypercholesterolemia:3 Smokers:5 Captopril use%:33.41±7.94 PLACEBO F/M:5/17 Age (yr):57±13 Ventricular tachycardia:18 BB:7 CK peak (U/L): 2,166±1,364 CK peak normalization time:59.2±11.5 EF (41) %:36.9±**11.6** PTCA/CABG:11 Hypertension:8 Diabetes:2 Hypercholesterolemia:2 Smokers:7 Captopril use%:0 Concomitant medications: all patients received standard treatment: nitrates heparin, aspirin, where possible metoprolol. Thrombolytic drug RTPA.						

Table 62: Kleber 1997[314]

Reference	Study type	No. pts	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Author Kleber et al for the ECCE study group. **Journal** Am J Cardiol 1997; 80: 162A-167A **Country:** Germany **Randomisation:** Not stated in this paper (another paper referenced) **Allocation Concealment:** Not stated in this paper **Blinding:** Double blind **Power Calculations:**	RCT (Effects of Captopril on Cardiopulmonary Exercise parameters [ECCE] study)	N= 208 **Drop outs** 3.8% captopril and 11.5% placebo terminate study medication before 4 weeks; cardiopulmonary exercise data missing in 14 patients captopril and 9 patients placebo **Analysis:** Not stated	**Inclusion criteria** Acute MI within 24-72 hours after onset of chest pain (MI acute); no contraindications to ACE inhibitors or exercise limitation due to concomitant disease or severe haemodynamic complications of acute MI; LV function – unselected (mixture of dysfunction or normal) **Exclusion criteria** None stated **Baseline characteristics** Age: range 25-79 years Gender: 167 male; 41 female MI: 100% Treatment thrombolysis 66/104 captopril and 65/105 placebo; PTCA 33/104 captopril and 30/105 placebo; CABG: 11/104 captopril and 9/105 placebo Concomitant medications (week 1): nitrates: 91% captopril and 89% placebo; beta-blockers: 51% captopril and 54% placebo; aspirin: 14% captopril and 19% placebo; diuretics: 34% captopril and 29%	Captopril initial dose 6.25mg, then titrated to mean 69mg/day at 4 weeks (n=104)	Placebo (n=104)	4 weeks	**Outcome 1** Death	3 captopril and 2 placebo	**Source of funding** Schwartz Pharma AG, Monheim, Germany **Limitations** Randomisation, allocation concealment and ITT not stated in this paper (another paper referenced)
							Outcome 2 Sudden death	1 captopril and 0 placebo	
							Outcome 3 Fatal reinfarction	1 captopril and 3 placebo	
							Outcome 4 Hypotension after initial dose Hypotension (diastolic BP <60mmHg)	38 (37%) captopril and 19 (18%) placebo 23 (22%) captopril and 12 (11.5%) placebo	
							Outcome 5 Adverse event (possible/ likely/ definite connection to therapy) Severe adverse event	37 (36%) captopril and 31 (30%) placebo 18 (17.3%) each group	

Reference	Study type	No. pts	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Sample size 101 per group required for increase of VO_2-AT of 2.2 (6.3) mL/kg at 4 weeks with p=0.05; power 80%			placebo; digitalis: 5% captopril and 5% placebo						

Table 63: Ferrari 2006[186]

Reference	Study type	No. pts	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Author Ferrari for the PREAMI investigators. **Journal** Arch Intern Med 2006; 166: 659-666. **Country:** 5 European countries	RCT (Perindopril and Remodelling in Elderly with Acute Myocardial Infarction	N= 1252 **Drop outs** 2 placebo patients lost to follow up;	**Inclusion criteria** 65 years or older and survived acute MI (MI non-acute; mean 11 (4) days after MI); with preserved ejection fraction (≥40%) (LV function – normal; mean 59.1 (7.7)%); and optimal apical 4- and 2-chamber views of the LV recorded for at least 5 complete cardiac cycles	Perindopril 2mg day 1; 4 mg day 2 for 1 month then 8mg to month 12 (n=631)	Placebo (n=621)	12 months	**Outcome 1** Death	40 (6%) perindopril and 37 (6%) placebo	**Source of funding** Stroder, Florence, Italy and Servier Italia, Rome, Italy **Limitations** Allocation concealmen
							Outcome 2 Hospitalisation for heart failure	22 (4%) perindopril and 30 (5%) placebo	
							Outcome 3 Cough requiring withdrawal	10 (1.6%) perindopril and 3 (0.5%) placebo	

Reference	Study type	No. pts	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Randomisation: Computer-generated **Allocation Concealment:** Not stated **Blinding:** Double blind **Power Calculations:** Allowing for 25% loss to follow up or unreadable echocardiographic tapes, 1250 patients needed for 20% or more relative reduction in primary endpoint at 12 months with 90% power and p=0.05	[PREAMI] study)	ECHO studies available for 455 (72%) perindopril and 441 (71%) placebo pts; at 1 year, 74% perindopril and 76% placebo taking study medication **Analysis:** ITT	**Exclusion criteria** Severe heart failure (NYHA class IV and need for IV inotropic support; CABG or PTCA; severe hypotension (systolic BP ≤100mmHg); serum creatinine >2.0mg/dL (>176.8micromol/L) **Baseline characteristics** Age: mean 73 (6) years Gender: 436 (35%) women MI: 100% Hypertension: 58% Treatment (thrombolysis 533 (43%) Concomitant medications: antithrombotics: 98% perindopril and 98% placebo; beta-blockers: 70% and 72%; lipid-lowering therapy: 49% and 52%; nitrates: 82% and 82%; calcium-channel blockers: 19% and 22%; diuretics: 28% and 26%						t not stated; large proportion dropping out of treatment and without outcome data for remodelling

Table 64: FOX 2003[195]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Author Fox **Journal**Lancet 2003; 362: 782-788. **Country:** Multi-national (Europe) **Randomisation:** Not stated **Allocation Concealment:** Not stated **Blinding:** Double blind **Power Calculations:** 775 primary endpoint events (cardiovascula	RCT (European trial on Reduction Of cardiac events with Perindopril in patients with stable coronary Artery disease [EUR	N= 12218 **Drop outs** At 3 years; 81% on perindopril and 84% on placebo were taking study medication. 3/6110 on perindopril had incomplete follow up; none of 6108 in placebo group **Analysis:**	**Inclusion criteria** Age at least 18; without heart failure (LV function – normal); coronary heart disease (previous MI > 3 months ago [64% of patients]; PCI or CABG > 6 months ago; or at least 70% narrowing of 1 or more major coronary arteries on angiogram); men could also be recruited if they had history of chest pain and positive ECG, echo or nuclear stress test **Exclusion criteria** Clinical heart failure, planned revascularisation, hypotension (sitting systolic BP <110mmHg), uncontrolled hypertension (systolic BP > 180mmHg +/or diastolic >100mmHg); recent (<1 month) use of ACE inhibitors or angiotensin-receptor blockers, creatinine >150micromol/L, serum potassium >5.5mmol/L **Baseline characteristics** Age: mean 60(9) perindopril and 60 (9) placebo Gender: 884/6110 perindopril and 895/6108 placebo female	Perindopril 8mg once daily (n=6110)	Placebo (n=6108)	Mean 4.2 years	**Outcome 1** All-cause mortality	P = 375/6110 Placebo=420/6108	**Source of funding** Servier, France **Limitations** Randomisation and allocation concealment not stated in this publication (but may be in previous publication referenced); not all patients had MI; only primary endpoint had data provided separately for these patients
							Outcome 2 Cardiac mortality	P = 215/6110 Placebo=249/6108	
							Outcome 3 MI(fatal and non-fatal)	P = 320/6110 Placebo =418/6108	
							Outcome 4 Stroke	P=98/6110 Placebo = 102/6108	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
r death, non-fatal MI, cardiac arrest with successful resuscitation) needed to provide 90% power to detect a 21% relative reduction in 1ry endpoint; significance adjusted to 0.041 for primary endpoint to account for 4 interim analyses	OPA] study)	ITT	MI: 3962/6110 (64.9%) perindopril and 3948/6108 (64.7%) placebo Hypertension: 1650 (27%) perindopril and 1662 (27.2%) placebo Treatment PCI 1173 (29%) perindopril and 1800 (29.5%) placebo CABG 1790 (29.3%) perindopril and 1797 (29.4%) placebo Concomitant medications: platelet inhibitors: 5613 (91.9%) perindopril and 5662 (92.7%) placebo; lipid-lowering therapy: 3534 (57.8%) and 3499 (57.3%); beta-blockers: 3790 (62%) and 3745 (61.3%); calcium-channel blockers: 1935 (31.7%) and 1891 (31.0%); nitrates: 2613 (42.8%) and 2629 (43.0%); diuretics: 555 (9.1%) and 573 (9.4%)				**Revascularisation**	P = 577/6110 Placebo = 601/6108	
							Hypotension	P =60/6110 Placebo =17/6108	
							Kidney failure	P=20/6110 Placebo =16/6108	
							Adverse events (intolerance)	P=144/6100 Placeob =80/61	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
								08	

Table 65: French 1999[202]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Author French JK, Amos DJ, Williams BF, Cross DB, Elliott JM, Hart HH, Williams MG, Norris RM, Ashton NG, Whitlock RM, McLaughlin SC, White	RCT	N=493 **Drop outs** unclear **Analysis:** ITT	Acute MI (<4 hours) Unselected LV function **Inclusion criteria** Patients aged <75 yrs presenting within 4 hours of onset of chest pain and with >1mm ST-segment elevation in contiguous ECG leads or >2mm in leads V1-V3. **Exclusion criteria** Patients receiving ACEi and SBP of <90 6hrs after thrombolysis were excluded. **Baseline characteristics**	Captopril n=243 2.5mg, then 12.5mg, 25mg, 3x50mg/d	Placebo n=250	30days	**Outcome 1** All-cause mortality 30 days	Captopril: 5/243 Placebo: 11/250	**Source of funding** Health research council of NZ and national heart foundation of NZ **Limitations:** unclear if blinded.
							Outcome 2 Sudden death 30 days	Captopril: 0/243 Placebo: 1/250	
							Outcome 3 Reinfarction (fatal+ non-fatal) 30 days	Captopril: 13/243 Placebo: 17/250	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
HD. **Title** Effects of early captopril administration on after thrombolysis on regional wall motion in relation to infarct artery blood flow. **Journal** J Am Coll Cardiol. 1999 Jan;33(1):139-45. **Country:** NZ **Randomisation:** Yes, no details **Allocation Concealmen**			CAPTOPRIL n=243 Age:58 ± 10 Male: 79% Hypertension:25% Diabetes:8% Smoker:42% Angina (>3m): 31% BB:11.5% Previous PTCA/CABG:0/0 Anterior infarction:48% Time to streptokinase hr:2.9±1.3 Time to captopril h:2.1±0.4 PLACEBO n=250 Age:59±10 Male:78% Hypertension:28% Diabetes:6% Smoker:36% Angina (>3m): 28% BB:14% Previous PTCA/CABG:3/1 Anterior infarction:48% Time to streptokinase hr:3.1±1.3 Time to captopril hr: 2.2±0.5 **Concomitant medications:**						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
t: Not stated **Blinding:** Unclear **Power Calculations:** Yes, to determine the effect of captopril in anterior infarction – primary outcome- the estimated sample size was 218. Further, assuming 50% had anterior infarction, the total estimated no. of patients required was 510.			BB therapy was continued or commenced on days 2-3 in patients without contraindications. BB At baseline: Captopril: 11.5% Placebo: 14% Medications at follow-up: CAPTOPRIL n=195 ACEi: 32% BB:52% ASA:88% Lipid modifying therapy:36% LIPD study:15% Long acting nitrates:27% Digoxin:4% Diurectics:11% Calcium antagonists:23% ACEi:32% BB:40% ASA:89% Lipid modifying therapy:34% LIPD study:16% Long acting nitrates:21% Digoxim:4% Diurectics:16% Calcium antagonists:17%						

Table 66: Galcera-Tomas 1993[208]

Reference	Study type	No. pts	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Reference Galcera-Tomas Eur Heart J 1993; 14: 259-266. **Country:** Spain **Randomisation:** Not stated **Allocation Concealment:** Not stated **Blinding:** Double blind **Power Calculations:** Not stated	RCT	N= 40 **Drop outs** 1 captopril and 2 placebo died before day 14 **Analysis:** Not stated	**Inclusion criteria** ST elevation MI within 24 hours (MI acute); age under 70 years; availability of radionuclide ventriculography study in first 24 hours; LVSD: mean 33 (10)% captopril and 34 (6)% placebo **Exclusion criteria** Declined to participate; previous valvulopathy or myocardiopathy; Killip grade III or IV or clinical or enzymatic evidence of infarct extension **Baseline characteristics** Age: mean 54 (10) captopril and 56 (10) placebo Gender: not stated MI: 100% Hypertension: 8 (40%) captopril and 8 (40%) placebo Treatment thrombolysis: 15 (75%) captopril and 16 (80%) placebo Concomitant medications: nifedipine: 3 captopril and 7 placebo; diltiazem: 2 and 2;	Captopril initial dose 6.25mg; if tolerated, titrated to target dose25mg three times daily (n=21)	Placebo (n=22)	**Mean** 14 days (range 11-16**)**	**Outcome 1** Death	1 captopril and 2 placebo	**Source of funding** Not stated **Limitations** Randomisation, allocation concealment, power calculation and ITT not stated; small sample size

Reference	Study type	No. pts	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
			beta-blockers: 1 and 1; nitroglycerine infusion: 20 and 20; oral nitrates: 5 and 8; diuretics: 2 and 2						

Table 67: Latini 1994[332]

Reference	Study type	No. pts	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Author Latini R, Avanzini F, De Nicolao A, Rocchetti M.	RCT	N= 1526 **Drop outs** Unclear **Analysis:** Reported in	Unclear LV status **Inclusion criteria** Patients had to be in stable hemodynamic conditions, with SBP >100mm Hg, no known renal dysfunction,	Lisinopril 5mg initial dose then 10mg daily for	Open control (n=440)	6 weeks	**Outcome 1** Death	ACE inhibitor: 59/431 Placebo: 112/440	**Source of funding** Zeneca Pharmaceutical; Schwartz Pharma
							Outcome 2 Hypotension	ACE inhibitor 92/431 Placeb:42/430	

Reference	Study type	No. pts	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Title Effects of lisinopril and nitroglycerin on blood pressure early after myocardial infarction: the GISSI-3 pilot study. **Journal** Clin Pharmacol Ther. 1994 Dec;56(6 Pt 1):680-92. Country: Italy Randomisation: Yes but no details		paper	Killip class <4, no history of bilateral stenosis of renal arteries and no allergy to one of the trial drugs. **Exclusion criteria** None provided **Baseline characteristics** No table provided. Mean age 64 ± 11 (31% older than 70) and 24% women. Diagnosis of AMI was confirmed in 95% of cases. **Concomitant medications:** Systemic thrombolysis, aspirin (325mg/d) and atenolol (10mg/) were recommended therapies for all patients. Thrombolytic agents were administered to 67% of patients, 30% atenolol and 85% ASA. Patients were not matched for atenolol use: placebo had	6 weeks (n=431)					**Limitations** Allocation concealment not stated; does not appear to be blinded

Reference	Study type	No. pts	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Allocation Concealment: Not stated Blinding: Unclear Power Calculations: None provided			higher use 34% vs. 27% for lisinopril. Overall the fraction of patients receiving concomitant vasoactive therapy during the first 3 days of AMI was higher in control group 79% than ACE lisinopril 59% group.						

Table 68: GISSI-3 1994[246]

Reference	Study type	No. pts	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments

Reference	Study type	No. pts	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Title: Gruppo Italiano per lo Studio delia Sopravvivenza nell'Infarcto Miocardico. **Journal:** Lancet 1994; 343: 1115-1122. **Country:** Italy **Randomisation:** Computer-generated **Allocation Concealment:** Not stated	RCT	N= 19394 **Drop outs** 97.4% had available data at 6 week follow up; the 2.6% lost to follow up were balanced in terms of randomisation groups **Analysis:** 2 x 2 factorial design; patients also randomised between trans-dermal GTN or no GTN;	**Inclusion criteria** Chest pain with elevated or depressed ST segment; within 24 hours of onset of MI (MI acute); no clear indications for or against study treatments LV function – mixture of dysfunction or normal **Exclusion criteria** Severe heart failure requiring study treatment; Killip class IV; risk of further serious haemodynamic deterioration after treatment with vasodilators (systolic BP ≤100mmHg); contraindications to study drugs (serum creatinine >177micromol/L +/or proteinuria >500mg/24 hours)bilateral stenosis of renal arteries; allergy to one of the study drugs; other life-threatening disorders;	Lisinopril 5mg initial dose then 10mg daily for 6 weeks (n=9435)	Open control (n=9460)	6 weeks	**Outcome 1** Death	597 (6.3%) lisinopril and 673 (7.1%) control	**Source of funding** Zeneca Pharmaceutical; Schwartz Pharma **Limitations** Allocation concealment not stated; not blinded
							Outcome 2 Reinfarction	303 (3.2%) lisinopril and 292 (3.1%) control	
							Outcome 3 Combined CABG or PTCA	314 vs. 291	
							Outcome 4 Persistent hypotension	852 (9.0%) lisinopril and 351 (3.7%) control	

Reference	Study type	No. pts	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Blinding: Open trial **Power Calculations:** To detect a rate reduction of mortality and combined endpoint of at least 20%, 20,000 patients needed to be randomised for "reasonable power"		ITT	previous randomisation within the trial **Baseline characteristics** Age: 26.8% over 70 years in lisinopril group and 27.4% in placebo group Gender: 22.3% lisinopril 22.1% and control were female MI: confirmed in 95%; 3.6% ACS and other diagnoses 1.4% Hypertension: 30.2% lisinopril and 29.6% control Treatment thrombolysis 71.7% Concomitant medications: IV beta-blockers: 30.1% lisinopril and 31.3% control; fibrinolytic treatments: 71.4% and 71.9%; aspirin: 83.5% and 84.2%; other antiplatelet agents: 3.6% and 3.5%				**Outcome 5** Renal dysfunction	226 (2.4%) lisinopril and 106 (1.1%) control	
							Outcome 6 Stroke	72 (0.8%) lisinopril and 68 (0.7%) control	

Reference	Study type	No. pts	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments

Table 69: Gotzsche 1992[235]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Author: Gøtzsche CO, Søgaard P, Ravkilde J, Thygesen K. **Title:** Effects of captopril on left ventricular systolic and diastolic function after acute myocardial infarction. **Journal:** Am J Cardiol. 1992 Jul 15;70(2):156-60.	RCT	N = 58 **Drop outs** Captopril n=1 lost to follow-up Placebo: none lost to follow-up **Analysis:** ITT	**Inclusion criteria** ≤70 yrs with acute MI and 1 of the following: signs of HF needing diuretics within 5 days of onset of AMI and LV EF ≤45% **Exclusion criteria** Receiving medication for HF prior to admission or had SBP <100mm Hg, AF, valvular heart disease, LV aneurysm, serious systemic disease, hepatic or renal impairment or EF <25% **Baseline characteristics** CAPTOPRIL n=30 Age:60 (35-70) W/M:4/26 Previous MI:2 Systemic hypertension:5 Diabetes:4 Anterior/Inf infarct:16/14 Killip Class I/II/III: 12/15/3	Captopril 2x25m/g N=30	Placebo N=28	6months	**Outcome 1** All-cause mortality **Outcome 2** Reinfarction **Outcome 3** Revascularisation (CABG)	Captopril = 1/30 Placebo=0/28 Captopril = 0/30 Placebo=2/28 Captopril =1/30 Placebo=1/28	**Source of funding** None provided **Limitations**

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Country: Denmark **Randomisation:** Yes, no details **Allocation Concealment:** No stated **Blinding:** Yes **Power Calculations:** None provided			Treated with streptokinase:24 PLACEBO n=28 Age:58(44-70) W/M: 2/26 Previous MI:1 Systemic hypertension:5 Diabetes:4 Anterior/Inf infarct:15/13 Killip Class I/II/III: 13/15/0 Treated with streptokinase:23 **Concomitant medications:** Furosemide: C: 11 and P:9 Antiischemic medication: end of trial: 49/53 BB: C: 19 and P:19						

Table 70: Hargreaves 1992[261]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Author: Hargreaves AD, Kolettis T, Jacob AJ, Flint LL, Turnbull LW, Muir AL,	RCT	N=72 **Drop outs** Placebo n=9	Acute MI (<24 hours) Unselected LV function **Inclusion criteria** Patients with suspected AMI within 24 hours of symptoms.	Captopril 3x12.5 mg/d n=36	Placebo n=36	28 days	**Outcome 1** All-cause mortality **Outcome 2** Reinfarction **Outcome 3** Hypotension	Captopril: n=5/36 Placebo: n=9/36 Captopril: n=1/36 Placebo: n=0/36 Captopril: n=0/36 Placebo: n=3/36	**Source of funding** Bristol-Myers Briggs and Stuart Pharmaceutic

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Boon NA. **Author:** Early vasodilator treatment in myocardial infarction: appropriate for the majority or minority? **Journal:** Br Heart J. 1992 Oct;68(4):369-73. **Country:** UK **Randomisation:** Yes, unclear **Allocation Concealment:** Not stated **Blinding:** Double blind		Captopril n=5 **Analysis:** ITT	**Exclusion criteria** None provided **Baseline characteristics** CAPTOPRIL n=36 M:F:30:6 Age:60.3 (9.4) Site of MI ant:Inf:12:23 Previous MI: 0 Receiving thrombolysis: 32 Time to thrombolysis hr: 3.2 (1.9) Peak creatine kinase U/L: 1494 (1178) Completing treatment:31 PLACEBO n=36 M:F:31:5 Age:60.8 (8.4) Site of MI ant:Inf: 14:21 Previous MI: 4 Receiving thrombolysis:30 Time to thrombolysis: 3.4 (1.7) Peak creatine kinase U/L: 1429 (1152) Completing treatment: 27 **Concomitant medications:** None provide besides thrombolysis				**Outcome 4** Renal dysfunction (glomerulonephritis)	Captopril: n=0/36 Placebo: n=1/36	als **Limitations** 3 groups, however only using 2

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Power Calculations: None provided									

Table 71: Hussain 2010[280]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
AuthoughHussain **Journal** AMJ 2010; 3 (11): 707-711. **Country:** China **Randomisation:** Not stated	RCT	N= 100 **Drop outs** Not stated **Analysis:** not stated if ITT	**Inclusion criteria** First time acute MI (MI acute); hospitalised within 72 hours of symptoms; LV function – unselected (mixture of dysfunction or normal):Mean LV ejection fraction 53.9 (12.8)% for patients ≤60 years on captopril; 53.2 (12.9%) for patients ≤60 years in control group; 54.8 (14.2)% for patients 60-70 years on captopril; 55.1 (14.7)% for patients 60-70 years in control group **Exclusion criteria**	Captopril 6.25mg orally immediately; then 12.5-25mg three times daily (n=60)	Conventional therapy (n=40)	In hospital (mean around 1 month) only	**Outcome 1** Death in hospital	4/60 (6.67%) captopril vs. 9/40 (22.5%) control, p<0.0001	**Source of funding** Not stated **Limitations** Randomisation and allocation concealment not stated; power calculation not stated; not stated if

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Allocation Concealment: Not stated **Blinding:** Not stated **Power Calculations:** Not stated			Severe extra-cardiac disease that could affect prognosis; hypotension (systolic BP <90mmHg), cardiogenic shock; severe hypertension (systolic BP >200mmHg or diastolic >120mmHg) **Baseline characteristics** Age: Mean 64 (10) years Gender: 53/100 male MI: 100% Treatment: Medical Concomitant medications: aspirin: 34/60 captopril and 18/40 control; beta-blockers: 31/60 and 13/40; thrombolysis: 30/60 and 16/40						ITT; short follow up

Table 72: ISIS-4 1995[285]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Title ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group.	RCT (ISIS-4)	N= 58050 **Drop outs** 83% still on captopril at discharge (or death) vs. 87%	**Inclusion criteria** Up to 24 hours after onset of acute MI (MI acute); no clear indications for any study treatment (ACE inhibitor, nitrate or magnesium) except those on non-study nitrates for a few days could still be entered; LV function – unselected (mixture of dysfunction or normal; 14% had clinical	Captopril 6.25mg initial dose; 12.5mg 2 hours later; 25mg 10-12 hours later then 50mg	Placebo (n=29022)	Day -0-1, day 2-35	**Outcome 1** Death in first 5 weeks	2088/29028 (7.19%) captopril and 2231/29022 (7.69%)	**Source of funding** Bristol-Myers Squibb, Astra-Hässle, Artesan

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Journal Lancet 1995; 345: 669-685. **Country:** Multinational (31 countries) **Randomisation:** Computer-generated **Allocation Concealment:** Not stated **Blinding:** Not stated **Power Calculations:** Aim was to		placebo; 1.8% captopril and 1.6% placebo forms missing at hospital discharge **Analysis:** ITT	heart failure) **Exclusion criteria** Contraindications to study treatments (e.g. cardiogenic shock, persistent hypotension [systolic BP <90-100mmHg], severe fluid depletion) or conditions associated with only a small likelihood of worthwhile benefit (e.g. negligibly low risk of cardiac death or high risk of death from some other life-threatening disease) **Baseline characteristics** Age: 28% aged 70 years or over Gender: 74% male MI: confirmed in 92% Treatment Medical Concomitant medications: IV nitrates: 47% of patients; other short-term non-study nitrates: 8%; diuretics: 12%; antiplatelet therapy: 94%; fibrinolytic therapy 70%; IV beta-blocker 9%; antiarrhythmic: 21%; non-study ACE inhibitor 5%	twice daily for 28 days (n=29028)				placebo	Pharma, Cassella-med **Limitations** Allocation concealment, blinding and details of power calculation not stated
							Outcome 2 Stroke (to day 35 or earlier discharge)	295/29028 (1.0%) captopril and 268/29022 (0.9%) placebo	
							Outcome 3 Reinfarction (to day 35 or earlier discharge)	1162/29028 (4.1%) captopril and 1101/29022 (3.9%) placebo	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
randomise at least 40,000 patients							**Outcome 4** Dizziness (to day 35 or earlier discharge)	155/29028 (0.54%) captopril and 110/29022 (0.39%) placebo	
							Outcome 5 Renal dysfunction (to day 35 or earlier discharge)	316/29028 (1.11%) captopril and 170/29022 (0.60%) placebo	
							Outcome 6 Any profound hypotension (to day 35 or earlier discharge)	5951/29028 (20.9%) captopril and 3130/29022 (11.0%) placebo	

Table 73: Køber 1995[316]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
AuthorKøber **Journal** N Engl J Med 1995; 333: 1670-1676 (see Buch 2005 for long-term follow-up) **Country:** Denmark **Randomisation:** Computer-generated **Allocation Concealment:** Not stated **Blinding:** Double blind	RCT (Trandolapril Cardiac Evaluation [TRACE] study)	N= 1749 **Drop outs** [316]Apart from the patients who died, 328 (37.4%) withdrawn from trandolapril group and 310 (35.5%) from placebo **Analysis:** ITT	**Inclusion criteria** MI acute (in last 3-7 days); aged over 18 years; LV dysfunction (wall motion index ≤1.2, corresponding to an ejection fraction ≤35%); consent; tolerated test dose 0.5mg trandolapril **Exclusion criteria** Contraindication to ACE inhibitor or definite need for ACE inhibitor; severe uncontrolled diabetes mellitus; sodium <125mmol/L; serum creatinine >2.3mg/dL (200 micromol/L); pregnancy; lactation; acute pulmonary embolism; vascular collagen disease; non-ischaemic obstructive heart disease; unstable angina requiring immediate invasive therapy; severe liver disease; neutropenia; immunosuppressive or antineoplastic therapy; drug or alcohol abuse; treatment with another investigational drug **Baseline characteristics** Age: mean 67.7 years trandolapril and 67.3 years placebo Gender: 72% male trandolapril and 71%	Trandolapril 1mg once daily; increased after 2 days to 2mg daily and after 4 weeks to 4mg daily (n=876)	Placebo (n=873)	24-50 months	**Outcome 1** All-cause mortality up to 50 months	304/876 trandolapril (34.7%) vs. 369/873 placebo (42.3%), p=0.001	**Source of funding** Roussel-Uclaf and Knoll **Limitations** Allocation concealment not stated; large proportion of patients dropped out
							Outcome 2 Cardiovascular deaths	226/876 trandolapril (25.8%) vs. 288/873 placebo (33.0%), p=0.001	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Power Calculations: Not stated in this paper but referenced to previous publication			placebo MI: 100% Hypertension: 23% each group Treatment thrombolysis 45% trandolapril and 44% placebo Concomitant medications: aspirin: 92% trandolapril and 90% placebo; beta-blockers: 17% vs. 15%; calcium-channel blockers: 28% vs. 28%; diuretics: 64% vs. 68%; nitrates: 56% vs. 50%; digoxin/digitalis: 26% vs. 29%				**Outcome 3** Sudden deaths	105/876 trandolapril (12.0%) vs. 133/873 placebo (15.2%), p=0.03	
							Outcome 4 Total (fatal or non-fatal) reinfarction	99/876 trandolapril vs. 113/873 placebo	
							Outcome 5 Cough	297 (39 withdrew) trandolapril vs. 183 (13 withdrew) placebo	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
							Outcome 6 Hypotension	272 (18 withdrew) trandolapril vs. 193 (7 withdrew) placebo	
							Outcome 7 Renal dysfunction	120 (18 withdrew) trandolapril vs.94 (6 withdrew) placebo	
							Outcome 8 Stroke	51/876 (5.8%) trandolapril vs. 50/873 (5.7%)	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
								placebo	

Table 74: Kongstad-Rasmussen 1998[319]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Author Kongstad-Rasmussen O, Blomstrand P, Broqvist M, Dahlström U, Wranne B. **Journal** Clin Cardiol. 1998 Nov;21(11):807-11. **Title** Treatment with	RCT	N =48 **Drop outs** All patients were accounted for. However 5 were excluded bc had CABG and 1 due to disease. **Analysis:** for our outcome n=10	Acute MI with clinical evidence of HF Used the same inclusion/exclusion criteria as the AIRE study: **Inclusion criteria** Definite acute MI; and clinical evidence of heart failure LV dysfunction (at least one of: pulmonary venous congestion with interstitial or alveolar oedema; pulmonary oedema with bilateral post-tussive crackles at least one third up lung fields; third heart sound and persistent tachycardia); aged at least 18 years **Exclusion criteria** Severe heart failure (usually NYHA grade IV); heart failure of primary valvular or congenital aetiology; unstable angina;	Ramipril n=25	Placebo n=23	6 months	**Outcome 1** All-cause mortality	Ramipril = 3/25 Placebo = 1/23	**Source of funding** Swedish heart-lung foundation and Swedish Medical Research Council **Limitations** Small patient number. Acute MI with clinical evidence of HF
							Outcome 2 Reinfarction	Ramipril = 5/25 Placebo = 5/23	
							Outcome 3 Revascularisation – percutaneous transluminal coronary angioplasty	Ramipril = 1/25 Placebo = 1/23	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
ramipril improves systolic function even in patients with mild systolic dysfunction and symptoms of heart failure after acute myocardial infarction. **Randomisation:** Yes, no details **Allocation Concealment:** Not stated **Blinding:** Double-blinded **Power Calculations:** None provided			contraindications to ACE inhibitor **Baseline characteristics** RAMIPRIL n=25 Age:69 M/F: 12/13 No. receiving thrombolytic treatment: 11 No with previous MI: 6 No. with previous HF:3 Hypertension: 8 Angina pectoris:8 Diabetes:5 HF: 68 (12) SBP:127 (18) DBP: 71 (9) **EF (%) = 46 (14.9)** PLACEBO n=23 Age:67 M/F:4/19 No. receiving thrombolytic treatment:12 No with previous MI:5 No. with previous HF:1 Hypertension:5 Angina pectoris:12 Diabetes:3 HF:65 (8) SBP:121 (15)						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
			DBP: 72 (11) **EF (%) = 45 (11)** **Concomitant medications:** Concomitant medications were similar in both treatment groups at baseline and during follow-up. 40 patients were on BB, 14 on calcium channel blockers; and 9 on long-term nitrates. At entry, 39 patients were treated with furosemide, 19 patients had potassium sparing diuretics, and 3 were treated with digoxin.						

Table 75: Flather 1994[189]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Author Flather M, Pipilis A, Collins R, Budaj A, Hargreaves A, Kolettis T, Jacob A, Millane T, Fitzgerald L, Cedro K, et al.	RCT	N=741 **Drop outs** Unclear **Analysis:** ITT	**Inclusion criteria** Suspected AMI <36 hrs (3-way) <24 hrs (2x2) before randomisation, no clear indications for or contraindications to nitrates. **Exclusion criteria** None stated **Baseline characteristics** **3-way study** CAPTOPRIL n=133 Age:61±1 Female:22%	Captopril Study 1: 3-way study design Combined with Study 2: 2x2	Placebo	In hospital	**Outcome 1** All-cause mortality	Captopril: 24/370 Placebo: 19/371	**Source of funding** Bristol-Myers Squibb, Schwartz harma, Astra Pharmaceuticals, Stuart Pharmaceuticals. **Limitations:** Two different
							Outcome 2 Reinfarction	Captopril: 14/370 Placebo: 10/371	
							Outcome 3	Captop	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Title Randomized controlled trial of oral captopril, of oral isosorbide mononitrate and of intravenous magnesium sulphate started early in acute myocardial infarction: safety and haemodynamic effects. ISIS-4 (Fourth International			Prior MI:8% Prior diabetes:7% Prior hypertension:20% PLACEBO n=134 Age:62±1 Female:18% Prior MI:15% Prior diabetes:4% Prior hypertension:25% CAPTOPRIL n=237 Age:59±1 Female:23% Prior MI:14% Prior diabetes:11% Prior hypertension:33% PLACEBO n=237				Adverse events	ril: 114/370 Placebo: 79/371	study designs. Combined the results from the two studies for the ACEi group and placebo
							Outcome 4 Hypotension	Captopril: 77/370 Placebo: 43/371	
							Outcome 5 Renal impairment	Captopril: 4/370 Placebo: 6/371	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Study of Infarct Survival) Pilot Study Investigators **Journal** Eur Heart J. 1994 May;15(5):608-19. **Author** Flather M, Pipilis A, Collins R, Budaj A, Hargreaves A, Kolettis T, Jacob A, Millane T, Fitzgerald L, Cedro K, et al. **Country:** POLAND **Randomisation:** Yes, no details **Allocation Concealmen**			Age:60±1 Female:24% Prior MI:20% Prior diabetes:12% Prior hypertension:32% **Concomitant medications:** Antiplatelets: 91-98% Fibrinolytic: 58-90% Oral BB: 40-48% Antiarrhythmic: 9-22% Diurectic: 33-42%						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
t: Central randomisation, but not details **Blinding:** Unclear, likely to be open trial **Power Calculations:** Yes, estimated that 800 patients could be randomised during the 3 yrs of recruitment, and that this should provide reasonable estimates of the incidence of hypotenstion, and other common side effects and of compliance									

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
to trial treatment needed for planned large-scale mortality trial									

Table 76: Lu 1993[348]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Author Lu CY. **Title** Treatment of acute myocardial infarction with oral captopril. A randomized, double blind and placebo	RCT – ABST-RACT	N=98 **Drop outs** NA **Analysis:** NA	Acute MI Classed as unselected LV function in NICE 2001 **Inclusion criteria** NA **Exclusion criteria** NA **Baseline characteristics** Only state satisfactory randomization. **Concomitant medications:**	Captopril n=43	Placebo n=55	In hospital	**Outcome 1** All-cause mortality	Captopril = 3/43 Placebo = 8/55	**Source of funding** **Limitations** Abstract only. Published in Chinese Included in CG48, originally in NICE2001

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
controlled pilot study]. **Journal** Zhonghua Xin Xue Guan Bing Za Zhi. 1993 Apr;21(2):74-6, 121-2. Chinese. **Country:** CHINA **Randomisation:** Yes, no details **Allocation Concealment:** Not stated **Blinding:** Double blind **Power Calculations:** None stated			NA						

Table 77: Pfeffer 1997[471]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Author Pfeffer MA, Greaves SC, Arnold JM, Glynn RJ, LaMotte FS, Lee RT, Menapace FJ Jr, Rapaport E, Ridker PM, Rouleau JL, Solomon SD, Hennekens CH. **Title** Early versus delayed angiotensin-converting enzyme inhibition therapy in acute myocardial infarction. The healing and early afterload reducing therapy trial. **Journal** Circulation.	RCT	N=236 **Drop outs** Not stated. **Analysis: ITT**	Acute MI Unselected LV function **Inclusion criteria** Men and women over the age of 21 years who had experienced an MI within 24 hours were considered to be eligible. **Exclusion criteria** were relative contraindications to the use of an ACE inhibitor, need of an ACE inhibitor for treatment of congestive heart failure, serum creatinine level of ≥2.5 mg/dL, presence of a major complication of infarction that was not stabilized before randomization (eg, cardiogenic shock, persistent ischemia, or unstable rhythm), systolic blood pressure of <100 mm Hg, or failure to complete all prerandomization evaluations within 24 hours from the onset of chest pain. Institutional review board approval was obtained, and all patients provided signed informed consent before randomization. **Baseline characteristics** **Placebo-High dose, Low-Low dose, High-High dose** Male, n 91 (77.8), 90 (77.6), 93 (78.2) Mean age, y (SD) 59.9 (12.7), 61.3 (11.8), 60.7 (13.3)	Ramipril. Full-dose, titrated from 1.25 to 10mg/d in 24 hours N=119	Placebo N=117	1-14 days	**Outcome 1** All-cause mortality 1-14 days **Outcome 2** MI 1-14 days **Outcome 3** Stroke 1-14 days **Outcome 4** Revascularisation 1-14days	Ramipril: 3/119 Placebo :3/117 Ramipril: .3/119 Placebo :5/117 Ramipril: 0/119 Placebo :0/117 Ramipril: 15/119 Placebo :6/117	**Source of funding** Grant from Hoechst Marion Roussel (formerly Hoechst Roussel Pharmaceuticals, Inc) and The Upjohn Company. **Limitations** Placebo data was only available for the first 14 days. Also 3 groups, but only using data from 2.

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
1997 Jun 17;95(12):2643-51. **Country:** USA **Randomisation:** Yes. Unclear methods. Assignment was accomplished through random assignment into one of 3 groups. Randomisation was stratified by centre. **Allocation Concealment:** Unclear, not stated. **Blinding:** Double blind **Power Calculations:**			Current smoker, n 42 (35.9), 39 (33.6), 43 (36.1) Diabetes, n 16 (13.7), 26 (22.4), 31 (26.1) Hypertension, n 51 (43.6), 44 (37.9), 51 (42.9) Prior MI, n 23 (19.8), 16 (13.8), 21 (17.7) Killip class I, n 92 (79.3), 93 (80.2), 90 (75.6) **Concomitant medications:** Medication Thrombolytic 85 (72.7), 84 (72.4), 86 (72.3) PTCA: 29 (24.8), 24 (20.7), 25 (21.0) ASA: 110 (94.0), 107 (92.2), 105 (88.2) Heparin: 108 (92.3), 105 (90.5), 110 (92.4) β-Blocker: 79 (67.5), 88 (75.9), 75 (63.0) Nitrate: 100 (85.5), 98 (84.5), 101 (84.9) Calcium channel blocker: 12 (10.3), 18 (15.5), 12 (10.1)						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
None given									

Table 78: Pfeffer 1988[472]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Reference Effect of captopril on progressive ventricular dilatation after anterior myocardial infarction.	RCT	N = 59 **Drop outs** Besides due to death: ACEi n=3; placebo n=3 **Analysis:**	**Inclusion criteria** Patients who entered the early convalescent period (2-4 wks) after having had their first MI. Age between 21 to 75 yrs and a radionucleotide EF of ≤45% **Exclusion criteria** Not correct EF. Active ischemia, concurrent medical conditions, relative	Captopril n=29	Placebo n=3-0	1 yrs	**Outcome 1** All-cause mortality	ACEI =1/29 Placebo =0/30	**Source of funding** Squibb and Sons **Limitations**

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Pfeffer MA, Lamas GA, Vaughan DE, Parisi AF, Braunwald E. N Engl J Med. 1988 Jul 14;319(2):80-6. **Country:** USA **Randomisation:** Yes, no details **Allocation Concealment:** Not stated **Blinding:** Double-blind **Power Calculations:** None provided			contraindication to captopril. Needing revascularisation. **Baseline characteristics** **CAPTOPRIL n=30** Age: 59 ± 2 M/F:26/4 Hypertension:12 (40%) Diabetes:3 (10%) Current Smoking:15 (50%) Angina before MI:5 (17%) High cholesterol:5 (17%) Peak creatine kinase:3149 ± 335 PTCA or thrombolytic therapy: 4(13%) Killip class I/II/III: 15/13/2 Radionuclide EF %:30±2 **PLACEBO n=29** Age: 56±2 M/F:28/1 Hypertension:8 (28%) Diabetes:2 (7%) Current Smoking:18 (62%) Angina before MI:3 (10%) High cholesterol:5 (17%) Peak creatine kinase:3235±329 PTCA or thrombolytic therapy:6(21%) Killip class I/II/III: 15/14/0 Radionuclide EF %:30±1						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
			Concomitant medications: Study medication was added to optimal conventional therapy, including BB. The use of digitalis, diuretics, and antiarrhythmic agents was left to the discretion of the physician. Vasodilators or ACEi not according to the study protocol was prohibited. No patient required long-acting nitrates at the time of randomisation.						

Table 79: Pffefer 1992[470]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Author Pfeffer **Journal** N Engl J Med 1992; 327: 669-77. **Country:** US and Canada **Randomisation:** Computer-	RCT	N= 2231 **Drop outs** Vital status not ascertained for 2 captopril and 4 placebo patients **Analysis:**	**Inclusion criteria** MI acute; survived the first 3 days; LV dysfunction (≤40% [mean 31% both groups]); aged at least 21 years; <80 years **Exclusion criteria** Failure to undergo randomisation within 16 days of MI; relative contraindication to ACE inhibitor or need to use ACE inhibitor to treat symptomatic congestive heart failure or systemic hypertension; serum creatinine	Captopril initial dose 12.5mg; target dose 25mg three times daily by hospital discharge, increased to maximum 50mg three times daily unless adverse events; 79%	Placebo (n=1116)	Minimum 2 years; mean 42 (10) months, range 24-60 months	**Outcome 1** Death	228/1115 (20%) captopril vs. 275/1116 placebo (25%), p=0.019	**Source of funding** Bristol-Myers Squibb **Limitations** Allocation concealment not stated; power calculation not stated; not all patients had
							Outcome 2 Cardiovasc	188/1115	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
generated **Allocation Concealment:** Not stated **Blinding:** Double blind **Power Calculations:** Not stated		ITT	>2.5mg/dL; other conditions believed to limit survival; unwilling/unable to participate in long-term trial; unstable course after infarction (if recurrent ischaemia 72 hours after onset and revascularisation required, this had to be performed before randomisation). **Baseline characteristics** Age: mean 59.3 years captopril group and 59.5 years placebo group Gender: 83% male captopril group and 82% male placebo group MI: 100% Hypertension: 44% captopril group and 42% placebo group Treatment: Thrombolytic therapy 34% captopril group and 32% placebo group; PTCA: 17% each group; CABG: 10% captopril group and 8% placebo group Concomitant medications: Antiarrhythmics: 14% captopril and 11% placebo; anticoagulant: 28% each group; aspirin: 59% each group; other antiplatelet agents 14% each group; beta-blockers: 35% captopril and 36% placebo; calcium-channel blockers: 42% each group; digitalis: 25% captopril and 27% placebo; diuretics: 35% each group; nitrates: 50% captopril and 53% placebo	reached 150mg/day (n=1115)			ular death **Outcome 3** Sudden death **Outcome 4** Fatal MI **Outcome 5** Non-fatal MI	captopril vs. 234/1116 placebo, 105/1115 captopril vs. 125/1116 placebo 108/1115 captopril vs. 129/1116 placebo 25/1115 captopril vs. 41/1116 placebo	repeat ejection fractions measured

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
							Outcome 6 Hospitalisation (due to HF)	154/1115 (14%) captopril vs. 192/1116 (17%%) placebo	
							Outcome 7 Dizziness	32/1115 captopril vs. 25/1116 placebo	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
							Outcome 8 Cough	27/1115 captopril vs. 9/1116 placebo, p=0.003	

Table 80: Foy 1994[197]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
AuthourFoy for the PRACTICAL investigators **Journal**Am J Cardiol 1994; 73; 1180-1186. **Country:** New Zealand **Randomisation:** Not stated	RCT (PRACTICAL study)	N= 225 **Drop outs** 42/225 withdrawn (18 [24%] captopril, 12 [16%] enalapril and 12 [16%] placebo); due to hypotension (5 captopril, 5 enalapril	**Inclusion criteria** Within 24 hours of onset of chest pain (MI acute); LV function – unselected (mixture of dysfunction [6 patients] or normal) **Exclusion criteria** Persistent hypotension (systolic BP <90mmHg); sensitivity to ACE inhibitors or use of ACE inhibitors within 1 week; haemodynamically significant valvular stenosis; clinically severe renal or hepatic disorders; clear indication for treatment with ACE inhibitor; no consent; expected to comply poorly with treatment	Oral captopril 6.25mg at 2-hour intervals for 3 doses, then 25mg 3 times daily (n=75; target dose achieved in 65%); or oral enalapril 1.25mg at 2-hour intervals for 3 doses, then 5mg 3 times daily (n=75; target dose achieved	Placebo (n=75; target dose achieved in 80%)	90 days and 12 m	**Outcome 1** Adverse effects not requiring withdrawal of treatment: **Outcome 2** Dizziness	18 captopril, 12 enalapril and 12 placebo 15 captopril, 14 enalapril and 6 placebo	**Source of funding** Merck sharp and Dohme, Bristol-Myers Squibb **Limitations** Randomisation and allocation concealment: not stated

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Allocation Concealment: Not stated **Blinding:** Double blind **Power Calculations:** 50 patients required in each group to detect a 3% difference in ejection fraction from baseline between combined ACE inhibitor group and placebo with p=0.05 and power 80%; target set at 75 per group to allow for attrition		and 2 placebo), rash (3, 4 and 1) or withdrawal of consent (1, 4 and 3) **Analysis:** ITT	**Baseline characteristics** Age: mean 64 years captopril, 63 years enalapril and 64 years placebo Gender: 75% male captopril, 79% enalapril and 77% placebo MI: 100% Treatment thrombolysis: 68% captopril, 75% enalapril and 73% placebo Concomitant medications: beta-blockers: 25% captopril, 11% enalapril and 15% placebo (p=0.046); calcium-channel blockers: 21%, 15% and 15%; digoxin: 3%, 4% and 4%; diuretics: 9%, 4% and 13%; NSAID: 11%, 12% and 4%	in 79%)			**Outcome 3** Hypotension	5 captopril,5 enalapril and 2 placebo	
							Outcome 4 Cough	6 captopril, 4 enalapril and 2 placebo	
							Outcome 5 Headache	0 captopril, 1 enalapril and 1 placebo	
							Outcome 6 Death by 90 days	9 captopril, 1 enalapril and 7 placebo	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
							Outcome 7 Cardiac death (LV failure, cardiac rupture, arrhythmia, ventricular fibrillation) – 90 days	7 captopril, 1 enalapril and 7 placebo; 1 not specified which group	
							Outcome 8 Sudden death -90 days	3 captopril, 1 enalapril and 1 placebo	
							Outcome 9 Death by 12 months	10 captopril, 2 enalapril and 12 placebo	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
							Outcome 10 Cardiac causes (12 months)	8 captopril, 1 enalapril and 12 placebo	
							Outcome 11 Sudden death (12 months)	4 captopril, 1 enalapril and 4 placebo	

Table 81: Ray 1993[493]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Author Ray. **Journal** Br Heart J 1993; 69: 215-222.	RCT	N= 99 **Drop outs** 22/99	**Inclusion criteria** Within 24 hours of acute MI (MI acute); clinically and haemodynamically stable; aged 40-75 years	Captopril 6.25mg; if tolerated, repeated at 1 hour; 12.5mg	Placebo (n=50)	12 months	**Outcome 1** Death at 1 year	8 captopril and 10 placeb	**Source of funding** Not stated

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Country: Scotland **Randomisation:** Not stated **Allocation Concealment:** Not stated **Blinding:** Double blind **Power Calculations:** Not stated		withdrawn; follow up data available for 73/99 **Analysis:** ITT	LV function – unselected (mixture of dysfunction or normal [mean 37.4 (1.8)% captopril and 35.2 (1.8)% placebo) **Exclusion criteria** Norris score <3.5; systolic BP <95mmHg; history of significant renal or cerebrovascular disease; contraindication to captopril; definite indication for its use; no consent **Baseline characteristics** Age: mean 61 (1) years captopril and 59 (1) years placebo Gender: 82 men; 17 women MI: 100% Treatment (Medical) Concomitant medications not stated	at 8 hours; then 12.5mg three times daily with target dose 25mg three times daily before discharge (n=49)				o	**Limitations** Randomisation, allocation concealment and power calculations not stated
							Outcome 2 Sudden death 1 year	4 captopril and 6 placebo	
							Outcome 3 Cardiac failure requiring withdrawal	2 captopril and 2 placebo	
							Outcome 4 Reinfarction	3 captopril, 1 placebo	
							Outcome 5 CABG	1 captopril, 1 placebo	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
							Outcome 6 Hypotension	0 captopril, 1 placebo	
							Outcome 7 Cough	1 captopril, 0 placebo	

Table 82: Sharpe 1988[538]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Author Sharpe N, Murphy J, Smith H, Hannan S. **Title** Treatment of patients with symptomless left ventricular dysfunction	RCT	N = 60 **Drop outs** Not for our relevant outcomes. Otherwise, captopril n=4. placebo n=6 **Analysis:**	Sub-acute MI (average 9 days post MI) LVSD **Inclusion criteria** Recent Q wave MI who were symptom free and clinically stable and not on cardiac drugs before discharge. **Exclusion criteria** Those requiring treatment for myocardial ischemia, arrhythmias, or HF, atrial fibrillation, valvular HD, chronic lung disease, other serious systemic	Captopril 3x25mg/d, N=20	Placebo N=20	12m	**Outcome 1** All-cause mortality	ACEi = 0/20 Placebo = 1/20	**Source of funding** National heart foundation of NZ **Limitations:** Unclear exactly how many in group.
							Outcome 2 Reinfarction	ACEi = 2/20 Placebo =2/20	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
after myocardial infarction. **Journal** Lancet. 1988 Feb 6;1(8580):255-9. **Country:** NZ **Randomisation:** Yes, no details **Allocation Concealment:** Not stated **Blinding:** Double blind **Power Calculations:** None provided		ITT	diseases, renal impairment. **Baseline characteristics** CAPTOPRIL Age: 59 (38-74) MF:19/1 Ant/Inf MI: 11/9 Peak creatine kinase U/L:2368 (1119) No with MI:0 No with hypertension:4 Time to entry post MI d):9 (4) EF %: 36.3 (1.2) PLACEBO Age:53 (31-72) MF:19/1 Ant/Inf MI:12/8 Peak creatine kinase U/L:2039 (1055) No with MI:3 No with hypertension:3 Time to entry post MI:9 (4) EF %: 37.9 (1.2) **Concomitant medications:** If symptoms or signs of HF occurred during treatment, the trial medication was doubled. If no improvement were evident after 1 week, frusemide 40mg daily was added openly and increased.						3-way study design with frusemide however only ACEi vs. placebo data was used

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
			1 patient in Captopril required doubling of trial medication after 1 month. 2 patients in placebo required doubling of trial medication and additional frusemide after 1 and 4 months.						

Table 83: Sharpe 1991[539]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Author Sharpe **Journal** Lancet 1991; 337: 872-876. **Country:** New Zealand	RCT	N= 100 **Drop outs** 12 captopril and 11 placebo withdrawn **Analysis:**	**Inclusion criteria** MI acute; definite Q-wave MI; clinically stable 24-48 hours after onset of symptoms, echocardiography with adequate image quality, consent, tolerated open dose captopril 12.5mg; LV function – unselected (mixture of dysfunction or normal)[mean 40.2 (7.0)% captopril and 41.1 (6.4)% placebo]	Captopril 25mg twice daily; increased to 50mg twice daily on 2nd day and continued for 3 months (n=50)	Placebo (n=50)	3 months	**Outcome 1** Sudden death	Captopril 3 patients; placebo 2 patients	**Source of funding** National Heart foundation of New Zealand and E R Squibb & Sons Ltd

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Randomisation: Not stated **Allocation Concealment:** Not stated **Blinding:** Double blind **Power Calculations:** Not stated		Not stated	**Exclusion criteria** Ongoing myocardial ischaemia; atrial fibrillation or other arrhythmia requiring treatment; valvular disease, clinical congestive cardiac failure, hypotension (systolic BP <90mmHg), chronic lung disease, serum creatinine >0.20mmol/L, other serious concomitant disease **Baseline characteristics** Age: mean 59 (8) years captopril, 56 (9) years placebo Gender: 41/50 male captopril; 42/50 male placebo MI: 100% Hypertension: 16 captopril and 16 placebo				**Outcome 2** Recurrent MI	Captopril 1 patient; placebo 4 patients	**Limitations** Randomisation and allocation concealment not stated; power calculation not stated; not stated if ITT
							Outcome 3 Hypotension	Captopril 1 patient; placebo 0 patients	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
			Treatment: thrombolysis: 38/50 captopril, 34/50 placebo (PCI, CABG, Medical) Concomitant medications: nitrates: 5 captopril and 6 placebo; beta-blockers: 11 captopril and 10 placebo; calcium-channel blockers: 8 captopril and 11 placebo; frusemide: 7 captopril and 7 placebo; digoxin: 0 captopril and 4 placebo; warfarin: 3 captopril and 5 placebo						

Table 84: Sogaard 1993[551]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Author Søgaard P, Gøtzsche CO, Ravkilde J, Thygesen K.	RCT	N = 64 **Drop outs** N=1 lost to follow-up	Sub-acute MI (after 7 days) LVSD – average 40 (30-45)	Captopril 2x 12.5mg/d N=32	Placebo N=32	180 days	**Outcome 1** All-cause mortality	Captopril = 1/32 Placebo = 1/32	**Source of funding** None stated

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Title Effects of captopril on ischemia and dysfunction of the left ventricle after myocardial infarction. **Journal** Circulation. 1993 Apr;87(4):1093-9. **Country:** USA **Randomisation:** Yes, no details **Allocation Concealment:** Not stated **Blinding:** Yes, double-blind		**Analysis:** ITT	**Inclusion criteria** Patients younger than 70 years of age, suffering from MI and had left EF <45% as evaluated by echocardiography on day 5 after MI. **Exclusion criteria** Patients who required an ACEi or digoxin. Subjected to CABG during the follow-up. **Baseline characteristics** CAPTOPRIL n=32 Age(yrs): 60 (35-70) MF: 28/4 Previous MI: 2 Hypertension:5 Diabetes:4 Ant/Inf MI:17/15 Peak creatinine kinase U/L:83 (17-210) Congestive HF: 20 Angina pectoris: 17 EF (%):39 (25-45) PLACEBO Age(yrs): 58 (43-70) MF:30/2 Previous MI:1 Hypertension:5 Diabetes:4				**Outcome 2** Revascularisation	Captopril =2/32 Placebo = 1/32	**Limitations:** Patients were given an initial blinded dose of 6.25mg on day 1 followed by placebo or captopril for next 14 days. Unclear what the initial dose was

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Power Calculations: None provided			Ant/Inf MI:18/14 Peak creatinine kinase U/L: 87 (17-276) Congestive HF:18 Angina pectoris:15 EF (%):40 (30-45) **Concomitant medications:** **CAPTOPRIL n=32** Metoprolol: 24 (75%) Diltiazem:6 (19%) Isosobide mononitrate:5 (16%) Streptokinase:25 (78%) Acetylsalicyclic acid: 32 (100%) Furosemide:20 (63%) **PLACEBO:32** Metoprolol: 23(72%) Diltiazem:8 (25%) Isosobide mononitrate: 5 (16%) Streptokinase:26 (18%) Acetylsalicyclic acid: 32 (100%) Furosemide: 18 (56%)						

Table 85: Wagner 2002[607]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Author Wagner A, Herkner H, Schreiber W, Bur A, Woisetschläger C, Stix G, Laggner AN, Hirschl MM. **Title** Ramipril prior to thrombolysis attenuates the early increase of PAI-1 in patients with acute myocardial infarction. **Journal** Thromb Haemost. 2002 Aug;88(2):180-5. **Country:** AUSTRIA	RCT	N = 99 **Drop outs** None **Analysis:** ITT	**Inclusion criteria** Acute MI patients undergoing thrombolysis Unclear of LV status **Exclusion criteria** Chest pain relieved by nitroglycerin or <30min in duration; history of MI; contraindication to thrombolytic therapy including history of bleeding disorder or cerebrovascular accident, gastrointestinal bleeding or genitourinary bleeding within 4 wks, major surgery, trauma or cardiopulmonary resuscitation within 14 days, uncontrolled hypertension, contraindications to ramipril, current therapy with cytotoxic drugs, serious advanced illness, hypotension of admission, cardiogenic shock, treatment with ACEI in last 2 wks, pregnancy or ability to become pregnant, lactation, physical or psychological inability to participate. **Baseline characteristics** RAMIPRIL n=51 Age: 55 (12) M/F:79/21 Hyptension:43 Diabetes:14 Current smoker:48	Ramipril 2.5mg, Before thrombolysis, then 2.5 mg after thrombolysis n=51	Placebo =48 Ramipril 2.5mg, Before thrombolysis, then placebo	24 hours – 1 week	**Outcome 1** All-cause mortality – 1 week **Outcome 2** Hypotensive events <24 hours	Ramipril: 1/51 Placebo: 1/48 Ramipril: 2/51 Placebo: 1/48	**Source of funding** Aventis Pharma, Austria provided medication. **Limitations.** All patients received ramipril after 24 hours with a starting dose of 2.5 mg

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Randomisation: Yes, no details **Allocation Concealment:** Unclear, not stated **Blinding:** Double blind **Power Calculations:** None provided			Hyperlipidemia:34 HR:80 (20) Ant/Inf MI:25/26 PLACEBO n=48 Age:55 (11) M/F: 69/31 Hyptension:29 Diabetes:16 Current smoker:52 Hyperlipidemia:36 HR:79(17) Ant/Inf MI: 22/26 **Concomitant medications**: RAMIPRIL: ASA:10 BB:24 Calciumantagonists:1 Diurectics:3 Nitrates:1 PLACEBO: ASA:14 BB:22 Calciumantagonists:2 Diurectics:4 Nitrates:1						

Table 86: Wu 1997[621]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
AuthorWu N, Fan Z for Beijing Collaborative Study Group. **Journal** Chinese Medical Journal 1997; 110: 602-606. **Country:** China **Randomisation:** Not stated **Allocation Concealment:** Not stated **Blinding:** Not stated **Power Calculations:** Not stated	RCT	N= 1106 **Drop outs** Not stated **Analysis:** ITT	**Inclusion criteria** Confirmed MI (drugs started 2-4 weeks after onset of MI; MI non-acute); age < 75 years; no contraindication to study medication; possibility of prolonged follow up LV function – unselected (mixture of dysfunction or normal): mean over 50% (from graph) **Exclusion criteria** None stated **Baseline characteristics** Age: mean 59.3 (9.2) years Gender: Male: female ratio 2.8:1 MI: 100% Treatment not stated Concomitant	Group E: Enalapril 10mg started 2-4 weeks after onset of MI (n=349)	Group C: control: Conventional therapy only (n=372)	19 months (568 +/- 341 days)	**Outcome 1** Sudden cardiac death **Outcome 2** Heart failure deaths **Outcome 3** CV deaths	Group E: n= 5/349 Group C: n= 6/372 group E: n=0/349 group C: n=3/372 group E: 5/349 Group C:= 8/372	**Source of funding** Ministry of Health **Limitations** Randomisation, allocation concealment and power calculations not stated; no placebo group used for controls; some outcomes not given as numbers of patients and not calculable; baseline LVEF unclear (shown graphically only) and no SDs for change scores

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
			medications: all given aspirin						

Table 87: Yusuf 2000[635]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Author Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. **Title** Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on	RCT	N **Drop outs** Ramipril = 1511/4645 (32.5%) Placebo = 1430/4652 (30.7%) **Analysis:** ITT	**Inclusion criteria** Men and women who were at least 55 years old were eligible for the study if they had a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes plus at least one other cardiovascular risk factor (hypertension,	Ramipril. A dose of 2.5 mg once a day for one week, 5 mg for the next three weeks, and then 10 mg. N=4645	Placebo N=4652	Mean 5 years	**Outcome 1** Composite outcome for post MI patients only. CV death, MI, stroke	Estimate Ramipril = 393/2410 Placebo = 519/2482 RR=0.78(0.69,0.88)	**Source of funding** Funded by the Medical Research Council of Canada, Hoechst–Marion Roussel, AstraZeneca, King Pharmaceuticals, Natural Source

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators **Journal** N Engl J Med. 2000 Jan 20;342(3):145-53. Erratum in: 2000 May 4;342(18):1376. N Engl J Med 2000 Mar 9;342(10):748 **Country:** CANADA **Randomisation:** Yes **Allocation Concealmen**			elevated total cholesterol levels, low high-density lipoprotein cholesterol levels, cigarette smoking, or documented microalbuminuria). **Exclusion criteria** Patients were excluded if they had heart failure, were known to have a low ejection fraction (<0.40), were taking an angiotensin-converting–enzyme inhibitor or vitamin E, had uncontrolled hypertension or overt nephropathy, or had had a myocardial infarction or stroke within four weeks before the study began. **Baseline characteristics**						Vitamin E Association and Negma, and the Heart and Stroke Foundation of Ontario. Dr. Yusuf was supported by a Senior Scientist Award of the Medical Research Council of Canada and a Heart and Stroke Foundation of Ontario Research Chair. **Limitations** Composite outcome only for post MI subgroup. Had to estimate the RR

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
t: **Blinding:** Double blind **Power Calculations:** The study was originally designed to follow participants for a mean of 3.5 years. However, before the end of this period, the steering committee (whose members were unaware of any of the results) recommend ed increasing the duration of follow-up to five years			**RAMIPRIL (n=4645)** Age — yr 66±7 Blood pressure — mm Hg 139±20/79±11 Heart rate — beats/min 69±11 Body-mass index 28±4 Female sex — no. (%) 1279 (27.5) History of coronary artery disease no. (%)3691 (79.5) Myocardial infarction2410 (51.9) Within «1 year452 (9.7) Within >1 year1958 (42.2) Stable angina pectoris2544 (54.8) Unstable angina pectoris1179 (25.4) CABG1192 (25.7) PTCA853 (18.4) Stroke or transient ischemic attacks— no. (%) 500 (10.8) Peripheral vascular disease— no. (%)†						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
to account for the impact of a possible lag before treatment had its full effect. Assuming an event rate of 4 percent per year for five years, we calculated that 9000 patients would be required for the study to have 90 percent power to detect a 13.5 percent reduction in the relative risk with a two-sided alpha level of 0.05 and with			1966 (42.3) Hypertension — no. (%) 2212 (47.6) Diabetes — no. (%) 1808 (38.9) Documented elevated total cholesterol level — no. (%) 3036 (65.4) Documented low HDL cholesterol level — no. (%) 842 (18.1) Current cigarette smoking — no. (%) 645 (13.9) Left ventricular hypertrophy on electrocardiography — no. (%) 379 (8.2) Microalbuminuria — no. (%) 952 (20.5) **PLACEBO (N=4652)** Age — yr 66±7 Blood pressure — mm Hg 139±20/79±11 Heart rate — beats/min 69±11 Body-mass index 28±4						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
data analyzed on an intention-to-treat basis			Female sex — no. (%) 1201 (25.8) History of coronary artery disease— no. (%)3786 (81.4) Myocardial infarction: 2482 (53.4) Within «1 year: 446 (9.6) Within >1 year: 2036 (43.8) Stable angina pectoris: 2618 (56.3) Unstable angina pectoris: 1188 (25.5) CABG: 1207 (25.9) PTCA: 806 (17.3) Stroke or transient ischemic attacks — no. (%) 513 (11.0) Peripheral vascular disease— no. (%)† 2085 (44.8) Hypertension — no. (%)2143 (46.1) Diabetes — no. (%)1769 (38.0) Documented elevated total						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
			cholesterol level — no. (%)3089 (66.4) Documented low HDL cholesterol level — no. (%)881 (18.9) Current cigarette smoking — no. (%) 674 (14.5) Left ventricular hypertrophy on electrocardiography — no. (%) 406 (8.7) Microalbuminuria — no. (%) 1004 (21.6) **Concomitant medications:** **RAMIPRIL** Medications — no. (%) Beta-blockers: 1820 (39.2) Aspirin or other antiplatelet agents: 3497 (75.3) Lipid-lowering agents: 1318 (28.4) Diuretics: 713 (15.3) Calcium-channel blockers: 2152 (46.3) **PLACEBO**						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
			Medications — no. (%) Beta-blockers 1853 (39.8) Aspirin or other antiplatelet agents: 3577 (76.9) Lipid-lowering agents: 1340 (28.8) Diuretics: 706 (15.2) Calcium-channel blockers: 2228 (47.9)						

Table 88: Yusuf 1992[6]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Author The SOLVD Investigators **Title** Effect of Enalapril on Mortality and the Development of Heart Failure in Asymptomatic Patients	RCT	N=4228 **Drop outs** Enalapril 8%; placebo 45% **Analysis:** ITT	Past MI (80%) EF <0.35 **Inclusion criteria** Patients known to have heart disease who had ejection fractions of 0.35 or less and who were not receiving diuretics, digoxin, or vasodilators for the treatment of heart failure were eligible for the Prevention Trial. Patients were allowed	Enalapril n=2111 Initial dose of 2x2.5 mg/d, which was gradually increased to 2x10 mg/d twice daily unless side effects developed.	Placebo n=2117	37.4m (14.6 to 62m)	**Outcome 1** All-cause mortality	Enalapril: 313/2111 Placebo: 334 /2117	**Source of funding** National heart, Lunch and Blood institute and Merck Sharp and Dohme. **Limitations** Unclear when the previous MI patients had their MI
							Outcome 2 CV mortality	Enalapril: 265/2111 Placebo: 298 /2117	
							Outcome 3 Reinfarction	Enalapril: 46/2111 Placebo: 52 /2117	
							Outcome 4 Stroke	Enalapril: 10/2111	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
with Reduced Left Ventricular Ejection Fractions **Journal** N Engl J Med 1992; 327:685-691 **Country:** USA **Randomisation:** Yes, no details **Allocation Concealment:** Not stated **Blinding:** Double-blinding **Power Calculations:** We estimated that a sample of 4100 patients			to receive diuretics for hypertension, digoxin for current or past atrial fibrillation, or nitrates for angina. Patients who had no evidence of overt heart failure at the end of the three-week run-in period, during which they were given enalapril for the first week and placebo for the remainder, were entered into the Prevention Trial. After randomization, the patients were seen after two weeks, six weeks, and four months, and every four months thereafter. **Exclusion criteria** None provided **Baseline characteristics** ENALAPRIL n=2111 Age:59.1 EF:0.28					Placebo: 13/2117	
							Outcome 5 Hospitalization (for CHF)	Enalapril: 242 /2111 Placebo: 375/2117	
							Outcome 6 Adverse events	Enalapril: 1604/2111 Placebo: 1524/2117	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
followed for an average of three years would provide a 90 percent power to detect a 25 percent reduction in mortality.1 , 6 The sample size was increased to 4600 in order to protect against unexpectedly low event rates or poor compliance.			HR:74/6 Serum creatinine (mg/dl):1.2 Males 88.5% <u>Race:</u> White 86.4% Black 9.2% Other:4.1% NYHA functional class I/II:66.3%:33.4% <u>History of:</u> MI:80.5% Ischemic heart disease:83.5% Hypertension:36.8% Diabetes:15.4% <u>At baseline:</u> Angina:33.8% AF:3.9% PLACEBO n=2117 Age:59.1 EF:0.28 HR:75.2 Serum creatinine (mg/dl): 1.2 Males: 88.6% Race: White:86.5%						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
			Black: 9.7% Other:3.4% NYHA functional class I/II: 67.1%:32.7% <u>History of:</u> MI:79.4% Ischemic heart disease:82.9% Hypertension:37.3% Diabetes:15.1% <u>At baseline:</u> Angina:33.8 AF:4.0 **Concomitant medications:** ENAPRIL Neither digoxin nor diurectics:74.9% Digoxin:11.7% Diurectics:16.2% Nitrates:30.6% Antiarrhythmic drugs:14.4% BB:24.3% CCB:35.6% Anticoagulants:11.2% Antiplatelet agents:55.7%						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
			Potassium supplements:5.5% PLACEBO Neither digoxin nor diurectics:72.3% Digoxin:13.2% Diuretics:17% Nitrates:29.9% Antiarrhythmic drugs:15.7% BB:23.7% CCB:34.1% Anticoagulants:12.3% Antiplatelet agents:52.7% Potassium supplements:6.4%						

G.4.2 Initiation of ACE inhibitors

Table 89: Pfeffer 1997 (HEART)[471]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Pfeffer MA, Greaves SC, Arnold JM, Glynn RJ, LaMotte FS, Lee RT, Menapace FJ Jr, Rapaport E, Ridker PM, Rouleau JL, Solomon SD, Hennekens CH. **Title** Early versus delayed angiotensin-converting enzyme inhibition therapy in acute myocardial infarction.	RCT	N=236 Drop outs Not stated. Analysis: ITT	Acute MI < 24 hours; Unselected LV function Inclusion criteria Men and women over the age of 21 years who had experienced an MI within 24 hours were considered to be eligible. Exclusion criteria were relative contraindications to the use of an ACE inhibitor, need of an ACE inhibitor for treatment of congestive heart failure, serum creatinine level of ≥2.5 mg/dL, presence of a major complication of infarction that was	Early initiation (1-14 days) of Ramipril full-dose N=117 The initial dose 1.25mg ramipril and then 2.5mg ramipril at 12 hours and titrated in 24-hour intervals to a maximum dose of 10mg/day.	Late initiation (14 to 90 days) of Ramipril full dose, N=119 The late initiation group had been receiving 0mg/day for 1-14 days as the placebo group, then were titrated to 10mg on day 14.	90 days	**Outcome 1** All-cause mortality	Early: 4/117 (3.41%) Late: 6/119 (5.04%)	**Source of funding** Grant from Hoechst Marion Roussel (formerly Hoechst Roussel Pharmaceuticals, Inc) and The Upjohn Company. Limitations 3 groups, but only using data from 2.Unclear randomisation method; no power calculation; no details of drop-outs. Differences at baseline for diabetes with the late
							Outcome 2 MI	Early : 6/117 (5.13%) Late : 8/119 (6.7%)	
							Outcome 3 Stroke	Early: 1/117 (0.85%) Late: 1/119 (0.98%)	
							Outcome 4 Revascularisation7	Early: 19/117 (16.24%) Late: 10/119 (8.4%)	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
The healing and early afterload reducing therapy trial. **Journal** Circulation. 1997 Jun 17;95(12):2643-51. Country: USA Randomisation: Yes. Unclear methods. Assignment was accomplished through random assignment into one of 3 groups. Randomisation was stratified by centre and			not stabilized before randomization (eg, cardiogenic shock, persistent ischemia, or unstable rhythm), systolic blood pressure of <100 mm Hg, or failure to complete all pre-randomization evaluations within 24 hours from the onset of chest pain. Institutional review board approval was obtained, and all patients provided signed informed consent before randomization. Baseline characteristics Placebo-High dose, Low-Low dose, High-High dose Male, n 91 (77.8), 90 (77.6), 93 (78.2) Mean age, y (SD)59.9 (12.7), 61.3 (11.8), 60.7 (13.3)						initiation group having lower diabetes. Statistical analyses were carried out on baseline data and the authors state that demographics were comparable but no further statistical details given. Trial stopped early because results from GISSI-3 and ISIS-4 showed substantial portion of lives are saved within the first several days of acute MI.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
use of reperfusion therapy. Allocation Concealment: Randomisation was carried out by the data coordinating centre. Blinding: Double blind Power Calculations: None given			Current smoker, n 42 (35.9), 39 (33.6), 43 (36.1) Diabetes, n 16 (13.7), 26 (22.4), 31 (26.1) Hypertension, n 51 (43.6), 44 (37.9), 51 (42.9) Prior MI, n 23 (19.8), 16 (13.8), 21 (17.7) Killip class I, n 92 (79.3), 93 (80.2), 90 (75.6) Concomitant medications: Medication Thrombolytic 85 (72.7), 84 (72.4), 86 (72.3) PTCA: 29 (24.8), 24 (20.7), 25 (21.0) ASA: 110 (94.0), 107 (92.2), 105 (88.2) Heparin: 108 (92.3), 105 (90.5), 110 (92.4) β-Blocker: 79 (67.5), 88 (75.9), 75 (63.0) Nitrate: 100 (85.5),						

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			98 (84.5), 101 (84.9) Calcium channel blocker: 12 (10.3), 18 (15.5), 12 (10.1)						

Table 90: Di Pasquale 1994A[155]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Di Pasquale P, Paterna S, Cannizzaro S, Bucca V. **Title** Does captopril treatment before thrombolysis in acute myocardial infarction attenuate reperfusion damage? Short-term and long-	RCT	N=371 randomised 51 dropped out as no enzymatic variations so classified as unstable angina; 61 were excluded as they did not fulfil the reperfusion criteria. Number studied: N=259 total; N= 131 in	Patients with acute myocardial infarction - STEMI <4 hours, unclear LV function. Inclusion criteria: Had a first episode of acute MI; Killip class I-II; acceptable echocardiographic window; admitted within 4 hours of onset of symptoms (pain); ST elevation of at least 1mm in the peripheral leads and 2mm in the	Captopril pre-treatment (6.25mg orally as first dose at least 15 minutes before thrombolysis and then every 8 hours for the first 2 days, from the third to the sixth day 12.5mg ever 8 hours). The captopril dose was subsequently increased depending on blood pressure change, to a	Late-treatment group: 6.25mg captopril as first dose 3 days after thrombolysis; the captopril dose was subsequently increased as pre-treatment group.	Minimum 6 months follow-up	Myocardial revascularisation (PTCA/CABG)	Pre-treatment: 44/131 (33.59%) Late treatment: 43/128 (33.59%)	Source of funding: no details. Limitations: unclear randomisation and allocation concealment; no power calculation; single-blinded Notes: 107 patients (58 from pre-treatment group and

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
term effects. **Journal** International Journal of Cardiology, 1994, 43; 43-50. Country: Italy Randomisation: unclear, no details. Allocation Concealment: unclear, no details. Blinding: single blinded. Power Calculations: No power calculations reported.		pre-treatment group; N= 128 late-treatment group. 23 died (11 in the pre-treatment group and 14 in the late-treatment group). Analysis: not stated but analysis included all patients who were left after exclusions for not meeting reperfusion and those classified as unstable angina.	precordial leads, involving more than one lead with concomitant alterations of the segmentary kinetic in the mono-2-dimensional echocardiograph (M-2D echo) (Aloka 720; Sonos HP); blood concentrations of CK, CK-MB at the basal sample before thrombolysis had to be within normal range. Exclusion criteria: Patients not suitable for thrombolysis; left branch block (LBB) on admission ECG, cardiomyopathy, or previous episodes of heart failure; not	maximum of 25mg every 8 hours.					49 from late treatment group) also received IV metoprolol.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			satisfying the reperfusion criteria; already receiving ACE-inhibitors. Baseline characteristics: Pre-treatment group: Sex (M/F): 106/25 Age (years): 61+/-2 Early VHA: 16 (12.2%) Lown's Class >2: 19 (14.5%) Associated therapy (BB): 58 (44.3%) Late-treatment: Sex (M/F): 102/26 Age (years): 59+/-2 Early VHA: 50 (39%) Lown's Class >2:						

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			34 (26.5%) Associated therapy (BB): 49 (38.3%)						

G.4.3 Titration of ACE inhibitors

Table 91: Flather 1994 [189]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Reference Flather M, Pipilis A, Collins R, Budaj A, Hargreaves A, Kolettis T, Jacob A, Millane T, Fitzgerald L, Cedro K, et al.	RCT	N=370 **Drop outs** unclear **Analysis:** ITT	**Inclusion criteria** Suspected AMI <36 hrs (3-way) <24 hrs (2x2) before randomisation, no clear indications for or contraindications to nitrates. **Exclusion criteria** None stated **Baseline characteristics**	Captopril Low: 3-way study design Initial =6.25mg 2hr=12.5mg/d 8-12hr = 37.5mg/d 12hr-28d = 37.5mg/d	Captopril High 2x2 Initial =6.25mg/d 2hr =12.5mg/d 8-12hr = 25mg/d 12hr-28d =100mg/d	In hospital	**Outcome 1** All-cause mortality	Captopril L: 3/133 Captopril H: 21/237	**Source of funding** Bristol-Myers Squibb, Schwartz harma, Astra Pharmaceutic als, Stuart Pharmaceutic als. **Limitations:** Two different study
							Outcome 2 Reinfarction	Captopril L: 5/133 Captopril H: 9237	
							Outcome 3 Adverse events	Captopril L: 29/133 Captopril H: 85/237	
							Outcome 4 Hypotension	Captopril L: 20/133 Captopril H: 57/237	
							Outcome 5	Captopril L: 0/133	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Randomized controlled trial of oral captopril, of oral isosorbide mononitrate and of intravenous magnesium sulphate started early in acute myocardial infarction: safety and haemodynamic effects. ISIS-4 (Fourth International Study of Infarct Survival) Pilot Study Investigators Eur Heart J. 1994 May;15(5):608-19. **Country:** POLAND			**3-way study** CAPTOPRIL LOW n=133 Age:61±1 Female:22% Prior MI:8% Prior diabetes:7% Prior hypertension:20% CAPTOPRIL HIGH n=237 Age:59±1 Female:23% Prior MI:14% Prior diabetes:11% Prior hypertension:33% **Concomitant medications:** Antiplatelets: 91-98% Fibrinolytic: 58-90% Oral BB: 40-48% Antiarrhythmic:				Renal impairment **Outcome 6** SBP Baseline- Day 7 **Outcome 7** DBP Baseline- Day 7	Captopril H: 4/237 Captopril: L 125±2 vs. 118±1 Captopril H: 113±1 to 120±1 Captopril: L 76±1 vs. 72±1 Captopril H: 82±1 to 74±1	designs. Combined the results from the two studies for the ACEi group and placebo Unclear which time point corresponds to in-hospital

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Randomisation: Yes, no details **Allocation Concealment:** Central randomisation, but no details **Blinding:** Unclear, likely to be blinded **Power Calculations:** Yes, estimated that 800 patients could be randomised during the 3 yrs of recruitment, and that this should provide reasonable estimates of			9-22% Diurectic: 33-42%						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
the incidence of hypotenstion, and other common side effects and of compliance to trial treatment needed for planned large-scale mortality trial									

Table 92: Pfeffer 1997[471]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Author Pfeffer MA, Greaves SC, Arnold JM, Glynn RJ, LaMotte FS, Lee RT, Menapace FJ Jr, Rapaport E, Ridker PM, Rouleau JL, Solomon SD, Hennekens	RCT	N=236 **Drop outs** Not stated. **Analysis: ITT**	Acute MI Unselected LV function **Inclusion criteria** Men and women over the age of 21 years who had experienced an MI within 24 hours were considered to be	Ramipril. Full-dose, titrated from 1.25 to 10mg/d in 24 hours N=119	Ramipril low: 0.625mg/d	1-14 days	**Outcome 1** All-cause mortality 1-14 days	Ramipril High: 3/119 Ramipril Low:2/116	**Source of funding** Grant from Hoechst Marion Roussel (formerly Hoechst Roussel Pharmaceuticals, Inc) and The Upjohn Company.
							Outcome 2 MI 1-14 days	Ramipril HIGH: .3/119 Ramipril LOW:1/116	
							Outcome 3 Stroke 1-14 days	Ramipril HIGH: 0/119 Ramipril LOW:1/116	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
CH. **Title** Early versus delayed angiotensin-converting enzyme inhibition therapy in acute myocardial infarction. The healing and early afterload reducing therapy trial. **Journal** Circulation. 1997 Jun 17;95(12):2643-51. **Country:** USA **Randomisation:** Yes. Unclear methods. Assignment was			eligible. **Exclusion criteria** were relative contraindications to the use of an ACE inhibitor, need of an ACE inhibitor for treatment of congestive heart failure, serum creatinine level of ≥2.5 mg/dL, presence of a major complication of infarction that was not stabilized before randomization (eg, cardiogenic shock, persistent ischemia, or unstable rhythm), systolic blood pressure of <100 mm Hg, or failure to complete all prerandomization evaluations within 24 hours from the onset of				**Outcome 4** Hypotension 1-14 days	Ramipril HIGH: 37/119 Ramipril LOW:26/116	**Limitations** Placebo data was only available for the first 14 days. Also 3 groups, but only using data from 2.
							Outcome 5 Revasculari7sation 1-14days	Ramipril HIGH: 15/119 Ramipril LOW:10/116	
							Outcome 6 Reached target dose 1-14 days	Ramipril HIGH: 105/119 Ramipril LOW:103/116	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
accomplished through random assignment into one of 3 groups. Randomisation was stratified by centre. **Allocation Concealment:** Unclear, not stated. **Blinding:** Double blind **Power Calculations:** None given			chest pain. Institutional review board approval was obtained, and all patients provided signed informed consent before randomization. **Baseline characteristics** **Placebo-High dose, Low-Low dose, High-High dose** Male, n 91 (77.8), 90 (77.6), 93 (78.2) Mean age, y (SD) 59.9 (12.7), 61.3 (11.8), 60.7 (13.3) Current smoker, n 42 (35.9), 39 (33.6), 43 (36.1) Diabetes, n 16 (13.7), 26 (22.4), 31 (26.1) Hypertension, n 51 (43.6), 44 (37.9),						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
			51 (42.9) Prior MI, n 23 (19.8), 16 (13.8), 21 (17.7) Killip class I, n 92 (79.3), 93 (80.2), 90 (75.6) **Concomitant medications:** Medication Thrombolytic 85 (72.7), 84 (72.4), 86 (72.3) PTCA: 29 (24.8), 24 (20.7), 25 (21.0) ASA: 110 (94.0), 107 (92.2), 105 (88.2) Heparin: 108 (92.3), 105 (90.5), 110 (92.4) β-Blocker: 79 (67.5), 88 (75.9), 75 (63.0) Nitrate: 100 (85.5), 98 (84.5), 101 (84.9) Calcium channel blocker: 12 (10.3), 18 (15.5), 12						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
			(10.1)						

G.4.4 ACE inhibitors vs. ARBs

Table 93: De la Serra 2009[138]. YUSUF ET AL 2008 [636]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author De La Serra (2009) **Title** Main results and clinical interpretations from the TRANSCEND study.	RCT	N= 5926 Drop outs 639 (21.6%)discontinued in the telmisartan group and 705 (23.7%)	Inclusion criteria Established coronary artery disease, peripheral artery disease, stroke or diabetes with end-organ damage; intolerant to ACE	Telmisartan 80mg/day N= 2961	Placebo N= 2965	Median 56 months	**Outcome 1** All-cause mortality	Telmisartan: 364/2961 (12.3%) Placebo: 349/2965 (11.7%) RR 1.05 (95% CI 0.91 to 1.22) P=0.491	Source of funding No details Limitations no details of sequence generation method,
							Outcome 2 Cardiovascular death	Telmisartan: 227/2961 (7.7%) Placebo:	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Journal Journal of Hypertension, 2009, 27 (suppl. 2) Country: Spain Randomisation: stratified by hospital. Allocation Concealment: trialists were blinded to allocation Blinding: Double blinded. Power Calculations: A sample size of 6000 patients was expected to have 94% power to detect a HR		discontinued in the placebo group, p=0.055. Analysis: ITT	INHIBITORSs (definition - a previous discontinuation due to a documented intolerance) Exclusion criteria HF patients, significant primary valvular or cardiac outflow tract obstruction, constrictive pericarditis, complex congenital heart disease, unexplained snycope, planned cardiac surgery or cardiac revascularisation within the previous 3 months, SBP over 160mmHg, heart transplantation, subarachnoic haemorrhage,					223/2965 (7.5%) RR 1.03 (95% CI 0.85 to 1.24) P=0.778	allocation concealment or if outcome assessor was blinded. There was no power calculation and authors state that no difference between groups at baseline, but the patient characteristics are not detailed. Other outcomes: the primary endpoint was a composite of cardiovascular death, myocardial
							Outcome 3 Myocardial infarction	Telmisartan: 116/2961 (3.9%) Placebo: 147/2965 (5%) RR 0.79 (95% CI 0.62 to 1.01) P=0.059	
							Outcome 4 Stroke	Telmisartan: 112/2961 (3.8%) Placebo: 136/2965 (4.6%) RR 0.83 (95% CI 0.64 to 1.06) P=0.136	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
of 0.81 for telmisartan vs. placebo.			significant renal artery stenosis, creatinine levels above 265 micromol/L, proteinuria, or hepatic dysfunction						infarction, stroke or hospitalisation for heart failure.
Lancet. 2008 Sep 27;372(9644):1174-83. Epub 2008 Aug 29. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled			Baseline characteristics: All patients Mean (SD) Age: 67 years Female: 43% Previous cardiovascular history: Coronary heart disease : 75% Previous stroke or transitory ischemic attack: 22% PAD: 11% Hypertension: 76%				Outcome 5 Hospitalisation for heart failure	Telmisartan: 133/2961 (4.5%) Placebo: 127/2965 (4.3%) RR 1.05 (95% CI 0.82 to 1.34) P=0.694	Notes: Single-blind run-in period of 1 week placebo followed by 2 weeks of telmisartan treatment (80mg)
							Outcome 6 Revascularisation procedures	Telmisartan: 349/2961 (11.8%) Placebo: 390/2965 (13.1%) RR 0.9 (95% CI 0.77 to 1.03) P=0.133	
							Outcome 7 Any cardiovascular hospitalisation	Telmisartan: 894/2961 (30.3%) Placebo: 980/2965 (33%) RR 0.92 (95% CI 0.85 to 0.99) P=0.025	
							Outcome 8 Renal abnormalities	Telmisartan:41/2954	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
trial. Telmisartan Randomised Assessment Study in ACE intolerant subjects with cardiovascular disease (TRANSCEND) Investigators, Yusuf S, Teo K, Anderson C, Pogue J, Dyal L, Copland I, Schumacher H, Dagenais G, Sleight P.			Diabetes: 36% Telmisartan Mean (SD) Age: 66.9 ± 7.3 M/W:57:43 CAD:74.8% MI:46.8% Angina:47.8% Medications: Statin:55.7% BB:59.3% Aspirin:75% Clopidogrel or ticlopidine:10.8% Antiplatelet:79.8% Diuretic:33.2% CCB:39.9% Placebo Mean (SD) Age: 66.9 ± 7.4 **.1.1**M/W: 43:57 CAD:74.3% MI:45.8% Angina:47.5%					Placebo:13/2972	
							Outcome 8 Hypotensive symptoms	Telmisartan:29/2954 Placebo:16/2972	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			Medications: Statin:54.7% BB:57.2% Aspirin:74.4% Clopidogrel or ticlopidine:10.6% Antiplatelet:79% Diuretic:32.8% CCB:40.4%						

Table 94: Granger 2003[243]

Reference	Study type	Number of patients	Patient Characteristics		Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-	RCT – CHARM Alternative	N = 1028 Drop outs/Lost to follow-up Candesartan n=2 Placebo n=1 Analysis: ITT	Inclusion criteria Patients aged 18 and older who had symptomatic HF (NYHA, Class II-IV) of at least 4 weeks duration, LV ejection fraction 40% or less and intolerance to ACE inhibitors.	Candesartan, n=1013	Placebo, n=1015	33.7 months	**Outcome 1** All-cause mortality	Candesartan n=265/1013 Placebo n=296/1015	Source of funding AstraZeneca, Limitations HF Population, not post MI
							Outcome 2 Myocardial infarction	Candesartan n=75/1013 Placebo n=48/1015	
							Outcome 3 Stroke	Candesartan n=36/1013 Placebo	

Reference	Study type	Number of patients	Patient Characteristics		Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
enzyme inhibitors: the CHARM-Alternative trial. Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, Ostergren J, Pfeffer MA, Swedberg K; CHARM Investigators and Committees. Lancet. 2003 Sep 6;362(9386): 772-6. Country: Sweden Randomisati			Baseline characteristics Candesartan n=1013 Age:66.3±11.0 M/W:68:32 Ethnic: European:88% Black:2.8% NHYA Class: II: 48% III:48% IV:3.6% HF cause: Ischaemic:70% Idiopathic:19% Hypertensive:5.7% Medical treatment: Diuretic:85.3% BB:54.6% Calcium antagonist:17.6% Oral					n=42/1015	
							Outcome 4 Revascularisation	Candesartan n=49/1013 Placebo n=50/1015	
							Outcome 5 Readmissions	Candesartan n=212/1013 Placebo n=291/1015	
							Outcome 6 AE hypotension	Candesartan n=37/1013 Placebo n=9/1015	
							Outcome 7 Hyperkalemia	Candesartan n=19/1013 Placebo n=3/1015	
							Outcome 8 Any adverse events	Candesartan n=218/1013 Placebo n=196/1015	

Reference	Study type	Number of patients	Patient Characteristics		Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
on: Randomly assigned, the assignment code was held by an independent centre and the data safety monitoring board. Allocation Concealment: Unclear Blinding: Double blinded. Power Calculations: The sample size of 2000 patients was designed to provide 80% power to			anticoagulant:31.6% Aspirin:57.1% Other antiplatelet drug:5.9% Lipid-lowering drug:42.7% Placebo n=1015 Age:66.8±10.5 M/W:68:32 Ethnic: European:89% Black:4.4% NHYA Class: II:47.2% III:49.2% IV:3.6% HF cause: Ischaemic:66.9% Idiopathic:20.3% Hypertensive:7.2% Medical treatment:						

Reference	Study type	Number of patients	Patient Characteristics		Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
detect an 18% relative reduction in primary outcome, assuming an annual placebo event rate of 15%			Diuretic:66.3% BB:54.5% Calcium antagonist:15.1% Oral anticoagulant:29.5% Aspirin:58.6% Other Antiplatelet drug:5.5% Lipid-lowering drug:40.3%						

Table 95: Kasanuki 2009 [310]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Kasanuki et al (2009) **Title** Angiotensin II receptor blocker-based vs non-angiotensin	RCT (multicentre, open-label)	N= 2049 Drop outs 3 in the Candesartan-based arm and 5 in the non-ARB arm lost to	**Inclusion criteria** Targeted hospitalised patients with CAD and hypertension between 20 and 80 years old; coronary angiography was	Candesartan-based treatment arm (ARB) 4-12mg/day N=1024	Non-ARB-based treatment arm N=1025	Median follow-up period of 4.2 years (IQR 3.5-4.9 years)	**Outcome 1** Total deaths	Candesartan: 69/1024 (6.7%) Non-ARB: 59/1025 (5.8%) HR (95% CI): 1.18 (0.83-1.67) P=0.358	Source of funding Japan Research Promotion Society for Cardiovascular Diseases
							Outcome 2 Cardiovascular death	Candesartan: 28/1024 (2.7%) Non-ARB:	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
II receptor blocker-based therapy in patients with angiographically documented coronary artery disease and hypertension: the Heart Institute of Japan Candesartan Randomised Trial for Evaluation in Coronary Artery Disease (HIJ-CREATE) **Journal** European Heart Journal (2009), 30, 1203-1212.		follow-up; 8 in the Candesartan-based arm and 9 in the non-ARB arm did not receive allocated therapy. Analysis: ITT	to be performed for the diagnosis of CAD when patients enrolled; patients with a history of revascularisation procedures or with coronary spastic angina documented by acetylcholine provocation test were included (even if no apparent stenotic lesion observed on angiography at enrolment) Hypertension was defined as systolic b.p >/=140mmHg, diastolic b.p >/=90mmHg or history of having received treatment for hypertension at time of enrolment.					25/1025 (2.4%) HR (95% CI): 1.14 (0.66-1.95) P=0.645	Limitations: open label trial, although study endpoints were blinded; underpowered due to event rate being lower than expected possibly due to low dose of candesartan. Other outcomes: Time to first major adverse cardiac event (MACE: a composite of cardiovascular death, non-fatal myocardial infarction, unstable
							Outcome 3 Stroke	Candesartan: 45/1024 (4.4%) Non-ARB: 49/1025 (4.8%) HR (95% CI): 0.92 (0.61 to 1.37) P=0.672	
							Outcome 4 PCI/CABG	Candesartan: 256/1024 (25%) Non-ARB: 271/1025 (26.4%) HR (95% CI): 0.93 (0.78-1.10) P=0.414	
							Outcome 5 Non-fatal MI	Candesartan: 29/1024 (2.8%) Non-ARB: 26/1025 (2.5%) HR (95% CI): 1.12 (0.66 to 1.88) P= 0.679	
							Outcome 6	Candesartan:	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Country: Japan Randomisation: computer-generated, stratified, permuted-block randomisation code Allocation Concealment: yes, computer-generated code at an independent statistical data centre Blinding: open-label trial but endpoint blinded. Power Calculations:			**Exclusion criteria** Patients with secondary hypertension; patients with acute myocardial infarction within the past week or cerebrovascular disorders within the past week or cerebrovascular disorders within the past 3 months; severe aortic valve stenosis; obstructive hypertrophic cardiomyopathy; serum creatinine level >2.0mg/dL; potassium >5mmo/L; female sex, of childbearing potential and not using contraception; history of serious				All adverse events	798/1024 (77.9%) Non-ARB: 808/1025 (78.8%) P= 0.621	angina, heart failure, stroke and other cardiovasulcar events requiring hospitalisation).
							Outcome 7 Hyperkalaemia	Candesartan: 14/1024 (1.4%) Non-ARB: 10/1025 (1.0%) P=0.410	
							Outcome 6 Liver dysfunction	Candesartan: 51/1024 (5%) Non-ARB: 40/1025 (3.9%) P= 0.236	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
yes and number required were included in study but authors point out that the study was underpowered because the actual event rate was much lower than the expected rate, possibly due to the low dose of candesartan.			or hypersensitivity reactions to other antihypertensive agents; acute liver disease or hepatic dysfunction (hepatic transaminases or bilirubin >1.5 x the upper limit of normal); known malignant neoplasm; and current condition requiring ACE inhibitors or ARBs. Acute MI was defined by the presence of typical clinical symptoms, electrocardiographic findings, and release of cardiac enzymes. **Baseline**							

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			characteristics Candesartan-based therapy Mean (SD) Age 64.5 (9.4) female 186 (18.2%) Cerebrovascular disease: 111 (10.8%) Peripheral vascular disease: 38 (3.7%) Atrial fibrillation: 58 (5.7%) Previous MI: 406 (39.6%) Medications at discharge: ACE-Is: 8 (0.8%) Diuretics: 103 (10.1%) Calcium-channel blockers: 457 (44.6%) Beta-blockers: 464 (45.3%) NYHA functional						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			class: I: 801 (78.2%) II: 185 (18.1%) III: 19 (1.9%) IV: 19 (1.9%) Diagnosis: Acute coronary syndrome: 346 (33.8%) Revascularisation Percutaneous coronary intervention:852 (83.2%) During enrolment hospitalisation: 538 (52.5%) Coronary artery bypass grafting: 124 (12.1%) During enrolment hospitalisation: 35 (3.4%) Standard therapy Mean (SD) Age 65 (8.9) Female 219 (21.4%)						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			Cerebrovascular disease: 94 (9.2%) Peripheral vascular disease: 26 (2.5%) Atrial fibrillation: 77 (7.5%) Previous MI: 373 (36.4%) Medications at discharge: ACE-Is: 723 (70.5%) Diuretics: 82 (8%) Calcium-channel blockers: 574 (56%) Beta blockers: 506 (49.4%) NYHA functional class: I: 826 (80.6%) II: 155 (15.1%) III: 22 (2.1%) IV: 22 (2.1%) Diagnosis: Acute coronary syndrome: 378						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			(36.9%) Revascularisation Percutaneous coronary intervention: 844 (82.3%) During enrolment hospitalisation: 542 (52.9%) Coronary artery bypass grafting: 112 (10.9%) During enrolment hospitalisation: 31 (3.0%)						

Table 96: Kondo 2003[318]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Kondo (2003) **Title** Effects of low-dose angiotensin	RCT	N=406 Drop outs 9 in candesartan had administrati	**Inclusion criteria** Current outpatients at Ogaki Municipal hospital; history of coronary intervention and showed no	Low-dose angiotensin II receptor blocker candesartan N=203	Control group N=203	Mean 24 months	**Outcome 1** Revascularisation	Candesartan: 8/194 Control: 15/203	Source of funding No details
							Outcome 2 Nonfatal MI	Candesartan: 2/194 Control: 1/203	Limitation No details of

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
II receptor blocker candesartan on cardiovascular events in patients with coronary artery disease. **Journal** Am Heart J, 2003, 146, e20 Country: Japan Randomisation: authors state that randomisation occurred but no further details Allocation Concealment: no details		on of candesartan discontinued due to adverse events (dizziness and lightheadedness); 2 patients in the control group relocated but their clinical conditions were confirmed by telephone interview. Analysis: ITT (although the results are presented with those who were discontinue	significant coronary stenosis on follow-up angiography 6 months after intervention. **Exclusion criteria** Patients with congestive heart failure (ejection fraction <0.40) or with malignancy; patients receiving dialysis treatment. **Baseline characteristics** Candesartan Mean (SD) Age 65 (9) Male 150 (74%) History of MI: 136 (67%) History of congestive heart				**Outcome 3** Cardiovascular death	Candesartan: 2/194 Control: 9/203	sequence generation or allocation concealment. Unblinded, no placebo. Relatively small sample size.
							Outcome 4 All-cause mortality (addition of cardiovascular death to non-cardiovascular death)	Candesartan: 4/194 Control: 11/203	
							Outcome 5 Composite outcome of revascularisation, nonfatal myocardial infarction, or cardiovascular death	Candesartan: 12/194 Control: 25/203	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Blinding: no placebo tablets Power Calculations: no calculation given		d in the candesartan group missing)	failure: 6 (3%) Placebo Mean (SD) Age 65 (10) Male 157 (77%) History of MI: 143 (70%) History of congestive heart failure: 3 (1%)						

Table 97: McMurray 2006[378]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
McMurray J, Solomon S, Pieper K, Reed S, Rouleau J, Velazquez E, White H, Howlett J, Swedberg K, Maggioni A,	RCT	N=14 703 Drop outs Not reported Analysis: ITT	**Inclusion criteria** Patients enrolled between 12 hrs and 10 days after the onset of acute MI and to have either left ventricular systolic dysfunction;	Captopril N=4909 Valsartan + Captopril N=4885	Valsartan N=4909	24.7 months	**Outcome 1** CV death or MI	Captopril (ACE inhibitors) = 1132/4909 Valsartan (ARB) = 1102/4909 HR 0.97 95%CI 0.89 to 1.05	Source of funding Novartis Limitations

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Køber L, Van de Werf F, Califf R, Pfeffer M. The effect of Valsartan, Captopril, or both on atheroscelrotic events after acute myocardial infarction: An analysis of the Valsartan in acute myocardial infarction trial (VALIANT) **Country:** Unclear **Randomisation:**			clinical evidence of heart failure; or both **Exclusion criteria** Hypotension or shock, renal impairment, ongoing clinical instability, and intolerance or contraindication to ACE inhibitors **Baseline characteristics** Captopril Age 64.9 yrs (SD11.8), female 31.3%, systolic 122.8 (SD17.0) mm Hg diastolic 72.4 (SD11.2) mm Hg, Medical history: myocardial infarction 27.2%, diabetes mellitus 22.8%, CABG 7.0%, PCI 7.2%, primary PCI					ACE inhibitors + ARB = 1096/4885 ACE inhibitors + ARB vs ACE inhibitors HR 0.96 95%CI 0.89 to 1.05	
							Outcome 2 Myocardial infarction (fatal)	Captopril (ACE inhibitors) = 798/4909 Valsartan (ARB) = 796/4909 ACE inhibitors + ARB = 756/4885	
							Outcome 3 Hospititalisation for angina	Captopril (ACE inhibitors) = 1021/4909 Valsartan (ARB) = 998/4909 ACE inhibitors + ARB = 1039/4885	
							Outcome 4 Stroke	Captopril (ACE inhibitors) = 211/4909	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Not reported **Allocation Concealment**: Not reported **Blinding:** Not reported **Power Calculations:** Not reported			14.6%, Medication: ACE inhibitors 38.5%, ARBs 1.4% Valsartan Age 65.0 yrs (SD11.8), female 31.5%, systolic 122.7 (SD16.8)mm Hg diastolic 72.3 (SD11.3)mm Hg, Medical history: myocardial infarction 28.4%, diabetes mellitus 23.1%, CABG 7.2%, PCI 7.7%, primary PCI 14.9%, Medication: ACE inhibitors 39.4%, ARBs 1.1% Valsartan and Captopril Age 64.6 yrs (SD11.9), female 30.5%, systolic 122.5 (SD17.1)					Valsartan (ARB) = 180/4909 ACE inhibitors + ARB = 183/4885	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			mm Hg diastolic 72.3 (SD11.4)mm Hg, Medical history: myocardial infarction 28.2%, diabetes mellitus 23.5%, CABG 6.7%, PCI 6.9%, primary PCI 14.9%, Medication: ACE inhibitors 40.8%, ARBs 1.1%						

Table 98: Montalescot 2009[396]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Effect of irbesartan and enalapril in non-ST elevation acute coronary	RCT	N=429 (ITT) Drop outs Irbesartan N=64 Enalapril N=59	**Inclusion criteria** Adults aged 18 yrs or older who were hospitalised with ischemic symptoms (last episode within 48	Irbesartan (300mg/d) N= 212	Enalapril (20mg/d) N= 217	60 days	**Outcome 1** Cardiovascular death	Irbesartan (ARB) = 2/212 Enalapril (ACE inhibitors) = 3/217	Source of funding Sanofi Aventis and Bristol-Lyers Squibb Limitations
							Outcome 2 Hospitalisation for	Irbesartan (ARB) = 8/212	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
syndrome: results of the randomised, double-blind ARCHIPELAGO study Montalescot, G., Drexler H., Gallo, R., Pearson T., Thoenes M., and Bhatt DL. Eur Heart J, 2009, 30, 2733-2741 Country: 11 countries (USA, Canada, Belgium, The Netherlands, Germany, Italy, Switzerland, Spain, Hungary, UK and France) Randomisati		Analysis: ITT	hrs before randomisation and at least one of the following characteristics of non-ST-segment elevation acute coronary syndrome (NSTEACS): electrocardiographic (ECG) ST or T changes (ST depression of transient elevation of at least 1 mm or T-wave changes in at least two leads) or positive troponin test. **Exclusion criteria** Persistent ST-segment elevation on ECG, coronary angiography or angioplasty planned before				recurrent angina + revascularisation	Enalapril (ACE inhibitors) = 7/217	Patients were treated either late or early
							Outcome 3 Hospitalisation for urgent revascularization	Irbesartan (ARB) = 4/212 Enalapril (ACE inhibitors) = 2/217	
							Outcome 4 MI	Irbesartan (ARB) = 9/212 Enalapril (ACE inhibitors) = 5/217	
							Outcome 5 Stroke	Irbesartan (ARB) = 0/212 Enalapril (ACE inhibitors) = 0/217	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
on: No details Allocation Concealment: Central randomised system (interactive voice response system) Blinding: Double blind Power Calculations: Sample size of 216 in each of the two study groups was estimated as sufficient to provide 80% power and a two-sided 0.05 significance level to detect a change on c-			baseline sampling, concomitant cardiovascular or renal disease, serum potassium > 5.5 mmol/L, creatinine clearance ≤ 30 mL/min, congestive heart failure with New York Heart Association class III or IV symptoms, angioplasty, surgery or trauma within the last 3 months, systolic blood pressure < 100 mm Hg, fever greater than 38 degrees centigrade, concomitant infection, chronic inflammatory drug or steroid use, administration of						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
reactive protein			an ARB or ACE inhibitors within the previous 3 days, or any investigational drug within the previous 30 days **Baseline characteristics** Irbesartan (early) Age 62.2 (SD11.5) Male 76%, diabetes 14.3%, previous cardiac intervention 18.1%, previous MI 14.3% Isbesartan (late) Age 60.9 (SD15) Male 76%, diabetes 13.1%, previous cardiac intervention 18.7%, previous MI 15.9% Enalapril (early) Age 62.4 (SD11.5)						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			Male 67%, diabetes 13.1%, previous cardiac intervention 12.1%, previous MI 7.5% Enalapril (late) Age 60.9 (SD11.8) Male 77%, diabetes 12.7%, previous cardiac intervention 10%, previous MI 9.1%						

Table 99: ONTARGET 2008[577]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author ONTARGET Investigators, Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, Schumacher	RCT	N= 25620 Drop outs Study drug was discontinued in 24.5 in	Inclusion criteria Patients with coronary, peripheral or cerebrovascular disease or diabetes with end-organ	Ramipril 10mg/day N= 8576	Telmisartan 80mg/day N=8542 Combination therapy	Median follow-up 56 months	**Outcome 1** All-cause mortality	Ramipril: 1014/8576 (11.8%) Telmisartan: 989/8542 (11.6%) Combination therapy: 1065/8502	Source of funding Grant from Boehringer Ingelheim, AstraZeneca, Sanofi-Aventis,

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
H, Dagenais G, Sleight P, Anderson C. **Title**Telmisartan, Ramipril, or both in patients at high risk for vascular events. **Journal** N. Engl. J Med 358, 15, 1547-1559 Country: UK, USA and NZ Randomisation: Unclear methods. Stratified according to the site with the use of permuted blocks		ramipril and 23% in telmisartan. Analysis: ITT	damage. Patients who could not tolerate ACE inhibitors were randomly assigned to receive either telmisartan or placebo in a parallel trial. Baseline characteristics Ramipril Mean (SD) Age 66.4 (7.2) Female 2331/8576 (27.2%) Clinical history n(%): Coronary artery disease: 6382(74.4%) Myocardial infarction: 4146 (48.3%) Angina pectoris		(Ramipril and Telmisartan) N=8502			(12.5%) Telmisartan vs. Ramipril RR 0.98 (95% CI 0.90-1.07) Combination therapy vs. ramipril: RR 1.07 (95% CI 0.98-1.16)	Servier, Bristo-Myers Squibb, and GlaxoSMithKline. Limitations Other outcomes: Composite of death from cardiovascular causes, myocardial infarction, or stroke or hospitalisation for heart failure; death from cardiovascular cause, myocardial infarction or stroke Notes: There was a
							Outcome 2 Death from cardiovascular causes	Ramipril: 603/8576 (7%) Telmisartan: 598/8542 (7%) Combination therapy: 620/8502 (7.3%) **I.2**Telmisartan vs. Rampipril RR 1.00 (95% CI 0.89 to 1.12) Combination therapy vs. ramipril RR 1.04 (95% CI 0.93-1.17)	
							Outcome 3 Revascularisation	Ramipril: 1269/8576 (14.8%) Telmisartan: 1290 /8542 (15.1%) Combination therapy:	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
through a central automated telephone service Allocation Concealment: Yes. Randomised using a 24 hr service computerized voice-activated telephone call to a central office. Blinding: double-blinded Power Calculations: yes. Original sample size of 7800 patients			stable: 3039 (35.4) Angina pectoris unstable: 1257 (14.7%) Stroke or transient ischemic attacks: 1805 (21%) PAD: 1136 (13.2%) Hypertension: 5918 (69%) Diabetes: 3146 (36.7%) Left ventricular hypertrophy: 1085 (12.7%) Microalbuminuria: 929 (13.1%) Previous procedures: Coronary-artery bypass grafting: 1862 (21.7%) Percutaneous transluminal coronary angioplasty: 2527 (29.5%)					1303/8502 (15.3%) Telmisartan vs. Ramipril RR 1.03 (95% CI 0.95-1.11) Combination therapy vs Ramipril RR 1.04 (95% CI 0.97 to 1.13)	single-blind run-in period
							Outcome 4 Stroke	Ramipril: 405/8576 (4.7%) Telmisartan: 369/8542 (4.3%) Combination therapy: 373/8502 (4.4%) Telmisartan vs Ramipril RR 0.91 (95% CI 0.79 to 1.05) Combination therapy vs Ramipril RR 0.93 (95% CI 0.81 to 1.07)	
							Outcome 5 Renal impairment	Ramipril: 871 /8576 (10.2%) Telmisartan: 906/8542 (10.6%)	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
were followed for a mean of 4.5yrs. this provided a power of 89% for a HR of 1.00. With a 3000 patients per group, a 94% power will be achieved.			Telmisartan Mean (SD) Age 66.4 (7.1) Female 2250/8542 (26.3%) Clinical history n(%): Coronary artery disease: 6367 (74.5%) Myocardial infarction: 4214 (49.3%) Angina pectoris stable: 2958 (34.6%) Angina pectoris unstable: 1296 (15.2%) Stroke or transient ischemic attacks: 1758 (20.6%) PAD: 1161 (13.6%) Hypertension: 5862 (68.6%)					Combination therapy: 1148/8502 (13.5%) Telmisartan vs Ramipril RR 1.04 (95% CI 0.96-1.14); Combination Therapy vs Ramipril RR 1.33 (95% CI 1.22-1.44)	
							Outcome 6 Renal failure requiring dialysis	Ramipril: 48/8576 (0.6%) Telmisartan: 52/8542 (0.6%) Combination therapy: 65/8502 (0.8%) Telmisartan vs Ramipril RR 1.09 (95% CI 0.74 to 1.61); Combination therapy vs Ramipril RR 1.37 (95% CI 0.94-1.98)	
							Outcome 7 Myocardial infarction	Ramipril: 413/8576 (4.8%) Telmisartan:	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			Diabetes: 3246 (38%) Left ventricular hypertrophy: 1120 (13.1%) Microalbuminuria: 923 (13.2%) Previous procedures: Coronary-artery bypass grafting: 1920 (22.5%) Percutaneous transluminal coronary angioplasty: 2476 (29%) Combination therapy Mean (SD) Age 66.5 (7.3) Female 2250/8502 (26.5%) Clinical history n(%): Coronary artery disease: 6353 (74.7%)					440/8542 (5.2%) Combination therapy: 438/8502 (5.2%) Telmisartan vs Ramipril: RR 1.07 (95% CI 0.94 to 1.22) Combination therapy vs Ramipril: RR 1.08 (95% CI 0.94 to 1.23)	
							Outcome 8 Hospitalisation for heart failure	Ramipril: 354/8576 (4.1%) Telmisartan: 394/8542 (4.6%) Combination therapy: 332/8502 (3.9%) Telmisartan vs Ramipril: RR 1.12 (95% CI 0.97 to 1.29); Combination therapy vs Ramipril: 0.95 (0.82 to 1.10)	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			Myocardial infarction: 4189 (49.3%) Angina pectoris stable: 2960 (34.8%) Angina pectoris unstable: 1264 (14.9%) Stroke or transient ischemic attacks: 1779 (20.9%) PAD: 1171 (13.8%) Hypertension: 5827 (68.5%) Diabetes: 3220 (37.9%) Left ventricular hypertrophy: 1082 (12.7%) Microalbuminuria: 929 (13.3%) Previous procedures: Coronary-artery bypass grafting: 1893 (22.3%) Percutaneous						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			transluminal coronary angioplasty: 2434 (28.6%)						

Table 100: Pfeffer 2003[473]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Pfeffer MA., McMurrary JJV., Velzquez MD., JL Rouleau, Kober L., et al **Title** Valsartan, Captopril, or both in lyocardial infarction complicated	RCT	N=14 808 (enrolled) N=105 censored (before unblinding) Included N=14 703 Drop outs Study medication was not administered to N=77. 24 in valsartan, 30 in	**Inclusion criteria** Men and women 18 yrs or older who had acute MI (between 0.5 and 10 days previously) that was complicated by clinical or radiologic signs of heart failure, evidence of left ventricular systolic dysfunction (an ejection fraction of ≤ 0.35 on echocardiography or contract	**1.1.3** Valsartan N= 4909 (160mg 2x/d) Vs Captopril (50mg 3x/d) Valsartan and captopril N=4885	Captopril N=4909	Median 24.7 mths	**Outcome 1** All-cause mortality	Val (ARB) = 979/4909 Cap (ACE inhibitors) = 958/4909 HR 1.00 (97.5% 0.90 to 1.00) Val + Cap = 941/4885 Cap (ACE inhibitors) = 958/4909 HR 0.98 (97.5% 0.89 to 1.09)	Source of funding Novartis Pharmaceuticals Limitations
							Outcome 2	Val = 827/4909	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
by heart failure, left ventricular dysfunction, or both **Journal** N Eng J of Medicine, 2003, November 13, 349 (20) p1893-906 Country: 23 countries Randomisation: No details Allocation Concealment: an automated, interactive voice-response system		captopril, 23 in dual-therapy. Vital status of N=139 patients unavailable Analysis: ITT Per-protocol for noninferiority assessment	angiography and ≤ on radio-nuclide ventriculography), or both, as defined in the three trials we used as reference studies, were eligible. Inclusion criteria included systolic blood pressure higher than 100 mm Hg and a serum creatinine concentration of less than 2.5 mg per decilitre. Patients were permitted to have received an ACE inhibitor or angiontensin-receptor blocker up to 12 hrs before randomisation Inclusion from				Death from cardiovascular events	Cap = 830/4909 HR 0.98 (0.87 to 1.09) Val + Cap = 827/4885 Cap = 830/4909 HR 1.00 (0.89 to 1.11)	
							Outcome 3 Hospitalisation for myocardial infarction and heart failure	Val = 919/4909 patients 1447 hospitalisations Cap = 945/4909 1437 hospitalisations Val + Cap = 834/4885	
							Outcome 4 Any adverse event (resulting in permanent discontinuation of study treatment)	Val = 282/4885 Cap = 375/4879 Val + Cap = 438/4862	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Blinding: Double blind Power Calculations: Trial designed to enrol approx 14,500 participants, with follow-up continuing until at least 2700 deaths had occurred, providing a power of 86 to 95% to detect a reduction of 15.0 to 17.5% in the risk of death from any cause. Numbers achieved			**Exclusion criteria** Intolerance or contraindication to an ACE inhibitor or angiotensin-receptor blocker, clinically significant valvular disease and limited life expectancy **Baseline characteristics** Valsartan Age 65 (SD11.8) yrs Female sex 31.5% BP mm Hg systolic 122.7 (SD16.8) Diastolic 72.3 (SD11.3) LVEF % 35.3 (SD10.4)						
							Outcome 5 Renal causes	Val = 53/4885 Cap = 40/4879 Val + Cap = 61/4862	
							Outcome 6 Hyperkalemia	Val = 7/4885 Cap = 4/4879 Val + Cap = 12/4862	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			Killip class no % I 26.5% II 49.2% III 17.9% IV 6.4% Medical history MI 28.4% Diabetes mellitus 23.1% Coronary-artery bypass grafting 7.2% Percutaneous coronary intervention 7.7% Medication ACE 39.4% Angiotensin-receptor blockers 1.1% Beta blockers 70.6% Aspirin 91.3% Valsartan and Captopril Age 64.6 (SD11.9) yrs Female sex 30.5%						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			BP mm Hg systolic 122.5 (SD17.1) Diastolic 72.3 (SD11.4) LVEF % 35.3 (SD10.3) Killip class no % I 28.4% II 47.9% III 17.3% IV 6.4% Medical history MI 28.2% Diabetes mellitus 23.5% Coronary-artery bypass grafting 6.7% Percutaneous coronary intervention 6.9% Medication ACE 40.8% Angiotensin-receptor blockers 1.1% Beta blockers 70.4%						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			Aspirin 91.1% Captopril Age 64.9 (SD11.8) yrs Female sex 31.3% BP mm Hg systolic 122.8 (SD17.0) Diastolic 72.4 (SD11.2) LVEF % 35.3 (SD10.4) Killip class no % I 29.1% II 48.0% III 16.6% IV 6.3% Medical history MI 27.2% Diabetes mellitus 22.8% Coronary-artery bypass grafting 7.0% Percutaneous coronary intervention 7.2% Medication						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			ACE 38.5% Angiotensin-receptor blockers 1.4% Beta blockers 70.1% Aspirin 91.4%						

Table 101: Rangoonwala 2010 [491]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Title Is Telmisartan clinically equivalent or more effective than Ramipril? Results of the ONTARGET study Country: Unclear	RCT	N=25 620 Drop outs Ramipril N=2029 Telmisartan N=1796 Rampril + Telmisartan N=1929 both drugs N=566 one drug Analysis:	**Inclusion criteria** High risk patients presenting with cardiovascular diseases and in patients with diabetes, but no evidence of heart failure **Exclusion criteria** Patients with coronary, peripheral or cerebrovascular disease or	Telmisartan (80mg/d) N=8542 Telmisartan + Ramipril N=8502	Ramipril (10mg/d) N=8576	Average 56 months	**Outcome 1** All-cause mortality	Telmisartan (ARB) = 989/8542 Ramipril (ACE inhibitors) =1014/8576 ACE inhibitors vs. ARB RR 0.98; 95%CI 0.90 to 1.07 ACE inhibitors + ARB no data provided Vs. ACE inhibitors	Source of funding None reported Limitations

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Randomisation: Not reported Allocation Concealment: Not reported Blinding: Double blind Power Calculations: None		Unclear	diabetes with end-organ damage. Patients who could not tolerate ACE inhibitors were randomly assigned to receive either telmisartan or placebo in a parallel trial. **Baseline characteristics** Mean age 66 yrs, female 27%, 85% cardiovascular disease, 69% hypertension, 38% diabetes, anti-platelet therapy 80.9%, beta-blockers 56.9% and diuretics 28.0%					RR 1.07 95%CI 0.98 to 1.16	
							Outcome 2 Renal dysfunction	Telmisartan (ARB) =906 /8542 Ramipril (ACE inhibitors) =871/8576 ARB + ACE inhibitors = 1148/8502	
							Outcome 3 Serum potassium > 5.5 mmol/litre	Telmisartan (ARB) = 287/8542 Ramipril (ACE inhibitors) =283/8576 ARB + ACE inhibitors = 480/8502	

Table 102: Suzuki 2009[561]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Suzuki H., Geshi E., Nanjyo S., Nakano H., Yamazaki J., Sato N. et al **Title** Inhibitory effect of Valsartan against progression of left ventricular dysfunction after myocardial infarction-T-Venture study **Journal** Circ J, 2009, 73, 918-924 Country:	RCT Study type RCT Study type RCT Study type RCT	N=256 Drop outs Reperfusion interventio n > 24 hrs post MI Valsartan 8/128 ACE inhibitors 7/128 N=241 (ITT population) Due to adverse events Valsartan 3/120 ACE inhibitors 8/121 Analysis:	**Inclusion criteria** All men and women presenting with their first episode of acute MI. The enrolled patients were successfully treated by coronary intervention within 24 hrs. of onset of acute MI. **Exclusion criteria** Presence of cardiogenic shock, haemodynamic ally significant valvular diseases and/or clinically significant hematologic or hepatic disorders. Patients with	Valsartan (max 160mg/d) N=120 Prescribed one of a number of valsartan drugs	ACE inhibitors (max dose) N=121 Prescribed one of a number of ACE inhibitors drugs	6 mths post MI	**Outcome 1** Death	Val (ARB) = 0/120 ACE inhibitors = 1/121	Source of funding Limitations Seven types of ACE inhibitors were administered in randomly enrolled patients in the ACE inhibitors group. Possible differences in the efficacy of the ACE inhibitors
							Outcome 2 Non-fatal MI	Val = 1/120 ACE inhibitors = 1/121	
							Outcome 3 Revascularisation	Val = 9/120 ACE inhibitors = 11/121	
							Outcome 4 Hospitalisation for heart failure	Val = 3/120 ACE inhibitors = 4/121	
							Outcome 5 Adverse events	Val = 4/120 ACE inhibitors = 15/121	
							Outcome 6	Val = 0/120	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Japan Randomisation: No details Allocation Concealment: No details Blinding: No details Power Calculations: None Reference Inhibitory effect of Valsartan against progression of left ventricular dysfunction after myocardial infarction-T-Venture study		Number of patients N=256 Drop outs Reperfusion intervention > 24 hrs post MI Valsartan 8/128 ACE inhibitors 7/128 N=241 (ITT population) Due to adverse events Valsartan 3/120 ACE inhibitors 8/121 Analysis:	systolic BP less than 100 mm Hg or serum creatinine concentration of more than 3.0 mg/dl were also excluded **Baseline characteristics** Valsartan Age 63.0 (SEM1.0) yrs Male/female 101/19 Stent 90.8% Diabetes mellitus 34.2% ACE inhibitors Age 62.9 (SEM1.0) yrs Male/female 99/22 Stent 87.6% Diabetes mellitus 33.9%				Renal dysfunction	ACE inhibitors = 1/121	
							Outcome 7 Hyperkalemia	Val = 0/120 ACE inhibitors = 1/121	
							Outcome 8 Hypotension	Val = 2/120 ACE inhibitors = 1/121	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Country: Japan Randomisation: No details Allocation Concealment: No details Blinding: No details Power Calculations: None Reference Inhibitory effect of Valsartan against progression of left ventricular dysfunction after myocardial infarction-T-Venture study		Number of patients N=256 Drop outs Reperfusion intervention > 24 hrs post MI Valsartan 8/128 ACE inhibitors 7/128 N=241 (ITT population) Due to adverse events Valsartan 3/120 ACE inhibitors 8/121 Analysis:	**Inclusion criteria** All mean and women presenting with their first episode of acute MI. The enrolled patients were successfully treated by coronary intervention within 24 hrs of onset of acute MI. **Exclusion criteria** Presence of cardiogenic shock, hemodynamically significant valvular diseases and/or clinically significant hematologic or hepatic disorders. Patients with systolic BP less than 100 mm Hg						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Suzuki H., Geshi E., Nanjyo S., Nakano H., Yamazaki J., Sato N. et al Circ J, 2009, 73, 918-924 Country: Japan Randomisation: No details Allocation Concealment: No details Blinding: No details Power Calculations: None Reference Inhibitory effect of Valsartan against		Number of patients N=256 Drop outs Reperfusion intervention > 24 hrs post MI Valsartan 8/128 ACE inhibitors 7/128 N=241 (ITT population) Due to adverse events Valsartan 3/120 ACE inhibitors 8/121 Analysis:	or serum creatinine concentration of more than 3.0 mg/dl were also excluded **Baseline characteristics** Valsartan Age 63.0 (SEM1.0) yrs Male/female 101/19 Stent 90.8% Diabetes mellitus 34.2% ACE inhibitors Age 62.9 (SEM1.0) yrs Male/female 99/22 Stent 87.6% Diabetes mellitus 33.9% Patient Characteristics **Inclusion criteria**						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
progression of left ventricular dysfunction after myocardial infarction-T-Venture study Suzuki H., Geshi E., Nanjyo S., Nakano H., Yamazaki J., Sato N. et al Circ J, 2009, 73, 918-924 Country: Japan Randomisation: No details Allocation Concealment: No details Blinding:			All mean and women presenting with their first episode of acute MI. The enrolled patients were successfully treated by coronary intervention within 24 hrs of onset of acute MI. **Exclusion criteria** Presence of cardiogenic shock, hemodynamically significant valvular diseases and/or clinically significant hematologic or hepatic disorders. Patients with systolic BP less than 100 mm Hg or serum						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
No details Power Calculations: None			creatinine concentration of more than 3.0 mg/dl were also excluded **Baseline characteristics** Valsartan Age 63.0 (SEM1.0) yrs Male/female 101/19 Stent 90.8% Diabetes mellitus 34.2% ACE inhibitors Age 62.9 (SEM1.0) yrs Male/female 99/22 Stent 87.6% Diabetes mellitus 33.9% Patient Characteristics Inclusion criteria All mean and						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			women presenting with their first episode of acute MI. The enrolled patients were successfully treated by coronary intervention within 24 hrs of onset of acute MI. **Exclusion criteria** Presence of cardiogenic shock, hemodynamically significant valvular diseases and/or clinically significant hematologic or hepatic disorders. Patients with systolic BP less than 100 mm Hg or serum creatinine concentration of						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			more than 3.0 mg/dl were also excluded **Baseline characteristics** Valsartan Age 63.0 (SEM1.0) yrs Male/female 101/19 Stent 90.8% Diabetes mellitus 34.2% ACE inhibitors Age 62.9 (SEM1.0) yrs Male/female 99/22 Stent 87.6% Diabetes mellitus 33.9%						

Table 103: Yano 2012 [625]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Yano H, Hibi K, Nozawa N, Ozaki H, Kusama I, Ebina T, Kosuge M, Tsukahara K, Okuda J, Morita S, Umemura S, Kimura K. **Title** Effects of valsartan, an angiotensin II receptor blocker, on coronary atherosclerosis in patients with acute myocardial infarction who receive an angiotensin-converting	RCT	N=160 **No. patients withdrew/lost to follow-up** N=28, 17% **Analysis:** ITT	**Inclusion criteria**: Men and women with acute MI aged 20-79 years and were admitted within 24 hr from onset of symptoms. All patients had successfully undergone percutaneous coronary intervention (PCI) of culprit lesions. **Exclusion criteria**: history of intolerance or contraindication to ACEi or ARBs, valvular disease and any other disease expected to seriously compromise life expectancy or cardiogenic shock.	ACE inhibitor (Captopril, 3x25mg/d) (n=81	ARB (2x40mg/d) + ACE (Captopril 3x25 mg/d) inhibitor n=79	7 months	**Outcome 1** Cardiac mortality	ACEi =0/81 ARB+ACEi=0/79	**Limitations:** Short follow-up High dropout in combination group.
							Outcome 2 Reinfarction	ACEi =0/81 ARB+ACEi=0/79	
							Outcome 3 Revascularisation	ACEi =12/81 ARB+ACEi=8/79	
							Outcome 4 Adverse events	ACEi =12/79 ARB+ACEi=16/81	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
enzyme inhibitor. **Journal** Circ J. 2012;76(6):1442-51 **Randomisation:** Yes, but no details. They said by a sealed envelope but no details, so risk of bias. **Allocation concealment:** Unclear **Blinding:** No, open label **Power calculations:**			ACEi n=58 Age: 61± 10 Males: 86% Prior MI: 2 Medications at discharge: ASA:100% Ticlopidine: 100% BB: 46% Statin: 62% ACEi+ARB Age: 59± 9 MalesL 85% Prior MI:8 Medications at discharge: ASA:100% Ticlopidine: 100% BB: 35% Statin: 59%						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
The smallest number of patient that could provide a 90% statistical power to detect a treatment-related difference of 3% with a SD of 5%, was calculated to be 120 in total at a 2-sided significance level of 5%. Given a 25% drop out, 160 would be needed.									

G.4.5 Antiplatelet therapy – duration of clopidogrel treatment

Table 104: Bernardi 2007[55]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Bernardi V, Szarfer J, Summay G, Mendiz O, Sarmiento R, Alemparte MR, Gabay J, Berger PB. **Title** Long-term versus short-term clopidogrel therapy in patients undergoing coronary stenting (from the Randomized Argentine Clopidogrel Stent [RACS] trial).	RCT RACS trial	N=1004 30 days n=502 180 days n=502 Analysis: PPA. Missing data. Lost to follow-up Clop 30 n=14 Clop 180d n=11 Inclusion criteria: Elective or urgent PCI, >18 yrs, CAD with ischemia, target lesion with >50% stenosis in	Patients had STEMI, ACS or stable angina 30 d Age = 61±11 Age>70yr=139 (28%) Men 397 (79%) Previous Revascularization= 94 (18.3%) MI=130 (25.9%) Cardiac heart failure =21 (4.2%) Stroke=9 (1.8%) PAD=25 (5%) Aspirin = 179 (35.8%) BB=268 (53.8%) Statin = 211 (42.1%) ACEi = 172 (34.2%) CCB=101 (20.2%)	Clopidogrel (300mg) +aspirin (75 to 325 mg) 30 d N=502	ASA (75 to 325 mg) 180 d N=502	1,3 and 6 m	**Outcome 1** Death 1-30d 30-180d	1-30d 30d = 10/502 (2%) 180d = 12/502 (2.4%) 30-180d 30d = 12/461(2.6 %) 180d = 4/460 (0.9%) Presented results at 6m follow-up to match Pekdemir et al. The results from 30d were added to 30-180d	**Source of funding** BMS and Sanofi/Aventis No control group of just ASA. Underpowered. Missing data.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Journal Am J Cardiol. 2007 Feb 1;99(3):349-52 Blinded: No Randomized Yes, using a central Internet-based computerized randomization service Allocation concealment: Unclear Stroke definition New focal neurologic deficit of vascular origin lasting >24 hrs and was		coronary artery, undergone successful PCI with placement of >1 stent without complication in <24 hrs Exclusion criteria: Allergy or contraindication to aspirin or clopidogrel, long-term clopidogrel therapy, NSAIDS other than aspirin <7days, glycoprotein IIb/IIIa <7d, target in-stent restenosis or vein graft lesion, stroke	180 d Age 60±11 Age>70yr=129 (24%) Men=407 (81%) Previous Revascularization= 111 (22.1%) MI=124 (24.7%) Cardiac heart failure=14 (2.8%) Stroke=7 (1.4%) PAD= 13 (2.6%) Aspirin = 181 (36.1%) BB=272 (54.3%) Statin=217 (43.2%) ACEi=176 (35.1%) CCB=107 (21.3%)					data and presented as ITT. Same Group 30d 12/502 180d (+4) 16/460	
							Outcome 2: MI 1-30d 30-180d	1-30d 30d = 10/502 (2%) 180d = 10/502 (2.0%) 30-180d 30d = 13/461(2.8 %) 180d = 7/460 (1.5%) Same group	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
further classified as intracranial hemorrhage, ischemic infarction, or of uncertain cause. Power calculation: 2,230 was required to indentify a composite outcome frequency of 23.4% in controls and 18.5% in clopiodgrel gp for 180 days. Enrolment was cut short post publication of CREDO trial. Ended up		or transient ischemic attack <12 m, a coagulation disorder, refusal to receive blood transfusion, major bleed <6 m, life expectancy >1 yr, another study, need for warfarin, or PCI or CABG <3 m, positive pregnancy result.						30d 10/502 180d (+7) 17/460	
							Outcome 3: Stroke 1-30d 30-180d	1-30d 30d = 4/502 (0.8%) 180d = 2/502 (0.4%) 30-180d 30d = 1/461(0.1%) 180d = 0/460 (0%) Same group 30d 2/502 180d (+0) 2/460	
							Outcome 4	1-30d	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
underpowered							PCI 1-30d 30-180d	30d = 17/502 (3.4%) 180d = 15/502 (0.4%) 30-180d 30d = 1/461(0.1%) 180d = 0/460 (0%) Same group 30d 15/502 180d (+0) 15/460	
							Outcome 5 CABG 1-30d	1-30d 30d = 3/502 (0.6%) 180d = 7/502 (1.4%)	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
							Outcome 6 Revascularization 180d	30-180d 30d = 26/461(5.6%) 180d = 18/460 (4.0%)	
							Outcome 7 Cardiovascular death 180 d	30-180d 30d = 8/461(1.7%) 180d = 4/460 (0.9%)	
							Outcome 8 Adverse events (stopped taking bc of AE)	30d = 11/461(2.4%) 180d = 5/460 (1.1%)	

Table 105: Bhatt 2007[65]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Bhatt DL, Flather MD, Hacke W, Berger PB, Black HR, Boden WE, Cacoub P, Cohen EA, Creager MA, Easton JD, Hamm CW, Hankey GJ, Johnston SC, Mak KH, Mas JL, Montalescot G, Pearson TA, Steg PG, Steinhubl SR, Weber MA, Fabry-Ribaudo L, Hu T, Topol EJ, Fox KA; CHARISMA Investigators.	RCT (subgroup analysis of CHARISMA)	N=9478 Drop outs Post-hoc analysis of CHARISMA In CHARISMA Follow-up data for primary efficacy was 99.6%: 99.5% Clopidogrel 7763/7802 99.6% Aspirin: 7770/7801 Analysis: ITT	**Inclusion criteria** patients were identified as "CAPRIE-like" if they were enrolled with a documented prior MI, documented prior ischemic stroke, or symptomatic PAD Inclusion from CHARISMA 45 years of age or older and had one of the following conditions: multiple atherothrombotic risk factors, documented coronary disease, documented cerebrovascular disease, or documented	Clopidogrel+Aspirin N=4735	Aspirin N=4743	28 months	**Outcome 1** All cause mortality	Clop+aspirin = 235/4735 ASA = 257/4743 HR: 0914 (0.964-1.090)	Source of funding Bristol-Myers Limitations
							Outcome 2 Cardiovascular mortality	Clop+aspirin = 142/4735 ASA = 163/4743 HR: 0.870 (0.695-1.090)	
							Outcome 3 MI	Clop+aspirin = 117/4735 ASA = 145/4743 HR: 0.805 (0.631-1.027)	
							Outcome 4 Ischemic stroke	Clop+aspirin = 144/4735 Aspirin = 179/4743 HR:0.828 (0.654-1.048)	
							Outcome 5 Hospitalisation	Clop+aspirin = 542/4735	

Title Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial. **Journal** J Am Coll Cardiol. 2007 May 15;49(19):1982-8. Epub 2007 Apr 11. Country: Germany/USA Randomisation: Subgroup analysis of randomised patients from			symptomatic peripheral arterial disease. **Exclusion criteria** Indications for open-label clopidogrel use or were at high risk of bleeding. **Baseline characteristics** A total of 3,846 patients had prior MI, with a median time from the qualifying event to randomization of 23.6 months; 3,245 patients had prior stroke, with a median time from event of 3.5 months; 2,838 patients had symptomatic PAD, with a median time from diagnosis of 23.6 months. Note that 443 (4.7%) patients					Aspirin = 626/4743 HR: 0.855 (0.762-0.960)	
							Outcome 6 Severe bleeding	Clop+aspirin = 79/4735 Aspirin = 71/4743 HR: 1.114 (0.808-1.535)	
							Outcome 7 Moderate bleeding	Clop+aspirin = 97/4735 Aspirin = 61/4743 HR 1.597 (1.159-2.200)	
							Outcome 8 CV death/stroke/MI	Prior MI patients Clop+aspirin= 125/1903 Aspirin=161/1943 HR: 0774 (0.613-0.978)	

CHARISMA trial Allocation Concealment :Yes, central interactive voice-response system Blinding: Double-blind Power Calculations:			fell into multiple categories because they actually had more than 1 prior event or disease location Characteristic Clopidogrel + aspirin (n = 4,735) Demographics Age (yrs), median (Q1, Q3) 64 (56, 71) Female patients, n (%): 1,292 (27.3) Ethnicity, n (% Caucasian: 3,859 (81.5) Hispanic: 454 (9.6) Asian: 226 (4.8) Black:141 (3.0) Other: 55 (1.2) Inclusion group, n (%) Prior myocardial infarction: 1,903 Prior ischemic stroke: 1,634						

			(34.5) Symptomatic PAD: 1,418 (29.9) Selected clinical characteristics, n (%) Smoking status Current 1,024 (21.6) Former 2,434 (51.4) Hypertensio: 3,236 (68.3) Hypercholesterolemia: 3,307 (69.8) Congestive heart failure: 298 (6.3) Prior myocardial infarction: 2,193 (46.3) Atrial fibrillation: 172 (3.6) Prior stroke: 1,764 (37.3) Transient ischemic attack: 326 (6.9) Diabetes1,457 (30.8) PAD: 1,529 (32.3) Percutaneous coronary						

			intervention: 1,209 (25.5) Coronary artery bypass graft surgery 809 (17.1) Carotid endarterectomy: 257 (5.4) Angioplasty or bypass 829 (17.5) Diabetic nephropathy: 195 (4.1) Characteristic Placebo aspirin (n = 4,743) Demographics Age (yrs), median (Q1, Q3) 64 (56, 71) Female patients, n (%)1,275 (26.9) Ethnicity, n (%) Caucasian: 3,851 (81.2) Hispanic 481 (10.1) Asian: 222 (4.7) Black: 137 (2.9)						

			Other: 52 (1.1) Inclusion group, n (%) Prior myocardial infarction: 1,943 (41.0) Prior ischemic stroke: 1,611 (34.0) Symptomatic PAD: 1,420 (29.9) Selected clinical characteristics, n (%) Smoking status: Current: 1,055 (22.2) Former: 2,435 (51.3) Hypertension: 3,317 (69.9) Hypercholesterolemia: 3,343 (70.5) Congestive heart failure:308 (6.5) Prior myocardial infarction:2,248 (47.4) Atrial fibrillation:160 (3.4) Prior stroke;						

			1,726 (36.4) Transient ischemic attack300 (6.3) Diabetes 1,484 (31.3)PAD 1,530 (32.3) Percutaneous coronary intervention:1,239 (26.1) Coronary artery bypass graft surgery 829 (17.5) Carotid endarterectomy235 (5.0) Peripheral angioplasty or bypass 812 (17.1) Diabetic nephropathy211 (4.4)						

Table 106: Bhatt 2006; Berger 2010[54,64]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Bhatt DL;Fox KAA;Hacke W;Berger PB;Black HR;Boden WE;Cacoub P;Cohen EA;Creager MA;Easton JD;Flather MD;Haffner SM;Hamm CW;Hankey GJ;Johnston SC;Mak KH;Mas JL;Montalescot G;Pearson TA;Steg PG;Steinhubl SR;Weber MA;Brennan DM;Fabry-Ribaudo L;Booth J;Topol E **Title** "Clopidogrel	RCT CHARISMA Categorised as STEMI in CG48 Analysis: ITT	Total=15603 Clopidogrel=7802 Placebo=7801 Drop-out: Follow-up data for primary efficacy was 99.6%: 99.5% Clopidogrel 7763/7802 99.6% Aspirin: 7770/7801 **Inclusion criteria:** Aged 45 years or older and one of the following conditions: atherothrombotic risk factors (such as diabetes,	Clopidogrel Age:64 Female: 2316 (29.7%) Inclusion subgroup Vascular disease: 6062 (77.7%) Multiple risk factors: 1659 (21.3%) Neither: 81 (1.0%) Selected clinical characteristics: Prior MI:2672 (34.2%) Prior stroke:1942 (24.9%) Prior transient ischemic attack:938 (12%) PAD:1760 (22.6%) Prior PCI:1750 (22.4%) Prior CABG or angioplasty:879 (11.3%) Placebo Age:64	Clopidogrel 75 mg once daily plus aspirin 75 to 162 mg once daily Concomitant therapy: All patients received standard therapy appropriate (eg. Statins or BB) at the discretion of the investigator and clinicians	Placebo once daily plus aspirin 75 to 162 mg once daily	Median follow-up 28 months. Follow-up 1 m, 3m, 6m and /6m until end of trial	**Outcome 1** Death from any cause	Clopidogrel: 371/7802 (4.8%) Aspirin: 374/7801 (4.8%)	**Source of funding** Sanofi-Aventis,Bristol-Myers Squibb. Other outcomes: Subgroup analysis Had intracranial hemorrhage and stroke as outcomes.
							Outcome 2 Death from CV causes	Clopidogrel: 238/7802 (3.1%) Aspirin: 229/7801 (2.9%)	
							Outcome 3 MI (nonfatal)	Clopidogrel: 147/7802 (1.9%) Aspirin: 1.59/7801 (2.0%)	
							Outcome 4 Ischemic stroke (nonfatal)	Clopidogrel: 132/7802 (1.7%) Aspirin: 160/7801 (2.1%)	
							Outcome 5 Any stroke	Clopidogrel: 149/7802	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
and aspirin versus aspirin alone for the prevention of Atherothrombotic events" **Journal** England Journal of Medicine:2006:354(16)1706-17 USA Randomization: Unclear, preestablished randomization scheme Allocation concealment: Yes, central interactive voice-response system		diabetic nephropathy, ankle-brachial < 0.9) documented coronary disease; documented cerebrovascular disease; or documented symptomatic peripheral arterial disease. **Exclusion criteria:** taking oral antihrombotic medications or NSAIDs on a long-term basis. Established indications for clopidogrel therapy (such	Female:2328(29.8%) Inclusion subgroup Vascular disease: 6091 (78.1%) Multiple risk factors: 1625 (20.8%) Neither: 85 (1.1%) Selected clinical characteristics: Prior MI:2725 (34.9%) Prior stroke:1895(24.3%) Prior transient ischemic attack:926 (11.9%) PAD:1771(22.7%) Prior PCI:1804 (23.1%) Prior CABG or angioplasty:858 (11%)				(nonfatal)	(1.9%) Aspirin: 185/7801 (2.4%)	
							Outcome 6 Rehospitalization (for unstable angina, transient ischemic attack, or revascularization)	Clopidogrel: 886/7802 (11.1%) Aspirin:957/7801 (12.3%)	
							Outcome 7 Severe bleeding+ Fatal bleeding Major bleeding	Clopidogrel156/7802 (1.7%) Aspirin: 121/7801 (1.3%) Clopidogrel130/7802 Aspirin: 104/7801	
							Outcome 8 Fatal bleeding	Clopidogrel26/7802 (0.3%)	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Blinded:Double blind Power calculations: 15,200 (7600/grp) and 1040 primary events needed to detect a 20% RR reduction, with 90% power, assuming an annual event rate of 3.1% in control group and 18 to 42 months follow-up		as acute coronary syndrome); undergoing revascularization. Asymptomatic carotid stenosis ≥ 70% of luminal diameter, ≥ 1 carotid						Aspirin: 17/7801 (0.2%)	
							Outcome 9 Primary intracranial haemorrhage	Clopidogrel26/7802 (0.3%) Aspirin 27/7801 (0.3%)	
							Outcome 10 Moderate bleeding	Clopidogrel164/7802 (2.1%) Aspirin 101/7801 (1.3%)	
							Outcome 11 Fatal bleed (HR)	Clopidogrel 26 (0.3%) Placebo 17 (0.2%) HR: 1.527 (0.829, 2.815)	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
							Outcome 12 Intracranial haemorrhage (HR)	Clopidogrel 26 (0.3%) Placebo 27 (0.3%) HR: 0.962 (0.561, 1.648)	

Table 107: Chen 2005[106]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Chen ZM;Jiang LX;Chen YP;Xie JX;Pan HC;Peto R;Collins R; **Title** Addition of clopidogrel to aspirin in 45852 patients with acute	RCT COMMIT-(STEMI) Analysis: ITT	Total = 45,852 Clopidogrel=22,961 Placebo=22,891 Lost to follow-up Clopidogrel=2 Placebo=0	Clopidogrel Age: 61.3±11.9 Female:6366 (27.7%) Time since onset (h):10.3±6.7 ECG abnormality at entry STelevation:19877 (86.5%) Bundle branch block:1505 (6.6%) STdepression (without ST	Clopidogrel: 162 mg aspirin + 75 mg clopidogrel Daily for up to 4 weeks (or, if earlier, until hospital discharge or death) Concomitant therapy:Fibrinolytic therapy (chiefly urokinase) was received by 50% of patients	Placebo: 162 mg aspirin + placebo Daily for up to 4 weeks (or, if earlier, until hospital discharg	Discharge or up to 4 weeks in hospital	**Outcome 1:** Death from any cause	Clopidogrel: 1726/22961 (7.5%) Placebo 1845/22891 (8.1%)	**Funded by** Sanofi-Aventis, Bristol-Myers Squibb, Astra-Zeneca, MRC UK, BHF, Cancer Research UK.
							Outcome 2: Death	Clopidogrel: 113/229	

myocardial infarction:randomised placebo-controlled trial **Journal** Lancet 2005;366:1607-21 China Randomization: Random allocation, unclear methods Allocation concealment: Yes, used sealed study treatment cases and assigned by removing allocated treatment from an opening at the bottom of the treatment case. Blinding: Unclear, single blind investigator		Inclusion criteria: Post MI recruited within 24 h of suspected acute MI onset (ST elevation Excluded: patients scheduled for PCI: small likelihood of worthwhile benefit, or high risk of AE.	elevation): 1579 (6.9%) Before admission: MI:1972 (8.6%) Aspirin:4214 (18.4%) BB:1457 (6.3%) Fibrinolytic: 11407 (49.7%) Non-trial treatment during trial Antiplatelet:2305 (10%) ACEi: 15649 (68.2%) Antiarrhythmic:5150 (22.4%) Calcium antagonist:2701 (11.8%) Placebo Age: 61.4±11.8 Female:6393 (27.9%) Time since onset (h):10.3 ±6.7 ECG abnormality at entry STelevation:19878 (86.9%) Bundle branch block:1423 (6.2%) STdepression (without ST elevation): 1590 (6.9%) Before admission: MI:1846 (8.1%) Aspirin:4230 (18.5%)	before or at or after randomisation. During hospital stay, 10% received antiplatelet and 75% received heparin. clopidogrel once daily for up to 4 weeks (or, if earlier, until hospital discharge or death) 22 961 patients	e or death)		from reinfarction:	61 (0.5%) Placebo 101/22891 (0.4%)	Sponsor: had no role in study design/data collection/data interpretation/or writing of the report Other outcomes Primary Composite of death, reinfarction, or stroke. Subgroup analysis, including ECG at entry Cardiogenic shock;Heart failure;Cardiac rupture;VF; other cardiac arrest;pulmonary embolus infarction
							Outcome 3: Stroke (died+survived) - haemorrhagic; ishaemic or unknown	Clopidogrel 217/22961 (0.9%) Placebo 250/22891 (1.1 %)	
							Outcome 4: Reinfaction (died + survived)	Clopidogrel: 479/22961 (2.1%) Placebo 553/22891 (2.4%)	
							Outcome 5: Adverse event – any bleeding (cerebral or major non-cerebral bleeding	Clopidogrel 134/22961 (0.58%) Placebo 125/22891 (0.55%)	

assessing ECG's blind Power calculations: To have at least 95% power to detecte a reduction of one tenth with a two-sided pvalue of 0.05 at least 45,000 patients needed to be recruited			BB:1533 (6.7%) Fibrinolytic:11387 (49.7%) Non-trial treatment during trial Antiplatelet:2280 (10%) ACEi: 15638 (68.3%) Antiarrhythmic:5093 (22.2%) Calcium antagonist:2705 (11.8%)				**Outcome 6:** Fatal bleeding	Clopidogrel 73/22961 (0.32%) Placebo 74/22891 (0.32%)	Stroke Cardiogenic shock Heart failure Presumed cardiac rupture Ventricular fibrillation Other cardiac arrest Pulmonary embolism

Table 108: Eisenstein 2007[173]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Eisenstein EL, Anstrom KJ, Kong DF, Shaw LK, Tuttle RH, Mark DB, Kramer JM, Harrington RA, Matchar DB, Kandzari DE, Peterson ED,	Cohort - Observational	Total = 4666 Clopidogrel+aspirin = 1054 Aspirin = 2555 BMS = 3165 DES = 1501	Clopidogrel+Aspirin DES n = 637 Age: 61 (53-71) Male sex: 398 (62.5%) History of MI: 247 (38.8%) Aspirin use 6 m: 600 (94.2%) 12 m 478 (91.2%) 24 m 179 (93.2%) Clopidogrel use	Clopidogrel+Aspirin (BMS vs. DES)	Aspirin (BMS vs. DES)	6, 12, 24 months	**Outcome 1** Death 24 m	Clop+DES=1.6%, 7/290 aspirin+DES=5.8%, 20/245 Clop+BMS=3.9%, 16/387 aspirin+BMS=4.5%, 88/1852	**Source of funding** Agency for heathcare and quality (AHRQ), US Dept of Health and Human services.
							Outcome 2	Clop+DES=0.	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Schulman KA, Califf RM. **Title** Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. **Journal** JAMA. 2007 Jan 10;297(2):159-68. Epub 2006 Dec 5		**Inclusion criteria** Patients who had an initial PCI with at least 1 bare-metal stent. Min 12 m follow-up. **Exclusion criteria:** congenital heart disease, moderate to severe valvular heart disease, prior CABG or PCI and significant >75% stenosis left main CAD. If intervention other than stent placement occurred during their PCI procedure or if not contacted for follow-up medication use	6 m 637 (100%) 12 m 382 (72.9%) 24 m 106 (55.2%) BMS n = 579 Age: 60 (53-70) Male sex: 368 (63.6%) History of MI: 221 (38.2%) Aspirin use 6 m: 430 (74.3%) 12 m: 371 (86.3%) 24 m: 148 (85.6%) Clopidogrel use 6 m: 0 12 m: 64 (14.9%) 24 m: 25 (14.5%) Aspirin DES Age 61 (53-70) Male sex: 266 (63.8%) History of MI: 213 (51.1%) Aspirin use 6 m 360 (86.3%) 12 m 335 (84%) 24 m 304 (82.2%) Clopidogrel use 6 m 417 (100%)				Non-fatal MI 24 m	8%, 5/290 Aspirin+DES =3.3%, 13/245 Clop+BMS=1.2%, 5/387 Aspirin+BMS =1.4%, 28/1852	Limitations: unclear how they derived at a number of data points
							Outcome 3: Death HR	DES. aspirin vs. Clop = HR 2.43 (1.12-5.26), p=0.03 DES+Clop, lower rates of death. BMS. aspirin vs.Clop =NS	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		for each analysis period.	12 m 309 (77.4%) 24 m 230 (82.2%) BMS Age 61 (52-71(Male sex: 1233 (62.4%) History of MI: 913 (46.2%) Aspirin use 6 m 1583 (80.1%) 12 m 1569 (85%) 24 m 1541 (87.1%) Clopidogrel use 6 m 12 m 93 (5%) 24 m 143 (8.1%)						

Table 109: Kulik 2010[327]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Kulik A, Le May MR, Voisine P, Tardif JC, Delarochellier e R, Naidoo S, Wells GA,	CASCADE RCT Phase II randomized	N=113 Clop+aspirin n=56 Aspirin n=56 Drop out Clop+aspirin	Aspirin+Clop n=56 Age= 64.9 ±7.5 Male=91.1% ACS =12.5% Heart failure NYHA 3-4% =23.2% Preoperative	Clopidogrel 75mg +ASA 162mg/d	Aspirin162 mg/d	12m	**Outcome 1** Death CV (same for all-cause)	Clop+aspirin n=0/56 Aspirin n=1/57	**Sourse of funding** Bristol-Myers Squibb Sanofi. They provided medication
							Outcome 2 MI	Clop+aspirin n=4/56 (7.1%)	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Mesana TG, Ruel M. **Title** Aspirin plus clopidogrel versus aspirin alone after coronary artery bypass grafting: the clopidogrel after surgery for coronary artery disease (CASCADE) Trial. **Journal** Circulation. 2010 Dec 21;122(25):2680-7. Epub 2010 Dec 6. Randomized Stratified according to surgical centre. Block randomization generated by		=n10 (17.9%) Aspirin n=12 (21.1%) Analysis =ITT Inclusion criteria scheduled to undergo first-time CABG with at least 2 SVGs with or without the use of cardiopulmonary bypass. Exclusion criteria required valve surgery or long-term anticoagulation	medication Aspirin=91.1% Clopidogrel=5.4% Statin=94.6% BB=83.9% ACEi=53.6% Aspirin n=57 Age=68.1±7.4 Male=87.7% ACS =22.8% Heart failure NYHA 3-4 =17.5% Preoperative medication Aspirin=93% Clopidogrel=15.8% Statin=84.2% BB=70.2% ACEi=47.4% Medications at discharge Clop+aspirin Statin = 91.1% BB = 94.6% ACEi = 37.5%					Aspirin n=1/57 (1.8%)	
							Outcome 3 Cerebrovascular accident (stroke)	Clop+aspirin n=0/56 ASA n=2/57	
							Outcome 4 Coronary intervention (Revascularization)	Clop+aspirin n=1/56 ASA n=2/57	
							Outcome 5 Major bleeding	Clop+aspirin= 1/56 ASA n=0/57	
							Outcome 6 Minor bleeding	Clop+aspirin n=3/56 ASA n=3/57	
							Outcome 7: AE (withdrew)	Clop+aspirin n=3/56 Aspirin n=5/57	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
SAS. Blinded Double blinded Allocation concealment Unclear. Organised by pharmacists. Power calculations 37 patients/gp were needed to detect a relative treatment difference of 20% in the primary outcome (combined), at a power of 90% and 2-sided alpha=0.05. Assuming a drop-out of 35% or more, a total of 110			Aspirin Statin = 91.2% BB = 91.2% ACEi =33.9%						

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
randomized patients were required.									

Table 110: Sabatine 2005[515]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Author Sabatine MS;Cannon CP;Gibson CM;L¾pez-Send¾n JL;Montalescot G;Theroux P;Claeys MJ;Cools F;Hill KA;Skene AM;McCabe CH;Braunwald E; **Title** "Addition of	RCT CLARITY-TIMI 28 (STEMI)	Total:3491 Intervention N=1752 Control: N=1739 Drop outs: Vital status ascertained in 3487/3491 (99.9%) Unclear how many were available for the 30d data. Analysis ITT	Clopidogrel Age =57.7±10.3 Male = 1400 (79.9%) Prior MI =159 (9.1%) Prior PCI=84 (4.8%) Angiography=1645 (93.9%) Medications during index hospitalization BB= 1554 (88.7%) Statins=1408 (80.4%) ACEi or ARBs=1273 (72.7%)	Clopidogrel 300 mg loading dose, followed by 75 mg once daily + Aspirin + Fibrinolytic agent	Placebo + Aspirin (150 to 325mg 1st day to 72 to 325mg thereafter) + Fibrinolytic agent (selected by physician)	30 days	**Outcome 1** Death by CV **Outcome 2** Stroke **Outcome 3** Recurrent MI	Clopidogrel= 77/1752 (4.4%) Placebo = 78/1739 (4.5%) Clopidogrel= 12/1752 (0.7%) Placebo=30/1739 (1.7%) Clopidogrel = 72/1752 (4.1%) Placebo = 103/1739 (5.9%)	Sanofi-Aventis, Bristol-Myers Squibb	Other outcomes: Primary Composite occluded infarct related artery on angiography, death or recurrent MI. Subgroup analysis of age <65 >65 Sex Infarct location Fibrinolytic agent

clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation" **Journal** New England Journal of Medicine 2005; 352: 1179-89 USA Randomization 1:1 ratio, computerized Allocation concealment: Yes, central system of randomization Blinding: Double blind		Inclusion criteria: enrolled within 12 h after onset ST-elevation MI, aged 18 to 75 years, mean 57 years, men and women (20%), scheduled to receive a fibrinolytic agent, an anticoagulant (if a fibrin-specific lytic agent was prescribed), aspirin and undergo angiography 48 to 192 hours after the start of study medication Exclusion criteria: treatment with clopidogrel	In hospital treatment PCI 57.2% CABG: 2.9% Placebo Age =57.2±103 Male = 1403 (80.7%) Prior MI =159 (9.1%) Prior PCI=85 (4.9%) Angiography=1638 (94.2%) Medications during index hospitalization BB= 1559 (89.6%) Statins=1410 (81.1%) ACEi or ARBs=1254(72.1%) In hospital treatment PCI 56.6% CABG: 6% Concomitant							Heparin before angiography Composite death from CV causes, recurrent MI, recurrent ischemia requiring revascular-isation at 30 days Secondary

Power calculations: 3500 patients would provide the study with statistical power of 95% to detect a relative reduction in the primary end point of 24% (19-14.4%) with a two-sided test at 5% level.		within 7 days before enrolment or planned treatment with clopidogrel or a glycoprotein 11b/11a inhibitor before angiography, contraindications to fibrinolytic therapy, planned angiography within 48 h in the absence of a new clinical indication, cardiac shock, prior CABG, weight 67 kg or less and receipt of more than 4000-U bolus of unfractionated heparin, weight more than 67 kg	therapy: All patients were to be treated with fibronolytic agent, aspirin,							
							Outcome 4 Urgent revascularization	Clopidogrel = 61/1752 (3.5%) Placebo = 78/1739 (4.5%)		
							Outcome 5 Major bleeding (TIMI criteria) Day 30	Clopidogrel = 33/1733 (1.9%) Placebo =30/1719 (1.7%)		

		and receipt of more than 5000-U bolus of unfractionated heparin, or receipt of more than standard dose of low-molecular-weight heparin					**Outcome 6** Minor bleeding (day 30)	Clopidogrel = 27/1733 (1.6%) Placebo = 16/1719 (0.9%)		

Table 111: Steinhubl 2002[559]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Author Steinhubl SR, Berger PB, Mann JT 3rd, Fry ET, DeLago A, Wilmer C, Topol EJ; CREDO Investigators. Clopidogrel	RCT (CREDO)	N=2116 Clopidogrel n=1053 Placebo=n=1063 Analysis ITT=2116 PPA = 1815 (900 vs 915)	PCI - 89% had STENTS Clopidogrel N=1053 Age: 61.5 (11.2) White race:929 (88.2%) Women (%):309 (29.3%) Previous Risk	Clopidogrel (300mg)+aspirin (325mg)	Aspirin(325 mg)+Placebo	28 d + 1 year	**Outcome 1** Death 1yr	Clopidogrel= 18/1053 (1.7%) Aspirin=24/1063 (2.3%) RRR 24.6 (-38.9,59.1)	Bristol=Myers Squibb/Sanofi-Synthelabo partnership. Latter provided clopidogrel and	Limitations:All patients received 75mg Clopidogrel for 1m post PCI Combined end point for stent vs. no
							Outcome 2 MI 1yr	Clopidogrel= 70/1053 (6.6%) Aspirin=90/10		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
for the Reduction of Events During Observation **Title** Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. **Journal** JAMA. 2002 Nov 20;288(19):2411-20. Blinding: Double blind Randomization: Patients randomly		Lost to follow-up: Clopidogrel n=38 Placebo n=48 1 yr did not complete treatment: Clop N=411 37% ASA n=420 39% Inclusion: symptomatic coronary artery disease with objective evidence of ischemia (eg, symptoms of angina pectoris, positive	factors: MI:353 (33.5%) stroke:67 (6.4%) PAD:102 (9.7%) Diabetes: 290 (27.5%) Baseline medications Aspirin: 315 (29.9%) BB:664 (63.1%) Stain:563 (53.5%) ACEi:347 (33%) CCB:268 (25.5%) Treatment after angiogram: PCI:902 (85.6%) Medical therapy: 87 (8.3%) CABG: 41 (3.9%) Indication for PCI: Recent MI:151 (14.3%) Unstable angina:553 (52.5%) Stable angina other other:345 (32.8%)					63 (8.5%) RRR 21.7 (-7.1,42.7)	matching placebo	stent
							Outcome 3 Stroke 1yr	Clopidogrel= 9/1053 (0.9%) Aspirin=12/1063 (1.1%) RRR 25 (-77.9,68.4)		
							Outcome 4 Revascularization (any) 1yr	Clopidogrel= 225/1053 (21.4%) Aspirin=223/1063 (21%) RRR -1.6 (-22.3,15.5)		
							Outcome 5 Combined death+MI+ stroke 1 yr	Stent n=1616 Clop vs. aspirin RR 28.8 (47.4, 3.6) No stent n=500 Clop vs. aspirin RRR 19 (57, -52.6)		
							Outcome 6	1 yr		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
assigned to groups using a prospective randomization schedule of blocks of 2 and stratified by centre. Site dispensed a drug package that contained a 4-digit random no. This was then associated with a drug. Allocation concealment Unclear Power: Based on 1 yr event rate of 20% for composite of death, MI+any revascularizat		stress test results, or dynamic electrocardiographic [ECG] changes); were referred for PCI, or thought to be at high likelihood for requiring PCI with either stent placement with or without conventional balloon angioplasty or another revascularization device; were at least 21 years old;	Placebo n=1063 Age: 61.8 (11%) White race:951 (89.5%) Women (%):297 (27.9%) Previous Risk factors: MI:366 (34.4) stroke:74 (7%) PAD:109 (10.3%) Diabetes:270 (25.4) Baseline medications Aspirin:315 (29.6%) BB: 696 (65.5%) Stain:609 (57.3%) ACEi:364 (34.2%) CCB:312 (29.4%) Treatment after angiogram: PCI:916 (86.2%) Medical therapy:81 (7.6%)				Minor bleeding, 1 yr and 28 d	Clopidogrel=56/1053 (5.3%) Aspirin=59/1063 (5.6%) 28d Clopidogrel=33/1053 (3.1%) Aspirin=24/1063 (2.3%)		
							Outcome 7 Major bleeding 1 yr and 28 d	1yr Clopidogrel=93/1053 (8.8%) Aspirin=71/1063 (6.7%) 28d Clopidogrel=50/1053 (4.7%) Aspirin=38/1063 (3.6%)		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
ion, 2 sided level of 0.05, a study with 1814 patients would have 80% power to detect a 25% RR reduction. A planned sample size of +10% was included to account for lost to follow-up		provided informed consent before randomization; and agreed to comply with all protocol-specified procedures. Major exclusion criteriafrom included contraindications to antithrombotic/ antiplatelet therapy; greater than 50% stenosis of the left main coronary artery; failed coronary intervention	CABG:42 (4%) Indication for PCI: Recent MI:139 (13.1%) Unstable angina:564 (53.1%) Stable angina other: 349 (32.8%)							

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
		in the previous 2 weeks; coronary anatomy not amenable to stent placement; persistent ST elevation within 24 hours prior to randomization; planned staged intervention al procedure; and administration of the following medications prior to randomization: GpIIb-IIIa inhibitor								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
		within 7 days, clopidogrel within 10 days, or thrombolytics within 24 Hours								

Table 112: Valgimigli 2012A[593]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Valgimigli M, Campo G, Monti M, Vranckx P, Percoco G, Tumscitz C, Castriota F, Colombo F, Tebaldi M, Fucà G, Kubbajeh M, Cangiano E, Minarelli M, Scalone A, Cavazza C, Frangione A,	RCT	Total: 1970	Inclusion criteria: ≥18 years of age with chronic stable coronary artery disease or acute coronary syndromes, including non–ST-elevation and ST-elevation myocardial infarction. They were eligible if they had at least 1 lesion with a diameter stenosis of ≥50% that was	Clopidogrel 24 months 160 to 325 mg orally or 500 mg IV as a loading dose and then 80 to 160 mg orally indefinitely 1:1:1:1 ratio to everolimus-eluting, paclitaxel-eluting,	Clopidogrel 6m 160 to 325 mg orally or 500 mg IV as a loading dose and then 80 to 160 mg orally indefinitely	24 months	**Outcome 1** All –cause mortality	24m: 65/987 6m: 65/983	Source of funding: Limitations In the 6-month dual-antiplatelet therapy group, clopidogrel discontinuation at any time after 30 days was allowed in
							Outcome 2 CV mortality	24m: 36/987 6m: 37/983	
							Outcome 3 Reinfarction	24m: 39/987 6m: 41/983	
							Outcome 4 Stroke	24m:21/987 6m:14/983	
							Outcome 5 Definite stent thrombosis	24m: 8/987 6m: 7/983	
							Outcome 6 Major Bleeding risk: (TIMI)	24m: 16/987 6m: 6/983	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Borghesi M, Marchesini J, Parrinello G, Ferrari R; Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study (PRODIGY) Investigators **Title** Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial. **Journal** Circulation. 2012 Apr 24;125(16):2015-26			suitable for coronary stent implantation in a vessel with a reference vessel diameter of ≥2.25 mm. Selection criteria were broad, reflecting routine clinical practice. We set no limit for the number of treated lesions, vessels, or lesion length. Exclusion criteria: we excluded no patients on the basis of comorbid disorders or age, apart from the following prespecified criteria: Known allergy to acetylsalicylic acid or clopidogrel; planned surgery within 24 months of percutaneous coronary intervention unless	zotarolimus-eluting Endeavor Sprint, or BMS (any thin-strut, uncoated-stent type approved by the regulatory agency)			**Outcome 7** Minor bleeding (TIMI)	24m: 11/987 6m: 9/983	patients who were randomized to a BMS if coronary intervention was indicated by the presence of stable coronary artery disease. This was driven by the lack of data showing the value of clopidogrel in addition to aspirin beyond 30 days in this patient population.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Blinding: No, open label Randomisation: 1:1:1:1 fashion to 1 of 4 stent types. At 30 days patients in each stent group were randomised in to either 6 or 24 months. Power calculation: Assuming an event rate of 8.0% at 2 years for the primary end point of death of any cause, nonfatal myocardial infarction, or cerebrovascular accident among patients who were assigned to 6-month			the dual-antiplatelet therapy could be maintained throughout the perisurgical period; history of bleeding diathesis; major surgery within 15 days; active bleeding or previous stroke in the past 6 months; concomitant or foreseeable need for oral anticoagulation therapy; pregnancy; life expectancy <24 months; participation in another trial; and inability to provide informed consent. Patient characteristics 24 MONTHS n=987 Age: 67.8±11 Male: 77% Prior MI: 270						

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
clopidogrel duration, we estimated that at least 1700 patients (850 in each group) would need to be enrolled to detect a 40% reduction in the relative risk of the primary end point in the 24-month clopidogrel group compared with 6-month duration of clopidogrel therapy, with statistical power of ≥80% at a 2-sided significance level of 0.05. The planned sample size was then increased up to 2000 to			(27.3%) Prior PCI: 184 (18.6%) Prior CABG: 110 (11.1%) Prior stroke or ischemic attack: 37 (3.7%) LVEF:55 (45-60) Clinical presentation, n (%) Stable angina: 257 (26%) ACS:732 (74.2%) NSTEMI:226 (22.9%) STEMI:321 (32.5%) Unstable angina:183 (18.5%) 6 MONTHS Age:67.9 ±11 Male:747 (76%) Prior MI:258 (26.2%) Prior PCI: 174 (17.7%) Prior CABG:105 (10.7%) Prior stroke or ischemic attack: 39						

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
allow for fatalities occurring within the first 30 days, noncompliance, and loss to follow-up.			(4%) LVEF:50 (43.3-60) Clinical presentation, n (%) Stable angina:250 (25.4%) ACS:733 (74.6%) NSTEMI:224 (22.8%) STEMI: 327 (33.3%) Unstable angina: 182 (18.2%) Concomitant medication Evaluated, total (DES/BMS) 24m 920 (690/230) 6m 920 (693/227) Aspirin 24m: 905 (98.4) 6m: 897 (97.5) Clopidogrel 24m: 880 (95.7) 6m: 5 (0.5) Aspirin and clopidogrel						

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			24m:871 (94.7) 6m:3 (0.3) ACE inhibitors 24m: 707 (76.8) 6m:708 (77.0) Angiotensin II receptor antagonist 24m: 112 (12.2) 6m:119 (12.9) β-blockers 24m: 750 (81.5) 6m:749 (81.4) Statins 24m: 818 (88.9) 6m:811 (88.2) Proton pump inhibitors 24m:344 (37.4) 6m:302 (32.8)						
Author Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, Malmberg K, Rupprecht H, Zhao F,		ITT analysis	Mehta: PCI was done after randomisation at the discretion of the local investigator and clopidogrel and placebo was continued up until				**Outcome 1** Reinfarction	Clopidogel =59/1313 Placebo= 85/1345	
							Outcome 2 CV death	Clop 32/1313 vs. Placebo 31/1345	
							Outcome 3 Revascularisation	Clop 186/1313 vs.	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Chrolavicius S, Copland I, Fox KA; Clopidogrel in Unstable angina to prevent Recurrent Events trial (CURE) Investigators **Title** Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. **Journal** Lancet. 2001 Aug 18;358(9281):			this point. PCI - 82% had STENTS Clopidogrel n=1313 N=344 took open label theinopyridine before PCI N=969 received drug up to PCI Placebo n=1345 N=329 took open label theinopyridine before PCI N=1016 received drug up to PCI					Placebo 230/1345	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
527-33.									
Author Fox KA, Mehta SR, Peters R, Zhao F, Lakkis N, Gersh BJ, Yusuf S; Clopidogrel in Unstable angina to prevent Recurrent ischemic Events Trial. **Title** Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: the Clopidogrel in Unstable angina to			CABG n=2072 In hospital n=1013 ~25 d later N=1057 Clopidogrel n=1011 Placebo n=1061 Median time from randomization to CABG was 25.5d (12 to 70.5d) The time to CABG for those undergoing the procedure during hospitalisation was 12-13d (8-21)				**Outcome 1** Major bleeding:[a]	Clopdigorel 97/1011 vs. Placebo 80/1061	
							Outcome 2 CV death/MI/stroke[a]:	147/1011 vs. 172/1061	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
prevent Recurrent ischemic Events (CURE) Trial. **Journal** Circulation. 2004 Sep 7;110(10):1202-8. Epub 2004 Aug 16.									
Author Yusuf S, Mehta SR, Zhao F, Gersh BJ, Commerford PJ, Blumenthal M, Budaj A, Wittlinger T, Fox KA; Clopidogrel in Unstable angina to prevent Recurrent Events Trial Investigators. **Title**									

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
"Early and late effects of clopidogrel in patients with acute coronary syndromes." **Journal** Circulation. 2003 Feb 25;107(7):966-72.									
							Outcome 1 CV death from PCI to end of follow-up[b]	Clopidogrel 32/1313 (2.4%) Placebo 31/1345 (2.3%)	
							Outcome 2 CV death from PCI to 30d[b]	Clopidogrel 14/1313 (1.1%) Placebo 13/1345 (1.0%)	
							Outcome 3 Myocardial	Clopidogrel 59/1313	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
							infarction from PCI to end of follow-up[b]	(4.5%) Placebo 85/1345 (6.4%)	
							Outcome 4 Myocardial infarction from PCI to 30d[b]	Clopidogrel 28/1313 (2.1%) Placebo 51/1345 (3.8%)	
							Outcome 5 Any revascularisation from PCI to end of follow-up[b]	Clopidogrel 186/1313 (14.2%) Placebo 230/1345 (17.1%)	
							Outcome 6 Any revascularisation from PCI to 30d[b]	Clopidogrel 25/1313 (1.9%) Placebo 38/1345 (2.8%)	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
							Outcome 7 Major bleeding from PCI to end of follow-up[b]	Clopidogrel 36/1313 (2.7%) Placebo 33/1345 (2.5%)	
							Ouctome 8 Major bleeding from PCI to 30 d[b]	Clopidogrel 21/1313 (1.6%) Placebo 19/1345 (1.4%)	

(a) Fox et al 2004
(b) Extracted from Mehta et al.2001

Table 113: Yusuf 2001; Yusuf 2003; Mehta 2001 ; Fox 2004[196,384,633,637]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Yusuf S;Zhao F;Mehta SR;Chrolavicius S;Tognoni G;Fox KK; **Title** Effects of clopidogrel in addition to aspirin in	RCT CURE-NSTE MI	Total =12,562 Clopidogrel = 6259 Placebo = 6303 Drop out. Clopidogrel, n=6 Aspirin	Clopidogrel Age = 64.2±11.3 Female=2420 (38.7%) Onset of pain to randomisation (hr) = 14.2±7.2 Diagnosis at entry Unstable angina =4690 (74.9%)	Clopidogrel 300 mg immediately followed by 75 mg daily plus aspirin	Placebo plus aspirin (75 to 325mg/d)	3 to 12 months, mean duration of treatment 9 months, no patient <	**Outcome 1** Death from CV causes	Clopiodogrel =318/6259 (5.1%) Placebo = 345/6303 (5.5%)	Source of funding not listed Other outcomes: Composite = nonfatal MI, stroke, or death from CV causes
							Outcome 2	Clopidogrel=	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
patients with acute coronary syndromes without ST-segment **Journal** New England J or Medicine:2001;345:494-502 Randomization: Central 24 hr computerized randomization service. Permuted block randomization, stratified according to clinical centre Allocation concealment: Yes see above Blinding: Double blind		n=7 0.1% Inclusion criteria: Hospitalised within 24 h of onset of symptoms of acute coronary syndromes characteristics without ST elevation Exclusion criteria: contraindications to antiplatelet / anticoagulant therapy, high risk for bleeding or heart failure, taking oral coagulants, revascularization in previous 3	Suspected MI =1569 (25.1%) Associated MI =1624 (25.9%) Mediations at time of randomisation Aspirin =4168 (66.6%(Heparin or LMW heparin =4522 (72.3%) ACEi=2347 (37.5%) BB=3678 (58.8%) CCB=1784 (28.5%) Lipid lowering agent =1599 (25.6%) Placebo Age=64.2±11.3 Female=2416 (38.3%) Onset of pain to randomisation (hr) = 14.1±7.1 Diagnosis at entry Unstable angina =4724 (74.9%) Suspected MI			3 months Included centers in wHich there was no routine policy of early use of invasive procedures. Such a policy would have led to a high rate of immediate discontinuation and the use of open label thienopyridine derivative.	Death from non-CV causes	41/6259 (0.7%) Placebo=45/6303 (0.7%)	
							Outcome 3 All cause mortality	Clopidogrel=359/6259 Placebo=390/6303	
							Outcome 4 Non-Qwave MI	Clopidogrel=216/6259 (3.5%) Placebo = 242/6303 (3.8%)	
							Outcome 5 Stroke	Clopidogrel =75/6259 (1.2%) Placebo=87/6303 (1.4%)	
							Outcome 6 Major bleeding	Clopidogrel 231/6259 (3.7%) Placebo 169/6303 (2.7%)	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Power calculations:Assuming a 10% rate in placebo group for the first primary outcome and a two-sided pvalue of 0.045, a study with 12,500 patients would have 90% power to detect a 16.9% reduction in risk. For second outcome, assuming 14% rate of events in placebo and two-sided pvalue of 0.01, the study had 90% power to detect a reduction of 16.4% in risk.		months, received intravenous glycoprotein IIb / IIIa receptor inhibitors in previous 3	=1579 (25.1%) Associated MI = 1659 (26.3%) Mediations at time of randomisation Aspirin =4134 (65.6%) Heparin or LMW heparin =4605 (73.1%) ACEi=2309 (36.6%) BB=3690 (58.5%) CCB=1771 (28.1%) Lipid lowering agent =1586 (25.2%)			Once a patient had been randomly assigned to a treatment group, there were no restrictions on the use of any therapy or intervention.		0-7 d[a] Clopidogrel 54/6259 (0.86%) Placebo 46/6303 (0.73%) RR: 1.18 (0.8 to 1.75) 8d to 30d[a] Clopidogrel 73/6259 (1.17%) Placebo 52/6303 (0.82%) RR: 1.43 (1.0 to 2.04) 0-30d[a] Clopidogrel 126/6259 (2.01%)	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
								Placebo 97/6303 (1.54%) RR: 1.31 (1.01 to 1.70) >30 d to 1 yr[a] Clopidogrel 110/6259 (1.75%) Placebo 74/6303 (1.18%) RR: 1.48 (1.10 to 1.99)	
							Outcome 7 Minor Bleeding	Clopidogrel 322/6259 (5.1%) Placebo 153/6303 (2.4%)	
Author Mehta SR, Yusuf S, Peters RJ,		ITT analysis	Mehta: PCI was done after randomisation at the discretion of				**Outcome 1** Reinfarction	Clopidogel =59/1313 Placebo= 85/1345	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Bertrand ME, Lewis BS, Natarajan MK, Malmberg K, Rupprecht H, Zhao F, Chrolavicius S, Copland I, Fox KA; Clopidogrel in Unstable angina to prevent Recurrent Events trial (CURE) Investigators **Title** Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE			the local investigator and clopidogrel and placebo was continued up until this point. PCI - 82% had STENTS Clopidogrel n=1313 N=344 took open label theinopyridine before PCI N=969 received drug up to PCI Placebo n=1345 N=329 took open label theinopyridine before PCI N=1016 received drug up to PCI				**Outcome 2** CV death	Clop 32/1313 vs. Placebo 31/1345	
							Outcome 3 Revascularisation	Clop 186/1313 vs. Placebo 230/1345	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
study. **Journal** Lancet. 2001 Aug 18;358(9281): 527-33.									
Author Fox KA, Mehta SR, Peters R, Zhao F, Lakkis N, Gersh BJ, Yusuf S; Clopidogrel in Unstable angina to prevent Recurrent ischemic Events Trial. **Title** Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-			CABG n=2072 In hospital n=1013 ~25 d later N=1057 Clopidogrel n=1011 Placebo n=1061 Median time from randomization to CABG was 25.5d (12 to 70.5d) The time to CABG for those undergoing the procedure during hospitalisation was 12-13d (8-21)				**Outcome 1** Major bleeding[b]	Clopdigorel 97/1011 vs. Placebo 80/1061	
							Outcome 2 CV death/MI/stroke[b]	147/1011 vs. 172/1061	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
elevation acute coronary syndrome: the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) Trial. **Journal** Circulation. 2004 Sep 7;110(10):1202-8. Epub 2004 Aug 16.									
Author Yusuf S, Mehta SR, Zhao F, Gersh BJ, Commerford PJ, Blumenthal M, Budaj A, Wittlinger T, Fox KA; Clopidogrel in							**Outcome 1** CV death from PCI to end of follow-up[c]	Clopidogrel 32/1313 (2.4%) Placebo 31/1345 (2.3%)	
							Outcome 2 CV death from PCI to 30d[c]	Clopidogrel 14/1313 (1.1%)	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Unstable angina to prevent Recurrent Events Trial Investigators. **Title** "Early and late effects of clopidogrel in patients with acute coronary syndromes." **Journal** Circulation. 2003 Feb 25;107(7):966-72.								Placebo 13/1345 (1.0%)	
							Outcome 3 Myocardial infarction from PCI to end of follow-up[c]	Clopidogrel 59/1313 (4.5%) Placebo 85/1345 (6.4%)	
							Outcome 4 Myocardial infarction from PCI to 30d[c]	Clopidogrel 28/1313 (2.1%) Placebo 51/1345 (3.8%)	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
							Outcome 5 Any revascularisation from PCI to end of follow-up[c]	Clopidogrel 186/1313 (14.2%) Placebo 230/1345 (17.1%)	
							Outcome 6 Any revascularisation from PCI to 30d[c]	Clopidogrel 25/1313 (1.9%) Placebo 38/1345 (2.8%)	
							Outcome 7 Major bleeding from PCI to end of follow-up[c]	Clopidogrel 36/1313 (2.7%) Placebo 33/1345 (2.5%)	
							Outcome 8 Major bleeding from PCI to 30 d[c]	Clopidogrel 21/1313 (1.6%) Placebo 19/1345 (1.4%)	

(a) Yusuf et al .2003
(b) Fox et al 2004
(c) Extracted from Mehta et al.2001

G.4.6 Late initiation of antiplatelet therapy

Table 114: Bhatt2007[65]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author: Bhatt DL, Flather MD, Hacke W, Berger PB, Black HR, Boden WE, Cacoub P, Cohen EA, Creager MA, Easton JD, Hamm CW, Hankey GJ, Johnston SC, Mak KH, Mas JL, Montalescot G, Pearson TA, Steg PG, Steinhubl SR, Weber MA, Fabry-Ribaudo L, Hu T, Topol EJ, Fox KA; CHARISMA	RCT (subgroup analysis of CHARISMA)	N=9478 Post-hoc analysis of CHARISMA In CHARISMA Follow-up data for primary efficacy was 99.6%: 99.5% Clopidogrel 7763/7802 99.6% Aspirin: 7770/7801 Analysis: ITT	**Inclusion criteria** patients were identified as "CAPRIE-like" if they were enrolled with a documented prior MI, documented prior ischemic stroke, or symptomatic PAD **Inclusion from CHARISMA** 45 years of age or older and had one of the following conditions: multiple atherothrombotic risk factors, documented	**Clopidogrel+ aspirin** N=4735	**Aspirin** N=4743	28 months	**Outcome 1** All-cause mortality	**Clopidogrel +aspirin**= 235/4735 **ASA** = 257/4743 HR: 0914 (0.964-1.090)	**Source of funding** Bristol-Myers
							Outcome 2 Cardiovascular mortality	**Clopidogrel +aspirin** = 142/4735 **ASA** = 163/4743 HR: 0.870 (0.695-1.090)	
							Outcome 3 MI	**Clopidogrel +aspirin**= 117/4735 **ASA** = 145/4743 HR: 0.805 (0.631-1.027)	
							Outcome 4 Ischemic stroke	**Clopidogrel +aspirin**=	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Investigators **Title:**Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial. **Journal**J Am Coll Cardiol. 2007 May 15;49(19):1982-8. Epub 2007 Apr 11. **Country:** Germany/USA **Randomisation**: Subgroup analysis of			coronary disease, documented cerebrovascular disease, or documented symptomatic peripheral arterial disease. **Exclusion criteria** Indications for open-label clopidogrel use or were at high risk of bleeding. **Baseline characteristics** A total of 3,846 patients had prior MI, with a median time from the qualifying event to randomization of 23.6 months; 3,245 patients had prior stroke, with a median time from event					144/4735 **ASA** = 179/4743 HR:0.828 (0.654-1.048)	
							Outcome 5 Hospitalisation	**Clopidogrel +aspirin** = 542/4735 **ASA** = 626/4743 HR: 0.855 (0.762-0.960)	
							Outcome 6 Severe bleeding	**Clopidogrel +aspirin**= 79/4735 **ASA** = 71/4743 HR: 1.114 (0.808-1.535)	
							Outcome 7 Moderate bleeding	**Clopidogrel +aspirin** = 97/4735 **ASA** = 61/4743 HR 1.597 (1.159-2.200)	
							Outcome 8 CV death/stroke/MI	**Prior MI patients** **Clopidogrel +aspirin**=	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
randomised patients from CHARISMA trial **Allocation Concealment**: Yes, central interactive voice-response system **Blinding**: Double-blind **Power Calculations:** None provided			of 3.5 months; 2,838 patients had symptomatic PAD, with a median time from diagnosis of 23.6 months. Note that 443 (4.7%) patients fell into multiple categories because they actually had more than 1 prior event or disease location **Characteristic Clopidogrel + Aspirin** (n = 4,735) **Demographics** Age (yrs), median (Q1, Q3) 64 (56, 71) Female patients, n (%): 1,292 (27.3) Ethnicity, n (%					125/1903 **Aspirin**=161/1943 HR: 0774 (0.613-0.978)	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			Caucasian: 3,859 (81.5) Hispanic: 454 (9.6) Asian: 226 (4.8) Black:141 (3.0) Other: 55 (1.2) Inclusion group, n (%) Prior myocardial infarction: 1,903 Prior ischemic stroke: 1,634 (34.5) Symptomatic PAD: 1,418 (29.9) Selected clinical characteristics, n (%) Smoking status Current 1,024 (21.6) Former 2,434 (51.4) Hypertensio: 3,236 (68.3) Hypercholesterolemia: 3,307						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			(69.8) Congestive heart failure: 298 (6.3) Prior myocardial infarction: 2,193 (46.3) Atrial fibrillation: 172 (3.6) Prior stroke: 1,764 (37.3) Transient ischemic attack: 326 (6.9) Diabetes1,457 (30.8) PAD: 1,529 (32.3) Percutaneous coronary intervention: 1,209 (25.5) Coronary artery bypass graft surgery 809 (17.1) Carotid endarterectomy: 257 (5.4) Angioplasty or bypass 829 (17.5)						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			Diabetic nephropathy: 195 (4.1) **Characteristic Placebo Aspirin** (n = 4,743) **Demographics** Age (yrs), median (Q1, Q3) 64 (56, 71) Female patients, n (%)1,275 (26.9) Ethnicity, n (%) Caucasian: 3,851 (81.2) Hispanic 481 (10.1) Asian: 222 (4.7) Black: 137 (2.9) Other: 52 (1.1) Inclusion group, n (%) Prior myocardial infarction: 1,943 (41.0) Prior ischemic stroke: 1,611						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			(34.0) Symptomatic PAD: 1,420 (29.9) Selected clinical characteristics, n (%) Smoking status: Current: 1,055 (22.2) Former: 2,435 (51.3) Hypertension: 3,317 (69.9) Hypercholesterolemia: 3,343 (70.5) Congestive heart failure:308 (6.5) Prior myocardial infarction:2,248 (47.4) Atrial fibrillation:160 (3.4) Prior stroke; 1,726 (36.4) Transient ischemic attack: 300 (6.3)						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			Diabetes: 1,484 (31.3) PAD: 1,530 (32.3) Percutaneous coronary intervention:1,239 (26.1) Coronary artery bypass graft surgery: 829 (17.5) Carotid endarterectomy: 235 (5.0) Peripheral angioplasty or bypass: 812 (17.1) Diabetic nephropathy: 211 (4.4) **Concomitant medication: Both groups**: ASA: 99.7% ARB: 33% BB: 56% CaAnt: 34%						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			Statins: 77% Diuretics: 44% Only difference was nitrate use: 25.8% in ASA group and 23.5% in Aspirin+Clopidogrel.						

G.4.7 Antiplatelet therapy in those with an additional indication for anticoagulation

This section was updated and replaced in 2020. See www.nice.org.uk/guidance/ng185 for the 2020 evidence review.

Table 115: Alexander 2011[20]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Alexander JH, Lopes RD, James S, Kilaru R, He Y, Mohan P, Bhatt DL, Goodman S, Verheugt FW, Flather M, Huber K, Liaw D, Husted SE, Lopez-Sendon J, De Caterina R, Jansky P, Darius H, Vinereanu D, Cornel JH, Cools F, Atar D, Leiva-Pons JL, Keltai M, Ogawa H,	RCT-APPRAISE-2	N=7392 Drop outs Among the patients who underwent randomization, 81 (1.1%) withdrew consent and 50 (0.7%) were lost to follow-up for the primary outcome during the intended treatment period. after	Inclusion criteria main inclusion criterion for the trial was an acute coronary syndrome (myocardial infarction, with or without ST-segment elevation, or unstable angina) within the previous 7 days, with symptoms of myocardial ischemia lasting 10 minutes or more with the patient at rest plus either elevated levels of cardiac	Apixaban (5mg 2xd) + ASA (97%) ±Clopidogrel (81%) N=3705	Placebo + ASA (97%) ±Clopidogrel (81%) N=3687	Median 241d	**Outcome 1** Death	Apixaban = 155/3705 Placebo = 143/3687	**Source of funding** Bristol-Myers Squibb and Pfizer. Limitations Unclear what % were taking clopidogrel
							Outcome 2 Cardiovascular death	Apixaban = 105/3705 Placebo = 109/3687	
							Outcome 3 Reinfarction	Apixaban = 182/3705 Placebo = 194/3687	
							Outcome 4 Ischemic stroke	Apixaban = 23/3705 Placebo = 34/3687	
							Outcome 5 Major bleeding TIMI criteria	Apixaban = 98/3705 Placebo = 40/3687	
							Outcome 6 Minor bleeding TIMI criteria	Apixaban = 34/3705 Placebo = 11/3687	
							Outcome 7	Apixaban = 12/3705	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Pais P, Parkhomenko A, Ruzyllo W, Diaz R, White H, Ruda M, Geraldes M, Lawrence J, Harrington RA, Wallentin L; APPRAISE-2 Investigators **Title** Apixaban with antiplatelet therapy after acute coronary syndrome. Alexander JH, Lopes RD, James S, Kilaru R, He Y, Mohan P, **Journal** N Engl J Med. 2011 Aug 25;365(8):69		approximately 7000 patients had been recruited, the independent data monitoring committee recommended that the trial be stopped, owing to an excess of clinically important bleeding events with apixaban in the absence of a counterbalancing reduction in ischemic events.	biomarkers or dynamic ST-segment depression or elevation of 0.1 mV or more. Patients who met this criterion were eligible for the study if their condition was clinically stable and they were receiving standard treatment after the acute coronary syndrome, including aspirin or aspirin plus any P2Y12-receptor antagonist. Eligible patients were also required to have two or more of the following high-risk				Intracranial bleeding	Placebo = 3/3687	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
9-708. Epub 2011 Jul 24. Country: 39 countries Randomisation: Randomization was performed in a blinded fashion with the use of an interactive voice-response system, in permuted blocks of two, stratified according to site and according to planned long-term use of aspirin or aspirin plus a		Analysis: ITT	characteristics: an age of at least 65 years, diabetes mellitus, myocardial infarction within the previous 5 years, cerebrovascular disease, peripheral vascular disease, clinical heart failure or a left ventricular ejection fraction of less than 40% in association with the index event, impaired renal function with a calculated creatinine clearance of less than 60 ml per minute, and no revascularization after the index event.						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
P2Y12-receptor antagonist. Allocation Concealment: Yes Blinding: Yes, double-blind. Power Calculations: Assuming a recruitment period of approximately 2 years, an average follow-up period of 1.25 years, and a rate of the primary efficacy outcome of 8% per year, we			Exclusion criteria Exclusion criteria included persistent severe hypertension, severe renal dysfunction with a calculated creatinine clearance of <20 mL/min; active bleeding or a high risk for bleeding; known coagulopathy; ischemic stroke within 7 days; New York Heart Association class IV heart failure; any history of intracranial bleeding; hemoglobin <9 g/dL; platelet count < 100,000 mm3; required ongoing						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
estimated that we would need to enroll 10,800 patients to achieve the desired target of 938 patients with a primary efficacy outcome. With this number of patients with events, we estimated that the study would have 80% power to detect a 20% reduction in relative risk with apixaban as compared with placebo at a one-			treatment with a parenteral or oral anticoagulant; required treatment with highdose aspirin (>325 mg daily) or a strong inhibitor of CYP3A4; a severe comorbid condition with a life expectancy of ≤6 months; acute pericarditis, active hepatobiliary disease, and women who were pregnant, breastfeeding, or of childbearing potential and unable to use an acceptable method of birth control.						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
sided alpha level of 0.005 and 93% power to detect the same reduction in risk at a one-sided alpha level of 0.025.									

Table 116: Anadi 1998[24]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Anand SS, Yusuf S, Pogue J, Weitz JI, Flather M **Title** Long-term oral anticoagulant therapy in	RCT pilot study. Phase I and Phase II.	N=506 Drop outs N=Unclear Analysis: ITT	Inclusion criteria in patients with AIS without ST elevation Patients were eligible if they were admitted to hospital within 12 hours of an episode of chest pain suspected	Phase I Warfarin (INR 1.5) + ASA(325mg/d) N=155 Phase II Warfarin (INR 2.3) + ASA N=98	Phase I ASA(325mg/d) N=154 Phase II. ASA (325 mg/d) N=99	Phase I 6m Phase II 3m	**Outcome 1** Stroke	Warfarin+ASA = Phase I 0/155 Phase II 0/98 Total = 0/253 ASA Phase I 0/154 Phase II 2/99 Total = 2/253	Source of funding Behringwerke Aktiengesellshaft, Germany: A. Jessel, M. Lutz, H. Heinrichs, H. Volpel, F.
							Outcome 2	Warfarin+ASA =	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
patients with unstable angina or suspected non-Q-wave myocardial infarction: organization to assess strategies for ischemic syndromes (OASIS) pilot study results. **Author** Anand SS, Yusuf S, Pogue J, Weitz JI, Flather M. Circulation. 1998 Sep 15;98(11):1064-70. Country: USA			to be due to unstable angina or MI without ST-segment elevation on their admission ECG. The diagnosis of unstable angina was based on symptoms of angina that were worsening or occurring with minimal activity associated with either current ECG evidence of ischemia or previously documented objective evidence of coronary artery disease. Exclusion criteria Patients who suffered major bleeding on or within 48 hours of the initial	Moderate-intensity anticoagulation (target INR, 2 to 2.5) by adjusting the INR or standard therapy for 3 months. Warfarin therapy was initiated 12 to 24 hours after the initiation of the intravenous infusion of heparin or hirudin. The recommended dose was 10 mg on day 1, 3 mg on day 2, and 3 mg on day 3. Thereafter, dose adjustments of warfarin were left to the discretion of the treating physicians to target an INR value of 2 to 2.5. The goal was to increase the INR			Minor bleeding	Phase I 22/155 Phase II 28/98 Total = 50/253 ASA Phase I 0/154 Phase II 12/99 Total = 12/253	Schindel. Hoechst Marion Roussel Canada, Montreal: B. Carter, J. Albert, J.P. St Pierre, M. Salama. Dupont, Delaware: W. Michaelis, B. Dusak Limitations Both of these studies were pilot studies conducted to assist in the design of a more definitive and larger study. Despite the small
							Outcome 3 Major bleeding	Warfarin+ASA = Phase I 5/155 Phase II 2/98 Total = 7/253 ASA = Phase I 0/154 Phase II 1/99 Total 1/2531	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Randomisation: Yes, unclear Allocation Concealment: Unclear Blinding: No. Open trial Power Calculations: The main goal of the study was to explore feasibility, the safety effects on the INR, and the preliminary clinical efficacy of warfarin versus			intravenous infusion, those who had a clear clinical indication for warfarin treatment, and those in whom CABG surgery was planned before or within 1 week of hospital discharge were excluded.	into the therapeutic range (INR, 2 to 2.5) by the time of hospital discharge					numbers of patients, the lack of benefit with warfarin in the first study is consistent with the results of 2 larger trials.7 8 The promising results of our second pilot are consistent with trials of moderate-intensity warfarin in unstable angina.16 Nevertheless, the apparent large treatment effect sizes in both

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
standard therapy. Therefore, the study was not formally powered to detect significant differences in clinical outcomes.									studies in unstable angina may be exaggerated by the play of chance, and it may be prudent to expect more moderate differences in a larger study. A second caution is that these studies were open, and all of the events were not adjudicated

Table 117: BROUWER2002[81]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Brouwer MA, van den Bergh PJ, Aengevaeren WR, Veen G, Luijten HE, Hertzberger DP, van Boven AJ, Vromans RP, Uijen GJ, Verheugt FW. **Title** Aspirin plus coumarin versus aspirin alone in the prevention of reocclusion after fibrinolysis for acute myocardial infarction: results of the Antithrombo	RCT APRICOT-2	N=308 randomised N=34 excluded from analysis bc flow in infarct artery was not considered TIMI grade 3 flow. N=274. Drop outs/data not available N=0	**Inclusion criteria** Patients with chest pain >30min and<6hrs, refractory to nitrates were treated with fibrinolytic therapy in the case of ST-elevation. Patients who were clinically stable. Coronary angiography had to be performed within 48 hrs after fibrinolytic therapy. Thrombolysis in MI (TIMI) grade 3 flow. **Exclusion criteria:** Older than 75 yrs, contraindication to antithrombotic therapy, bypass	Coumarin (INR2-3)+ASA (160mg 80mg) N=135 Heparin: Adjunctive therapy was given for 48hrs. Continued until moderate-intensity anticoagulant was achieved, INR 2-3.	ASA(160mg-80mg) N=139 Heparin: discontinued after 48 hrs	3m	**Outcome 1** Death	Coumarin+ASA = 1/135 ASA =0/139	
							Outcome 2 Reinfarction	Coumarin+ASA = 3/135 ASA =11/139	
							Outcome 3 Revascularisation	Coumarin+ASA = 17/135 ASA =43/139	
							Outcome 4 Bleeding (TIMI criteria)	Coumarin+ASA = 7/135 ASA =4/139	
							Outcome 5 Major bleeding	Coumarin+ASA = 2/135 ASA =2/139	
							Outcome 6 Minor bleeding	Coumarin+ASA = 5/135 ASA =2/139	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
tics in the Prevention of Reocclusion In Coronary Thrombolysis (APRICOT)-2 Trial. **Journal** Circulation. 2002 Aug 6;106(6):659-65. Country: USA Randomisation: Block randomisation, stratified per centre. Allocation Concealment: Yes, telephone			graft as the infract-related vessel. Culprit stenosis that had previously dilated and left main stem stenosis or an unidentifiable culprit lesion.						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
service Blinding: No. Open label. Power Calculations: The estimated incidence of reocclusion for APRICOT-2 was therefore set at 30%. The trial was designed to have 80% power to demonstrate a relative reduction of 50% in the incidence of reocclusion, with a 2-sided α of 5%. This would require 266									

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
patients with angiographic follow-up.									

Table 118: **Cohen 1994A**[114]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Cohen M, Adams PC, Parry G, Xiong J, Chamberlain D, Wieczorek I, Fox KA, Chesebro JH, Strain J, Keller C, et al. **Title** Combination antithrombotic therapy in unstable rest	RCT ATACS	N=214 Drop outs Warfarin+ASA n= 33/109 (31%) ASA n= 49/109(45%)	**Inclusion criteria**. All patients enrolled in the study met all of the following three inclusion criteria: (1) over age 21, male or female (pregnant women were excluded) and (2) presented to hospital with ischemic pain caused by either unstable angina or non-Q-wave infarction defined	Warfarin (INR 2-3)+ ASA (162.5mg/d) N=105 Heparin: 100U/kg heparin IV bolus, 3-4d, when INR 2-3. Concomitant therapy: See baseline characteristics	ASA (162.5mg/d) N=109	12 wks	**Outcome 1** All-cause death	Warfarin+ASA =2/105 (2%) ASA =2/109 (2%)	**Source of funding** This study was supported by the Heart Research Foundation, New York, NY; Dupont Pharmaceutical, Wilmington Del; and Glenbrook Labs of Sterling Drug, New
							Outcome 2 Reinfarction	Warfarin+ASA =6/105 (6%) ASA =9/109 (8%)	
							Outcome 3 Revascularisation (PTCA or CABG)	Warfarin+ASA =16/105 (15%) ASA =12/109 (11%)	
							Outcome 4 Major bleeding	Warfarin+ASA =3/105 (2.9%) ASA =0/109 (0%)	
							Outcome 5 Minor bleeding	Warfarin+ASA =7/105 (6.7%)	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
angina and non-Q-wave infarction in nonprior aspirin users. Primary end points analysis from the ATACS trial. Antithrombotic Therapy in Acute Coronary Syndromes Research Group. **Journal** Circulation. 1994 Jan;89(1):81-8. Country: USA Randomisation: Unclear methods.			as (a) recent onset of prolonged (>10 minutes) or recurrent chest pain suggestive of acute myocardial ischemia, (b) pain occurring at rest with no provoking factors, and (c) the last attack of pain must have occurring within 48 hours of randomization. (3) In addition to the above, there must have been definite evidence of underlying ischemic heart disease, as shown by at least one or more of the following: (a) ECG changes during chest pain or on					ASA =3/109 (2.8%)	York, NY. Limitations

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Patients were prospectively stratified into either nonprior aspirin users or prior aspirin users. Allocation Concealment: Unclear Blinding: No, open label Power Calculations: To perceive a 40% reduction in events (from 17% to 10%, with a power of 85%)			admission suggesting ischemia (if ST-segment elevation was present, it must have resolved within 30 minutes of relief of pain after nitroglycerin; patients with persistent ST elevation were not randomized), (b) previous documented myocardial infarction, (c) a previous positive exercise test or a previous coronary angiography showing a 250% luminal narrowing in any coronary artery, or (d)						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
by the addition of anticoagulation, 427 patients needed to be randomized into each cell.			history of typical exertional angina, with chest pain precipitated by effort and relieved by rest and/or nitroglycerin. Exclusion criteria. Exclusion criteria included (1) ischemic pain caused by evolving Q-wave myocardial infarction, (2) left bundle branch block or permanent pacemaker, (3) angina precipitated by congestive heart failure, tachyarrhythmia, hypertension (systolic blood pressure .160 mm Hg and/or diastolic						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			blood pressure 2100 mm Hg), valvular heart disease, Q-wave myocardial infarction within 4 weeks, anemia (hemoglobin <11 g/dL), or cocaine or other illicit drug use, (4) contraindications to anticoagulation, eg, allergy to heparin or aspirin, active peptic ulcer or other ulcerative disease of the gastrointestinal tract within 6 months, bleeding diathesis, or prior cerebral hemorrhage or nonhemorrhagic stroke within 2 months, (5) current need for						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			anticoagulation, eg, pulmonary embolism, (6) chronic use of steroids or nonsteroidal antiinflammatory drugs, (7) intravenous heparin therapy within 24 hours of randomization, (8) percutaneous transluminal coronary angioplasty (PTCA) within 6 months or coronary artery bypass grafting (CABG) within 1 year, (9) other serious disease, eg, severe liver disease or diabetes with proliferative retinopathy, (10) history of						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			noncompliance or unlikely to return for follow-up, and (11) personal physician planning immediate intervention regardless of response to medical therapy. 12) prior ASA users						

Table 119: DeEugenio 2007[143]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author DeEugenio D, Kolman L, DeCaro M, Andrel J, Chervoneva	Retrospective cohort study	N=194 Drop outs/lost to follow-up	**Inclusion criteria** Treatment: PCI and long-term use of oral anticoagulants.	PCI + Warfarin+Clopidogrel+ASA N=97	PCI Clopidogrel+ASA N=97	6months (median 182 days)	**Outcome 1** Major bleeding	W+C+ASA = 14/97 C+ASA = 3/97	Limitations Warfarin dose NA in W gp. Not RCT

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
I, Duong P, Lam L, McGowan C, Lee G, DeCaro M, Ruggiero N, Singhal S, Greenspon A. **Title** Risk of major bleeding with concomitant dual antiplatelet therapy after percutaneous coronary intervention in patients receiving long-term warfarin therapy. **Journal** Pharmacotherapy. 2007		W N=11 Control n=9	Control: individually matched to active patients in a 1:1 fashion by procedure type (bare-metal stent, sirolimus drug-eluting stent, paclitaxel DES, brachytherapy), procedure year, age and stent. All discharged with ASA + Clopidogrel. **Exclusion criteria** None given. **Baseline characteristics** Warfarin Age 69.8±10.7 Male: 57 (59) Female: 40 (41) Caucasian: 81 (84) BMS: 63 (65)						One outcome. No MI?

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
May;27(5):691-6. Randomisation: No. NA Allocation Concealment: No. NA Blinding: No. NA Power Calculations: No.			DES: 31 (32) Brachytherapy: 3(3) Major surgical procedure <30d: 0 Av. INR intensity goal 2: NA 2.5: NA 3: NA Control Age 69.9±11 Male: 56 (58) Female: 41 (42) Caucasian: 83 (86) BMS: 72 (74) DES: 24 (25) Brachytherapy: 1 (1) Major surgical procedure <30d 3 (3) Av. INR intensity goal 2: 2 (2) 2.5: 88 (91)						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			3: 7 (7)						

Table 120: Fiore 2002[188]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Fiore LD, Ezekowitz MD, Brophy MT, Lu D, Sacco J, Peduzzi P; Combination Hemotherapy and Mortality Prevention (CHAMP) Study Group. **Title** Department of Veterans Affairs Cooperative Studies	RCT	N=5059 Drop outs/Data not available. N=71 (28 in ASA, 33 in W+ASA) Analysis = ITT	**Inclusion criteria** Briefly, veterans of either sex and of any age were eligible to participate in the study if they sustained a qualifying AMI within the preceding 14 days and fulfilled none of the exclusion criteria (Table 1). Each participating site was instructed to screen all patients with AMI for study	Warfarin (INR 1.5-2.5IU)+ ASA (81mg/d) N=2522	ASA (162mg/d) N=2537	2.7 yrs median	**Outcome 1** All-cause mortality	W+ASA = 444/2522 ASA = 438/2537	**Source of funding** Cooperative Studies Program of the Department of Veterans Affairs Office of Research and Development and in part by DuPont Pharmaceuticals and Bayer Pharmaceuticals
							Outcome 2 Mortality CV reasons	W+ASA = 267/2522 ASA = 266/2537	
							Outcome 3 Reinfarction	W+ASA = 336/2522 ASA = 333/2537	
							Outcome 4 Stroke	W+ASA = 4/2522 ASA = 4/2537	
							Outcome 5 Minor bleeding	W+ASA = 349/2522 ASA = 77/2537	
							Outcome 6 Major bleeding	W+ASA = 87/2522 ASA = 50/2537	
							Outcome 7 Intracranial bleeding	W+ASA = 14/2522 ASA = 15/2537	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Program Clinical Trial comparing combined warfarin and aspirin with aspirin alone in survivors of acute myocardial infarction: primary results of the CHAMP study. **Journal** Circulation. 2002 Feb 5;105(5):557-63. Country: USA Randomisation: Yes. Unclear methods			eligibility. **Exclusion criteria** Comorbidity limiting life expectancy to <2 yrs; Screened >14 days after infarction; Incompetent to give informed consent; Ongoing bleeding or bleeding risk; Alternative indication for anticoagulant therapy; Refusal to participate in trial; Entered into a competing study; Treatment with high dose ASA or NSAID; Excessive travel distance to the VA;						Limitations

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Allocation Concealment: Unclear Blinding: Open label. Power Calculations: All analyses were conducted according to the intention-to-treat principle. Sample size was determined to detect a 15% reduction in annual mortality with combination therapy relative to aspirin alone. The			Alcohol or drug dependency; Hypersensitivity to aspirin or warfarin.						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
target sample size to detect this effect size with 80% power and 5% type I error was 8000 patients and 1000 deaths									

Table 121: Herlitz 2004[269]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Herlitz J, Holm J, Peterson M, Karlson BW, Haglid Evander M, Erhardt L; LoWASA study group **Title** Effect	RCT (LoW ASA)	N=3300 Drop outs N=0 No patient lost to follow-up Analysis = ITT	Inclusion criteria Hospitalization for AMI according to set criteria within 42 days prior to randomization Exclusion criteria 1.Indication of full-dose	Warfarin (1.25mg/d) + ASA (75mg/d) N=1648	ASA (75mg/d) N=1641	Mean 5 yrs	**Outcome 1** All-cause mortality	W+ASA = 311/1649 ASA = 323/1641	**Source of funding** Limitations 1.The trial was powered to detect a difference in cardiovascul
							Outcome 2 Reinfarction	W+ASA = 283/1649 ASA = 268/1641	
							Outcome 3 Stroke	W+ASA = 78/1649 ASA = 116/1641	
							Outcome 4 Minor bleeding	W+ASA = 96/1649 ASA = 43/1641	
							Outcome 5 Major bleeding	W+ASA = 36/1649 ASA = 16/1641	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
of fixed low-dose warfarin added to aspirin in the long term after acute myocardial infarction; the LoWASA Study. **Journal** Eur Heart J. 2004 Feb;25(3):232-9. Country: Sweden Randomisation: Yes, via telephone or fax. Unclear methods. Allocation			anticoagulation 2.Unwillingness to participate 3.Inability to participate 4.Contraindications for anticoagulants and aspirin 5. Participation in other studies 6. Expected survival less than one month (for example, terminal heart failure) 7.Other disease associated with shorter survival, such as cancer, severe renal failure and so on 8.Daily treatment with non-steroidal anti-inflammatory drugs				Outcome 6 Revascularisation	W+ASA = 465/1649 ASA = 481/1641	ar events. It was, therefore, underpowered to detect a difference in cardiovascular deaths. 2.Originally, there were plans to analyse all hospitalizations during follow-up. However, due to a lack of capacity, we were only able to analyse rehospitalization for cardiovascular etiology in a subset of patients.

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Concealment: Yes, central centre Blinding: Single. Patients No. Assessors: Yes Power Calculations: With a two-sided test at the 5% level with 90% power if only 25% of the patients who received the combination therapy developed an end-point during the same time period; a normal-theory-based test for binominal									3.The study included a relatively low-risk group of post-myocardial patients. As a result, only 13% had a history of diabetes and only slightly more than 30% had had an anterior infarction. 4.Patients were allowed to be randomized up to 42 days after the onset of infarction. Previous

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
distribution was therefore assumed. According to these assumptions, 3400 patients needed to be randomized.									experience indicates that many recurrent ischaemic events occur within the first month post STEMI.

Table 122: Hurlen 2002[278]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. **Title** Warfarin, aspirin, or both after myocardial	RCT (open label)	N=3630 Drop outs/lost to follow-up N=14 (all known to be alive at follow-up) The study was closed	Inclusion criteria Patients of either sex who were younger than 75 years of age were eligible for the study if they were hospitalized for acute myocardial infarction defined by the presence of two or more of	Warfarin (INR 2.0 to 2.5) + ASA (160mg/d) N=1208	W (INR 2.8 to 4.2) N=1216 ASA (160mg) N=1206	1445±592 d. Approx 4 yrs	**Outcome 1** All-cause mortality	W+ASA = 95/1208 ASA = 92/1206 W = 96/1216	Source of funding Norwegian Council on Cardiovascular Disease. Limitations
							Outcome 2 Reinfraction	W+ASA = 69/1208 ASA = 117/1206 W = 90/1216	
							Outcome 3 Stroke	W+ASA = 17/1208	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
infarction. **Journal** N Engl J Med. 2002 Sep 26;347(13):969-74 Country: Norway Randomisation: The randomization was administered centrally with the use of permuted blocks. Data were stratified according to site. Allocation Concealment: Unclear		on September 1, 2000, when the predetermined number of composite events, 613, had occurred. Analysis: ITT	the following criteria, according to the recommendations of the World Health Organization27: a history of typical chest pain; electrocardiographic changes typical of myocardial infarction; and a creatine kinase level greater than 250 U per liter, an aspartate aminotransferase level greater than 50 U per liter, or both, of probable cardiac origin. Exclusion criteria Patients were excluded if they had any indication for or contraindication against either of					ASA = 32/1206 W = 17/1216	
							Outcome 4 Minor bleeding	W+ASA = 133/1208 ASA = 39/1206 W = 103/1216	
							Outcome 5 Major bleeding	W+ASA = 28/1208 ASA = 8/1206 W = 33/1216	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Blinding: No. open label Power Calculations: Given a two-sided probability of 0.05 and a power of 80 percent, the number of patients needed in each treatment group was calculated to be 1202. Thus, a total of 3606 patients were needed			the study drugs, if they had a malignant disease, or if poor compliance was anticipated.						

Table 123: Huynh 2001[281]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Huynh T, Théroux P, Bogaty P, Nasmith J, Solymoss S. **Title** Aspirin, warfarin, or the combination for secondary prevention of coronary events in patients with acute coronary syndromes and prior coronary artery bypass surgery. **Journal** Circulation. 2001 Jun	RCT	N=135 Drop outs N= The study was terminated prematurely after enrollment of half the planned number of patients because of difficulty in recruiting because of the high rate of conventional or investigative procedures performed in otherwise	Inclusion criteria All patients who presented with a diagnosis of unstable angina or non–ST-elevation myocardial infarction and prior CABG were considered for the study Exclusion criteria Patients who had coronary angioplasty or repeat CABG during the index hospitalization were excluded; therefore, the study population was limited to patients who were poor candidates for a revascularization	Warfarin (INR 2 to 2.5) + ASA (80mg/d) N=44	Warfarin(INR 2 to 2.5) + Placebo N=45 ASA (80mg/d) + Placebo N=46	12 m	Outcome 1 All-cause mortality	W+ASA=2/44 ASA = 0/46 W = 1/45	Source of funding None stated Limitations
							Outcome 2 Reinfarction	W+ASA=2/44 ASA = 1/46 W = 4/45	
							Outcome 3 Minor bleeding	W+ASA=9/44 ASA = 2/46 W = 10/45	
							Outcome 4 Major bleeding	W+ASA=2/44 ASA = 0/46 W = 1/45	
							Outcome 5 Revascularisation	W+ASA=5/44 ASA = 3/46 W = 8/45	
							Outcome 6	W+ASA=13/44	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
26;103(25):3069-74. Country: Canada Randomisation: Yes, Unclear Allocation Concealment: Unclear Blinding: Double-blind Power Calculations: Unclear.		qualifying patients.	procedure. Other exclusion criteria were as follows: contraindication to the use of aspirin or warfarin, a treatable cause for angina pectoris, any major concomitant illness, congestive heart failure class 3 or 4 (New York Heart Association), uncontrolled systemic hypertension (blood pressure >180/95 mm Hg), recent major trauma, alcohol or drug abuse, females with child-bearing potential, coronary angioplasty within the last 6				Hospitalisation	ASA = 10/46 W = 16/45	
							Outcome 7		

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			months, conditions mandating treatment with aspirin (such as previous stroke) or with warfarin (such as metallic valve prosthesis), atrial fibrillation, or intracardiac thrombi.						

Table 124: Khurram 2006[312]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Khurram Z, Chou E, Minutello R, Bergman G, Parikh M, Naidu S, Wong SC, Hong MK **Title** Combination therapy with aspirin,	Retro specti ve	N=214 Drop outs N=unclear	**Inclusion criteria** 107 consecutive patients on chronic warfarin therapy who underwent stent implantation and were discharged on ASA, Clopidogrel, Warfarin	Stent+ Warfarin+ASA+Cl opidogrel (75mg/d-325mg/d) N=107	Stent+ ASA+Clopidog rel (75mg/d) N=107	1 yr. Mean 211±11 4	**Outcome 1** Major bleeding	W+ASA+C = 7/107 ASA+C = 0/107	**Source of funding** None listed Limitations Very little detail Not RCT No MI?

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
clopidogrel and warfarin following coronary stenting is associated with a significant risk of bleeding. **Journal** J Invasive Cardiol. 2006 Apr;18(4):162-4. Country: Randomisation: No. NA Allocation Concealment: No. NA Blinding:			**Exclusion criteria** None listed Baseline characteristics Triple therapy Age: 69 ±11 Male:68% Hypertension:82% Diabetes:31% Prior stroke:5.6% Prior bleeding history: Major: 0.9% Minor:6.5% DES = 50% Control Age: 74±6 Male:64% Hypertension:68% Diabetes:40% Prior stroke:3.7% Prior bleeding history:						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
No. NA Power Calculations: No.			Major: 1.9% Minor:2.8% DES = 100% Warfarin: Chronic AF after a large anterior MI: 13% Prosthetic valve: 5% Pulmonary embolism: 2% Lost fractured guidewire in the coronary artery in 1 patient						

Table 125: Karajalainen[307]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Karjalainen PP, Porela P, Ylitalo A, Vikman S, Nyman K, Vaittinen	Observational. Retrospective regist	N=478 Drop outs N=unclear.	Inclusion criteria All patients undergoing PCI and having an indication for long-term AC with warfarin	Coronary stent: Warfarin + Clopidogrel + ASA N=239 Long term AC	Coronary stent: ASA + Clopidogrel N=239	12m long-term follow-up	**Outcome 1** Death	W+ASA+C = 19/219 ASA+C =4/227	**Source of funding** Finnish Foundation for Cardiovascular
							Outcome 2 MI	W+ASA+C = 22/219 ASA+C =11/227	
							Outcome 3 Revascularisation	W+ASA+C = 24/219 ASA+C =17/227	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
MA, Airaksinen TJ, Niemelä M, Vahlberg T, Airaksinen KE. **Title** Safety and efficacy of combined antiplatelet-warfarin therapy after coronary stenting. **Journal** Eur Heart J. 2007 Mar;28(6):726-32. Epub 2007 Jan 31 Country: Finland Randomisation: No. NA Allocation	ry		were identified between 2003 and 2004 in two hospitals and in 2004 in other hospitals. In each centre, an age- (±5 years) and sex-matched control group with similar disease (unstable or stable symptoms) was collected from a total PCI population of ~4200 patients treated during the study period. Matching was successful except for differences in disease type in three pairs and in age (6–10 years) in four pairs. Exclusion criteria None listed.	with warfarin Warfarin patients (n = 219) Aspirin + clopidogrel, n (%) 34 (15.5) Warfarin + aspirin + clopidogrel, n (%) 106 (48.4) Warfarin + aspirin, n (%) 33 (15.1) Warfarin + clopidogrel, n (%) 45 (20.5) Warfarin monotherapy, n (%) 1 (0.5) Clopidogrel monotherapy, n (%) 0 (0) Aspirin monotherapy, n (%) 0 (0)	Matched with similar disease (unstable or stable) Control patients (n = 227) Aspirin + clopidogrel, n (%)214 (94.3) Warfarin + aspirin + clopidogrel, n (%)1 (0.4) Warfarin + aspirin, n (%)0 (0) Warfarin + clopidogrel, n (%)0 (0) Warfarin monotherapy, n (%)) 0 (0) Clopidogrel monotherapy, n (%)10 (4.4) spirin	4-6m treatment.	**Outcome 4** Stent thrombosis **Outcome 5** Stroke **Outcome 6** Major bleeding	W+ASA+C = 9/219 ASA+C =3/227 W+ASA+C = 7/219 ASA+C =5/227 W+ASA+C = 18/219 ASA+C =6/227	Research, Helsinki, Finland. Limitations Not a matched population. Comparisons group didn't appear to have an indication or AC. 15% of warfarin group didn't take warfarin. 217/239 in W group had coronary stenting. 227/239 in control grp. Warfarin dose NA No MI?

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Concealment: No. NA Blinding: No. NA Power Calculations: No.			Baseline characteristics Warfarin patients (n = 239) Male, n (%) 177 (74) Age, (years) 70 ± 9 Diabetes, n (%) 71 (30) Hypercholesterolaemia, n (%) 167 (70) Current smoking, n (%) 70 (29) Hypertension, n (%) 160 (67) Ejection fraction,a % 50 ± 14 Previous heart failure, n (%) 58 (24) Previous stroke, n (%) 49 (21) Previous MI, n (%) 99 (41) Previous PCI, n (%) 35 (15)		monotherapy, n (%)2 (0.9)				

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			Previous CABG, n (%) 48 (20) Acute STEMI, n (%) 22 (9) Acute NSTEMI, n (%) 60 (25) Unstable angina, n (%) 46 (19) Medications at discharge Beta-blockers, n (%) 212 (89) Lipid-lowering agents, n (%) 186 (78) ACE-inhibitors/ARB, n (%) 157 (66) Indications for AC Atrial fibrillation, n (%) 168 (70) Previous cerebrovascular accident, n (%) 26 (11) Mechanical heart valve, n (%) 10 (4) Pulmonary embolus or venous						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			thromboembolism, n (%) 23 (10) Other indication, n (%) 12 (5) Control patients (n = 239) Male, n (%) 177 (74) Age, (years) 70 ± 9 Diabetes, n (%) 47 (20) Hypercholesterolaemia, n (%) 164 (69) Current smoking, n (%) 55 (23) Hypertension, n (%) 136 (57) Ejection fraction,a % 56 ± 11 0.003 Previous heart failure, n (%) 12 (5) Previous stroke, n (%) 13 (5) Previous MI, n						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			(%) 69 (29) Previous PCI, n (%) 33 (14) Previous CABG, n (%) 21 (9) Acute STEMI, n (%)33 (14) Acute NSTEMI, n (%)55 (23) Unstable angina, n (%) 41 (17) Medications at discharge Beta-blockers, n (%) 225 (94) Lipid-lowering agents, n (%) 200 (84) ACE-inhibitors/ARB, n (%) 121 (51)						

Table 126: Leon 1998[338]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author	RCT	N=1965	**Inclusion criteria**	Warfarin (INR 2-	ASA	30 days	**Outcome 1**	W+ASA = 0/550	Source of

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Leon MB, Baim DS, Popma JJ, Gordon PC, Cutlip DE, Ho KK, Giambartolomei A, Diver DJ, Lasorda DM, Williams DO, Pocock SJ, Kuntz RE. **Title** A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study		Drop outs N=unclear Analysis= ITT	had one or two target lesions with more than 60 percent stenosis in a 3-to-4-mm native coronary artery, not involving the left main coronary artery or a major coronary bifurcation. **Exclusion criteria** Other exclusion criteria were the presence of additional stenoses within the target vessel; recent (within 7 days before enrollment) acute myocardial infarction; known contraindications to the use of aspirin, ticlopidine, or warfarin; a history of	2.5) +ASA N=550	(325mg/d) N=557 ASA (325mg/d)+Ticlopidine (250mg/d) N=546		All–cause mortality	ASA = 1/557 ASA + T = 0/546	funding Limitations
							Outcome 2 Revascularisation	W+ASA =14/550 ASA = 19/557 ASA + T = 3/546	
							Outcome 3 Reinfarction	W+ASA =14/550 ASA = 19/557 ASA + T = 3/546	
							Outcome 4 Stroke – cerebrovascular accident	W+ASA =1/550 ASA = 2/557 ASA + T = 0/546	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Investigators **Journal** N Engl J Med. 1998 Dec 3;339(23):1665-71 Country: USA Randomisation: randomly assigned in equal proportions with use of a prespecified randomization sequence Allocation Concealment: Unclear Blinding: Single. Patients No.			bleeding diathesis; current treatment with abciximab; and planned angioplasty of another lesion within 30 days after enrollment						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Investigators - All end points were adjudicated by a clinical events committee whose members were unaware of the patients' treatment assignments Power Calculations: For the study to have the ability to detect a 30-day stent-thrombosis rate of 1.1 percent or less in the group assigned to ticlopidine and aspirin with a									

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
statistical power of 80 percent and a one-sided alpha error of 0.025, 527 patients were required for each group. The trial was therefore designed to enroll 550 patients per group, for a total of 1650 patients.									

Table 127: MACHRAOUI1999 [366]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Machraoui A, Germing A, von Dryander S,	RCT	N=186 Drop outs N= Unclear	**Inclusion criteria** Symptomatic CAD or myocardial ischemia,	Coumadin (INR 3.5-4.5) + ASA (100mg) N=85	ASA (100mg) N=79	3m	**Outcome 1** All-cause mortality	ASA+W=0/85 ASA =2/79	**Source of funding** None provided.
							Outcome 2 Reinfarction	ASA+W=4/85	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Lange S, Jäger D, Lemke B, Barmeyer J Am Heart J. 1999 Oct;138(4 Pt 1):663-9. **Title** Comparison of the efficacy and safety of aspirin alone with coumadin plus aspirin after provisional coronary stenting: final and follow-up results of a randomized study. **Journal** Am Heart J. 1999		Analysis: ITT	coronary artery diameter stenosis > 50% and successful stent implantation in 1 target vessel with > 1 lesion. Patients with ref diameter < 3mm, unstable angina, or acute or chronic occlusion. **Exclusion criteria** Any contraindication to study medication, previously on coumarin or ASA; a failed stent implantation; coronary artery closure during stenting; and acute MI during stenting.					ASA =8/79	Limitations Small sample size.
							Outcome 3 Revascularisation	ASA+W=8/85 ASA =10/79	
							Outcome 4 Cerebral bleeding	ASA+W=0/85 ASA =1/79	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Oct;138(4 Pt 1):663-9. Country: Germany Randomisation: Yes. Unclear Allocation Concealment: Unclear Blinding: No. Open label Power Calculations: Assuming a cumulative event rate of 10% in ASA and 30% in courmarin+ASA, each treatment									

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
group needed to have 70 patients to obtain a power of80%. At least 180 successful procedures were needed.									

Table 128: Mega 2009[382]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Lancet. 2009 Jul 4;374(9683): 29-38. doi: 10.1016/S0140-6736(09)60738-8. Epub 2009 Jun 17. Rivaroxaban versus	RCT – Phase II	N=1347 Only extracted data on dose relevant for AF 20mg/day **Drop outs/early**	**Inclusion criteria** >18 yrs who had symptoms suggestive of an acute coronary syndrome and either a diagnosis of STEMI, NETMI or unstable angina. **Exclusion criteria**	Rivaroxaban (5mg/d) + ASA (75-100mg/d) + thienopyridine N=153 Rivaroxaban (10mg/d) + ASA (75-100mg/d) + thienopyridine N=851	Placebo + ASA (75-100mg/d) + thienopyridine N=901	6m	**Outcome 1** **Minor bleeding TIMI**	5mg/d rivaroxaban =1/153 10mg/d rivaroxaban = 6/851 15m/d rivaroxaban =4/353 20mg/Rivaroxaban = 4/446	**Source of funding** Johnson&Johnson and Bayer Healthcare **Limitations** Unclear how many in rivaroxaban

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
placebo in patients with acute coronary syndromes (ATLAS ACS-TIMI 46): a randomised, double-blind, phase II trial. Mega JL, Braunwald E, Mohanavelu S, Burton P, Poulter R, Misselwitz F, Hricak V, Barnathan ES, Bordes P, Witkowski A, Markov V, Oppenheimer L, Gibson CM; ATLAS ACS-TIMI 46 study group. **Country:** 27 countries		**discontinuation.** Unclear	Haemoglobin concentration of less than 100g/L, platelet count <90,000 percubic millimetre, a history of intracranial haemorrhage. If needed continued or planned treatment with warfarin (eg AF) or had planned PCI within 30 days of randomisation, severe concomitant disease or life expectancy <6months. **Baseline characteristics** **Placebo** STEMI – 55.2% UNSTEMI-31.3% Unstable angina 13.5%	Rivaroxaban (15mg/d) + ASA (75-100mg/d) + thienopyridine N=353 Rivaroxaban (20mg/d) + ASA (75-100mg/d) + thienopyridine N=446				Placebo = 3/901	group took full dose 2xday Only a sub-set of data used.
							Outcome 2 **TIMI major bleeding**	5mg/d rivaroxaban = 1/153 10mg/d rivaroxaban =12/851 15mg/d rivaroxaban =6/353 20mg/d Rivaroxaban = 8/446 Placebo = 1/901	
							Outcome 3 **Bleeding requiring medical attention**	5mg/d rivaroxaban =13/153 10mg/d rivaroxaban = 80/851 15md/ rivaroxaban =34/353 20mg/d Rivaroxaban =	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Randomisation: Unclear methods. 1:1:1 fashion **Allocation Concealment:** Unclear			PCI for index 78.7% Aspirin 98.9% Thienopyridine 99.1% **Rivaroxaban** STEMI – 53.9% UNSTEMI-32.7%					62/446 Placebo =30/901	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Blinding: Double-blind **Power Calculations:** At least 225 patients per dose tier and stratum to provide an estimate of the bleeding rate for each treatment			Unstable angina 13.3% PCI for index 79.8% Aspirin 98.8% Thienopyridine 99.3%						

Table 129: Mega 20011[382]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Mega JL, Braunwald E,	RCT – Phase III	N=15,526	Inclusion criteria >18 yrs who had symptoms	Rivaroxaban combined (2.5mg, 5mg 2xd) + ASA	Placebo+ ASA (low-dose)+ Clopidogrel	13.3m mean	**Outcome 1** All-cause death	Rivaroxaban = 245/10,229	Source of funding Johnson&Jo

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Wiviott SD, Bassand JP, Bhatt DL, Bode C, Burton P, Cohen M, Cook-Bruns N, Fox KA, Goto S, Murphy SA, Plotnikov AN, Schneider D, Sun X, Verheugt FW, Gibson CM; ATLAS ACS 2–TIMI 51 Investigators **Title** Rivaroxaban in patients with a recent acute coronary syndrome. Country:	trial (ATLAS ACS-TIMI46, Phase II)	Drop outs/early discontinuation Riv 2.5mg =26.6% Riv 5mg 26.4% ASA = 26.4%	suggestive of an acute coronary syndrome and in whome STEMI, NETMI or unstable angina had been diagnosed. Patients <55yrs, had either DM or previous MI in addition to an index event. Exclusion criteria Platelet count <90,000 percubic millimetre, a haemoglobin level <10g/dL, or a creatinine clearance <30m/min; significant gastrointestinal bleeding <12m, previous intracranial bleeding; previous stroke or transient	(low-dose)+ Clopidogrel (or ticlopidine) N=10,229	(or ticlopidine) N=5113			Placebo = 153/5113	hnson and Bayer Healthcare Limitations
							Outcome 2 Cardiovascular death	Rivaroxaban = 226/10,229 Placebo = 143/5113	
							Outcome 3 Reinfarction	Rivaroxaban = 384/10,229 Placebo = 229/5113	
							Outcome 4 Stroke (any)	Rivaroxaban = 100/10,229 Placebo = 41/5113	
							Outcome 5 TIMI major bleeding (not associated with CABG)	Rivaroxaban = 147/10,229 Placebo = 19/5113	
							Outcome 6 Minor bleeding TIMI	Rivaroxaban = 81/10,229 Placebo = 20/5113	
							Outcome 7 Intracranial hemorrhage	Rivaroxaban = 32/10,229 Placebo = 5/5113	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
44 countries Randomisation: Unclear methods. 1:1:1 fashion Based on planned use of thienopyridine. Allocation Concealment: Unclear Blinding: Double-blind Power Calculations: 983 primary efficacy end-points would provide a power of approx 96% to detect a 22.5%			ischemic attack in patients taking ASA + thienopyridine. Baseline characteristics STEMI – 50.3% UNSTEMI-25.6% Unstable angina 24%						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
relative reduction bw combined-dose grp receiving rivaroxaban and placebo with a 2-sided type I error of 0.05. Had approx 90% power to detect a RR reduction of 22.5%									

Table 130: Nguyen 2007[423]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Nguyen MC, Lim YL, Walton A, Lefkovits J, Agnelli G, Goodman SG, Budaj A, Gulba DC,	Prospective cohort	N=800 Lost to follow-up N=129 W+D=101 W+S=28	**Inclusion criteria** We analysed data from 800 patients (entered between April 1999 and September 2006) who underwent coronary stenting	Stent + Warfarin + Clopidogrel + ASA N=580 Reasons for treatment	Stent + Warfarin + ASA N=220 Reasons for treatment	6m	**Outcome 1** Death	W+D=23/453 W+S=12/184	Limitations Not RCT 49% in dual therapy were on single therapy after 6m. 27% on
							Outcome 2 Stroke	W+D=3/426 W+S=6/179	
							Outcome 3 Revascularisation	W+D=34/424 W+S=22/176	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Allegrone J, Brieger D; GRACE Investigators **Title** Combining warfarin and antiplatelet therapy after coronary stenting in the Global Registry of Acute Coronary Events: is it safe and effective to use just one antiplatelet agent? **Journal;** Eur Heart J. 2007 Jul;28(14):1717-22. Epub 2007 Jun 11. Country:		Analysis=PPA	following presentation with an ACS and who were subsequently discharged on warfarin and dual antiplatelet therapy or warfarin and single antiplatelet therapy. **Exclusion criteria** None given **Baseline characteristics** Combination discharge therapy Warfarin/dual antiplatelet (n = 580) Demographics n (%) Median age, years (IQR) 55–75 (64)	STEMI: 335 (61) NSTEMI 134 (23) Unstable angina 91 (16) Indications for warfarin therapy n (%) Prior warfarin (n = 226) Atrial fibrillation or flutter 182 (80%) STEMI 0 Prosthetic valve surgery 20 (9) Venous thrombo-embolism 20 (9) Unidentified 4 (2) New warfarin therapy (n = 574) Atrial fibrillation or flutter 137 (24%) STEMI 343 (60) Prosthetic valve surgery 0	STEMI: 134(61) NSTEMI: 50(23) Unstable angina: 36 (16)		**Outcome 4** MI	W+D=13/391 W+S=7/154	none. 12% on dual in single therapy and 39% were on none.

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Europe, Australia, NZ and USA Randomisation: No. Aimed to enrol an unbiased population by recruiting the first 10-20 consecutive eligible patients each month Allocation Concealment: No. NA Blinding: No. NA Power Calculations: No.			Men 432 (74) 129 (Prior angina 227 (39) Prior myocardial infarction 59 (27) Prior heart failure 60 (10) Prior coronary intervention 108 (19) Prior CABG surgery 86 (15) Prosthetic valve 20/356 (5.6) Smoker (current or former) 336 (58) Diabetes 130 (23) Hypertension 331 (57) Hyperlipidaemia 301 (52) Atrial fibrillation 130 (22) Major surgery/trauma 26 (4.5) Clinical	Venous thrombo-embolism 12 (2) Unidentified 82 (14)						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			presentation n (%) Cardiac arrest 15 (2.6) 8 Killip class I 452 (80) Killip class II–IV 114 (19) STEMI 355 (61) Non-STEMI 134 (23) Unstable angina 91 (16) Combination discharge therapy Warfarin/single antiplatelet (n = 220) Demographics n (%) Median age, years (IQR)) 58–77 (66) Men 129 (70) Prior angina 105 (48) Prior myocardial						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			infarction 58 (26) Prior heart failure 29 (13) Prior coronary intervention 34 (16) Prior CABG surgery 27 (12) Prosthetic valve 5/124 (4.0) Smoker (current or former) 116 (53) Diabetes 49 (23) Hypertension 129 (59) Hyperlipidaemia 100 (47) Atrial fibrillation 52 (24) Major surgery/trauma 13 (5.9) Clinical presentation n (%) Cardiac arrest 8 (3.7) Killip class I 180						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			(84) Killip class II–IV 35 (16) STEMI 134 (61) Non-STEMI 50 (23) Unstable angina 36 (16)						

Table 131: **OASIS 2001[9]**

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
[No authors listed] **Title** Effects of long-term, moderate-intensity oral anticoagulation in addition to aspirin in unstable	RCT	N=3712 Drop outs N=11 5months Analysis: ITT	**Inclusion criteria** Patients eligible for the main OASIS-2 trial, which compared a three-day regimen of hirudin vs. heparin (3), were those who could be randomized within 12 h of an episode of chest	Warfarin (INR 2-2.5) + ASA	ASA	5m	**Outcome 1** All strokes	W+ASA = 11/1848 ASA = 18/1864	**Source of funding** None stated Limitations
							Outcome 2 Reinfarction	W+ASA = 89/1848 ASA = 95/1864	
							Outcome 3 Revascularisation (PCTA/CABG)	W+ASA = 445/1848 ASA = 460/1864	
							Outcome 4 Cardiovascular death	W+ASA = 74/1848	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
angina. The Organization to Assess Strategies for Ischemic Syndromes (OASIS) Investigators. **Journal** J Am Coll Cardiol. 2001 Feb;37(2):475-84. Randomisation: Unclear, randomized by a toll-free telephone call to a 24-h automated randomization service. After key data were recorded, the patients were allocated to			pain suspected to be due to UA or MI without ST segment elevation on their admission electrocardiogram. **Exclusion criteria** Additional exclusions for the warfarin part of the study were a clear indication for warfarin, bleeding during heparin or hirudin, coronary artery bypass graft surgery planned within a week, normal coronary anatomy, contraindications to oral AC therapy and physician or patient reluctance.					ASA = 69/1864	
							Outcome 5 Major bleeding (includes hemorrhagic strokes)	W+ASA = 49/1848 ASA = 25/1864	
							Outcome 6 Minor bleeding	W+ASA = 85/1848 ASA = 50/1864	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
receive warfarin or to a control group for five months Allocation Concealment : Yes, see above. Blinding: Single. Patients - Open trial. Assessors-blinde11d. Power Calculations: We anticipated an event rate of 9% for the composite outcome of cardiovascular									

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
death/new MI/stroke and 20% for cardiovascular death/MI/stroke/readmission to the hospital for UA at five months. With 4,000 patients, we would have 80% power ($2\alpha = 0.05$) to detect a 26% relative risk (RR) reduction in the primary outcome and a 21% RR reduction in the secondary outcome.									

Table 132: Oldgren2011 (RE-DEEM)[438]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Oldgren J, Budaj A, Granger CB, Khder Y, Roberts J, Siegbahn A, Tijssen JG, Van de Werf F, Wallentin L; RE-DEEM Investigators . **Title** Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial. **Journal** Eur Heart J. 2011		N=1861 Drop outs N= unclear Analysis: ITT	**Inclusion criteria** males and females aged 18 years or older, hospitalized with non-ST or ST-segment elevation myocardial infarction within the last 14 days, and receiving treatment with dual antiplatelet therapy (aspirin and clopidogrel or another thienopyridine). The index event had to be documented by elevated values of cardiac biomarkers (preferably troponin T or I) above the 99th percentile of the upper reference limit together	Dabigratran 50, 75, 110, 150 mg 2xd + ASA (100mg) + Clop (75mg) Concomitant medication Aspirin only Randomization= 0.4% 28wks = 18.2% Aspirin and Clopidogrel Randomization =99.2% 28wks =79.6%	ASA (100mg) + Clop (75mg)	28 wks	**Outcome 1** All-cause death	Dab 50mg = 8/369 Dab 75mg = 10/368 Dab 110mg = 7/406 Dab 150mg = 7/347 Total = 32/1490 Placebo = 14/371	**Source of funding** Boehringer Ingelheim. Limitations
							Outcome 2 Cardiovascular death	Dab 50mg = 8/369 Dab 75mg = 9/368 Dab 110mg = 5/406 Dab 150mg = 4/347 Total = 26/1490 Placebo = 9/371	
							Outcome 3 Reinfaction (non-fatal)	Dab 50mg = 9/369 Dab 75mg = 8/368 Dab 110mg = 7/406 Dab 150mg = 8/347 Total = 32/1490 Placebo = 4/371	
							Outcome 4 Stroke (Non-haemorrhagic)	Dab 50mg = 0/369 Dab 75mg = 1/368 Dab 110mg = 0/406	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Nov;32(22):2781-9. Epub 2011 May 7 Country: 24 countries in Asia, Europe, and North America. Randomisation: Yes, centralized interactive voice response system (IVRS) Allocation Concealment :Yes Blinding: Yes, double blind Power Calculations:			with ischaemic symptoms or ECG changes (ST-T changes, new left bundle branch block, or new Q-waves). Additionally, participants were required to have at least one risk factor for subsequent cardiovascular complications: age 65 years or above, diabetes mellitus on treatment, previous myocardial infarction, left bundle branch block, congestive heart failure requiring treatment or left ventricular ejection fraction <40%, peripheral arterial disease, moderate renal					Dab 150mg = 0/347 Total = 1/1490 Placebo = 3/371	
							Outcome 5 Major bleeding(TIMI)	Dab 50mg = 1/369 Dab 75mg = 0/368 Dab 110mg = 5/406 Dab 150mg = 1/347 Total = 7/1490 Placebo = 1/371	
							Outcome 6 Major bleeding (ISTH)	Dab 50mg = 2/369 Dab 75mg = 1/368 Dab 110mg = 6/406 Dab 150mg = 4/347 Total = 13/1490 Placebo = 1/371	
							Outcome 7 Minor bleeding (clinically relevant)	Dab 50mg = 9/369 Dab 75mg = 15/368 Dab 110mg = 23/406 Dab 150mg = 23/347	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
The sample size was driven by the primary endpoint, i.e. to detect a statistically significant dose response (at the 5% significance level) for bleeding rates across the five treatment groups. With a sample size of 286 patients per-treatment group, a two-sided $\chi 2$ test of trend in proportions based on the logistic model would have 90% power to			insufficiency [creatinine clearance (CrCl) ≥30–60 mL/min], or no revascularization for the index even **Exclusion criteria** ongoing or planned treatment with vitamin K antagonists, severe disabling stroke within the previous 6 months or any stroke within the previous 14 days, conditions associated with an increased risk of bleeding such as major surgery (including bypass surgery) in the previous month, history of severe bleeding,					Total = 70/1490 Placebo = 6/371	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
detect a difference in proportions predicted to be 5, 5, 7, 9, and 11% (placebo, 50, 75, 110, and 150 mg, respectively). Subsequently, at least 340 patients were included per-treatment group which allowed for potential drop outs or non-evaluable patients of ~15%.			gastrointestinal haemorrhage within the past year, gastroduodenal ulcer in the previous 30 days, fibrinolytic agents within 48 h of study entry, uncontrolled hypertension, haemoglobin <10 g/dL or platelet count <100 × 109/L, normal coronary arteries at angiogram for index event, congestive heart failure New York Heart Association Class IV, and severe renal impairment (CrCl <30 mL/min).						

Table 133: Patel 2011[457]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Manesh R. Patel, M.D., Kenneth W. Mahaffey, M.D., Jyotsna Garg, M.S., Guohua Pan, Ph.D., Daniel E. Singer, M.D., Werner Hacke, M.D., Ph.D., Günter Breithardt, M.D., Jonathan L. Halperin, M.D., Graeme J. Hankey, M.D., Jonathan P. Piccini, M.D., Richard C. Becker, M.D., Christopher	RCT	N= 14,264 MI Subgroup Prior MI= 2468 Drop outs/no longer eligible. In larger trial = 32 lost to follow-up Analysis: ITT	**Inclusion criteria** We recruited patients with nonvalvular atrial fibrillation, as documented on electrocardiography, who were at moderate-to-high risk for stroke. Elevated risk was indicated by a history of stroke, transient ischemic attack, or systemic embolism or at least two of the following risk factors: heart failure or a left ventricular ejection fraction of 35% or less, hypertension, an age of 75 years or more, or the presence of diabetes mellitus (i.e., a CHADS2	Rivaxaban 20mg/d or 15mg/d	Warfarin INR 2-3	590 days median.	**Outcome 1** Major and non-major clinically relevant bleeding	Rivaxaban = 287/1182 Warfarin = 268/1286	Source of funding Supported by Johnson & Johnson Pharmaceutical Research and Development and Bayer HealthCare. Limitations

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
C. Nessel, M.D., John F. Paolini, M.D., Ph.D., Scott D. Berkowitz, M.D., Keith A.A. Fox, M.B., Ch.B., Robert M. Califf, M.D., and the ROCKET AF Steering Committee for the ROCKET AF Investigators **Title** Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation **Journal** N Engl J Med 2011			score of 2 or more, on a scale ranging from 1 to 6, with higher scores indicating a greater risk of stroke). According to the protocol, the proportion of patients who had not had a previous ischemic stroke, transient ischemic attack, or systemic embolism and who had no more than two risk factors was limited to 10% of the cohort for each region; the remainder of patients were required to have had either previous thromboembolism or three or more risk factors.						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Country: 45 countries Randomisation: Yes, central 24 hour computerized, automated voice response system. Allocation Concealment: Yes, see above Blinding: Double-blind Power Calculations: For the primary			**Exclusion criteria** See supplementary appendix. In brief: Cardiac related problems; Haemorrhage risk; concomitant conditions and therapies.						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
analysis, we determined that a minimum of 363 events would provide a power of 95% to calculate a noninferiority margin of 1.46 with a one-sided alpha level of 0.025. However, 405 events were selected as the prespecified target to ensure a robust statistical result. On the basis of a projected event rate of 2.3% per 100 patient-years									

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
in the warfarin group and a projected 14% rate of annual attrition, it was estimated that approximately 14,000 patients would need to be randomly assigned to a study group.									

Table 134: Rossini 2008[510]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author: Rossini R, Musumeci G, Lettieri C, Molfese M, Mihalcsik L, Mantovani P,	Prospective observational study	N=204 **Drop outs/no longer eligible**. none	**Inclusion criteria** All patients undergoing coronary stent implantation treated with aspirin and clopidogrel and	Triple therapy: Anticoagulant + clopidogrel (75mg/d)+ ASA (100mg/d)	Dual therapy: clopidogrel (75mg/d)+ ASA (100mg/d)	18 months Mean duration of TT was 157	**Outcome 1** All-cause mortality	**TT** = 3/102 **DT** = 1/102	**Source of funding** None provided **Limitations:**
							Outcome 2 CV death	**TT** = 1/102 **DT** = 1/102	
							Outcome 3 Reinfarction (non-	**TT** =2/102 **DT** = 2/102	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Sirbu V, Bass TA, Della Rovere F, Gavazzi A, Angiolillo DJ. **Title:** Long-term outcomes in patients undergoing coronary stenting on dual oral antiplatelet treatment requiring oral anticoagulant therapy. **Journal:** Am J Cardiol. 2008 Dec 15;102(12):1618-23. doi: 10.1016/j.amjcard.2008.08.021. Epub 2008 Sep 24.		**Analysis** ITT	who required oral anticoagulant therapy from 3 institutions. **Exclusion criteria** Mechanical valve prothesis **Triple therapy (n=102)** **Age:**67.9 ± 9.3 **Men:** 82 (80.4%) **Diabetes:** 23 (22.5%) **Previous MI:** 28 (27.4%) **Clinical presentation:** **Stable angina:** 22 (21.6%) **Unstable angina/NSTEMI:**45 (44.1%) **STEMI: 35 (34.3%)** **Drug eluting stent:** 48(47%) **Left EF:** 47.6±8.7 **Medications at discharge:**	Target INR: 2 and 2.5		days (30 to 540)	fatal) **Outcome 4** Stroke (all stroke) **Outcome 5** Major bleeding (including intracranial) **Outcome 6** Minor bleeding	 **TT** = 1/102 **DT** = 2/102 **TT**= 3/102 **DT** = 2/102 **TT**= 8/102 **DT** = 3/102	Non-RCT Dual therapy patients did not need antiocoagulantss

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Country: ITALY **Randomisation:** No, observational study **Blinding**: No. **Power Calculations:** No.			**Nitrates:** 18 (17.6%) **ACEi:** 80 (78.4%) **Angiotensin II receptor blockers:** 9 (8.8%) **Ca antagonist:** 23 (22.5%) **BB:**78 (76.5%) **Statin:** 64(62.7%) **Diuretic:** 53(52%) **Proton pump inhibitor:** 92 (90.2%) **Indication for OAC:** **AF:** 68 (66.6%) **Left ventricular mural thrombus:** 18(17.6%) **Left ventricular aneurysm:**5(4.9%) **Pulmonary embolism:**5 (4.9%) **Other indication:** 6 (5.8%) **Dual therapy (n=102)** **Age:** 68.2±81. **Men:**81 (79.4%)						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			Diabetes: 24 (23.5%) **Previous MI:** 26 (25.5%) **Clinical presentation:** **Stable angina:** 21 (20.6%) **Unstable angina/NSTEMI:**46 (45%) **STEMI:** 35(34.3%) **Drug eluting stent:** 49 (48%) **Left EF:** 48.1±9.2 **Medications at discharge:** **Nitrates:** 20 (19.6%) **ACEi:** 83 (78.4%) **Angiotenis II receptor blockers:**6 (5.9%) **Ca antagonist:** 21 (20.6%) **BB:**79 (77.4%) **Statin:** 66 (64.7%) **Diuretic:** 51 (50%) **Proton pump inhibitor:** 91 (89.2%) **Indication for OAC:**						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			none						

Table 135: Rubboli 2012[511]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author: Rubboli A, Magnavacchi P, Guastaroba P, Saia F, Vignali L, Giacometti P, Franco N, Benassi A, Varani E, Campo G, Manari A, De Palma R, Marzocchi A. **Title:** Antithrombotic management and 1-year outcome of patients on	Non-RCT	N=622 DAPT =306 TT (OAC, aspirin+clodiogrel) =205 OAC + ASA =111 Drop outs/no longer eligible. Registry data so not relevant Analysis: ITT	**Inclusion criteria** Consecutive patients who undergo PCI at 13 hospitals in the Italian region. From 2003-2007 **Exclusion criteria** None provided Baseline characteristics Age:73.1 ± 8.4 Men:460 (73%) HF:221 (35%) Kidney disease: Previous MI:234 (37%) Previous PCI:70	OAC + dual antiplatelet therapy (TT)	Dual antiplatelet therapy (DAPT) Or OAC + aspirin	12m	**Outcome 1** All-cause mortality	TT = 66/205 DAPT = 75/306 OAC+asa=27/111	**Source of funding** None Limitations Non-RCT
							Outcome 2 CV mortality	TT = 21/205 DAPT = 26/306 OAC+asa=11/111	
							Outcome 3 Reinfarction	TT = 23/205 DAPT = 17/306 OAC+asa=10/111	
							Outcome 4 Stroke	TT = 0.2/205 DAPT = 13/306 OAC+asa=0.1/111	
							Outcome 5 Major bleeding	TT = 10/205 DAPT = 6/306 OAC+asa=3/111	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
oral anticoagulation undergoing coronary stent implantation (from the Registro Regionale Angioplastiche Emilia-Romagna Registry). **Journal:** Am J Cardiol. 2012 May 15;109(10):1411-7 Country: ITALY Randomisation: Non-RCT Blinding:			(11%) Indication for OAC: AF:367 (58%) Deep vein thrombosis/pulmonary embolism: 60 (10%) Mechanical heart valve:45 (7%) Dilated cardiomyopathy: 43 (6%) Ischemic heart disease: 26 (4%) Cardiac thrombus:20 (3%) Previous stroke/transient ischemic attack:15 (2%(Biologic heart valve:4 (1%) Left ventricular aneurysm: 4 (1%) Indication for PCI: STEMI: 108 (17%) nonSTEMI: 294						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
No Power Calculations: No			(46%) Other: 231 (37%) Type of stent Drug eluting: 156(25%) Bare metal: 449 (71%) Other: 27 (4%) Other medication: Use of glycoprotein IIb/IIIa inhibitors: 96(25%)						

Table 136: Sarafoff 2008[522]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Sarafoff N, Ndrepepa G, Mehilli J, Dörrler K, Schulz S, Iijima R,	Observational. Prospective	N=515 Drop outs N=0	Inclusion criteria Consecutive patients who were on chronic OAC (>6m) at the time of DES	OAC – continue with phenprocoumon (INR 2) Clopidogrel (75mg/d) + ASA (100m, 2xd) .	Discontinued OAC + Clopidogrel (75mg/d) + ASA (100m, 2xd)	Median therapy 12ks Triple therapy 4 wks dual	**Outcome 1** All-cause death	Triple = 6/306 Dual = 9/209	Limitations Not RCT Unclear what time period the follow-up
							Outcome 2 Reinfarction	Triple = 4/306 Dual = 4/209	
							Outcome 3 Stroke	Triple = 0/306 Dual = 3/209	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Byrne R, Schömig A, Kastrati A. **Title** Aspirin and clopidogrel with or without phenprocoumon after drug eluting coronary stent placement in patients on chronic oral anticoagulation. **Journal** J Intern Med. 2008 Nov;264(5):472-80. Epub 2008 Jun 25. Country: Germany	cohort.		implantation. Exclusion criteria Patients with known malignancies Baseline characteristics Demographic, clinical and angiographic data Triple therapy mean (%) Age, years 71.4 ± 9.9 Women75 (25) Arterial hypertension270 (88) Diabetes80 (26) Current smoker29 (10) Hypercholesterolaemia230 (75) Unstable angina100 (33)	after PCI During PCI. All patients were treated wtih heparin and ASA iv. Indication and duration of dual antithrombotic or triple therapy was made on an individual assessment of the coronary status and the risk for emboli or stent thrombosis in each patient. The criteria used to identify patients in need of triple therapy were prosthetic heart valves, presence of recent thrombus at one of heart chambers, pulmonary		therapy. Results are reported from time during therapy.	**Outcome 4** Major bleeding **Outcome 5** Minor bleeding	Triple = 4/306 Dual = 3/209 Triple = 22/306 Dual = 16/209	SRAT period corresponded to. No MI?

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Randomisation: No/NA Allocation Concealment: No/NA Blinding: No/NA Power Calculations: Unclear			Previous myocardial infarction98 (32) Previous bypass surgery74 (24) Previous PCI130 (42) Left ventricular ejection fraction47.3 ± 14.6a Multivessel disease238 (78) Indication for oral anticoagulation Atrial fibrillation/flutter 207 (67) Deep vein thrombosis11 (4) Pulmonary embolism19 (6) Left ventricular aneurysm14 (5) Left ventricular ejection fraction<30%3(1.4) Prosthetic heart	embolism or deep vein thrombosis. Patients with atrial fibrillation/flutter received triple therapy if they had at least one of the following conditions: prior stroke/thromboembolism, heart failure with left ventricular ejection fraction of ≤30%, left atrium size ≥50 mm, mitral stenosis or mitral regurgitation ≥2 degree					

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			valve52 (17) Duration of the recommended therapy (weeks) 4 weeks134 (44) 8 weeks8 (3) 12 weeks19 (6) 26 weeks64 (21) 52 weeks70 (23) Indefinite11 (4) Dual therapy Age, years 72.4 ± 9.3 Women 52 (25) Arterial hypertension188 (90) Diabetes59 (28) Current smoker21 (10) Hypercholesterolaemia128 (61) Unstable angina 70 (33) Previous myocardial infarction 66 (32) Previous bypass						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			surgery 34 (16) Previous PCI 78 (37) Left ventricular ejection fraction 48.9 ± 14.5b Multivessel disease 163 (78) Indication for oral anticoagulation Atrial fibrillation/flutter 194 (93) Deep vein thrombosis 3 (1) Pulmonary embolism 3 (1) Left ventricular aneurysm 7 (3) Left ventricular ejection fraction<30% 2 (1) Prosthetic heart valve Duration of the recommended therapy (weeks) 4 weeks 119						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			(57) 8 weeks 3 (1) 12 weeks 16 (8) 26 weeks 40 (19) 52 weeks 30 (15) Indefinite 1 (0.5)						

Table 137: Tenberg 2000[574]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Berg JM, Kelder JC, Suttorp MJ, Mast EG, Bal E, Ernst SM, Verheugt FW, Plokker HW. **Title** Effect of coumarins started before	RCT (BAAS)	N=1058 Drop outs N=unclear Analysis: ITT	Inclusion criteria Patients with symptomatic coronary artery disease planning to undergo PTCA were eligible. Exclusion criteria Exclusion criteria were acute myocardial infarction within 24 hours before PTCA, current use	Coumarin (INR: 2.1 to 4.8) + 100mg/d N=528 All patients were given aspirin (loading dose, 300 mg, then 100 mg/d) ≥24 hours before PTCA. Heparin was used only during PTCA: 10 000 U	ASA (100mg/d) N=530	Treatment 6m, follow-up 30d + 12m	**Outcome 1** Death	0-30d Coumarin+ASA =2/530 ASA = 3/528 0-365d Coumarin+ASA =6/530 ASA = 6/528	Limitations 12m follow up but only 6m treatment During the trial period, ticlopidine became available in the Netherlands, which led to
							Outcome 2 Reinfarction	0-30d Coumarin+ASA	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
coronary angioplasty on acute complications and long-term follow-up: a randomized trial. **Journal** Circulation. 2000 Jul 25;102(4):386-91. Country: Netherlands Randomisation: Unclear - randomized by an independent telephone Allocation Concealment: Yes			of oral anticoagulants, contraindications to coumarins or aspirin, target lesion in a bypass graft, and unwillingness or inability to provide written informed consent to participate in the trial Approximately 25% of the patients were hospitalized before PTCA, and 12% had been admitted for unstable angina with ST-segment changes and were "cooled off" with aspirin and heparin before PTCA	immediately before and 5000 U every hour during the procedure When a stent was placed, it was left to the discretion of the operator to start ticlopidine (loading dose, 500 mg, followed by 250 mg twice a day for 4 weeks). When ticlopidine was given to patients randomized to coumarins, the oral anticoagulants were discontinued.				=14/530 ASA = 21/528 0-365d Coumarin+ASA =14/530 ASA = 21/528	differences in antithrombotic treatment after stenting. However, we do not think that this difference has essentially influenced the study results. The better results in the coumarin group cannot be due to the use of ticlopidine, because only 12% of the stented coumarin patients were
							Outcome 3 Revascularisation	0-365d Coumarin+ASA =67/530 ASA = 97/528	
							Outcome 4 Stroke	0-30d Coumarin+ASA =1/530 ASA = 0/528 0-365d Coumarin+ASA =3/530 ASA = 3/528	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Blinding: Unclear (likely no) Power Calculations: Assuming a rate of clinical end points in the control group of 30%, a reduction to 25% by the use of coumarins, and values of α=0.05 and ß=0.8, almost 500 patients per group were required. Because we anticipated 5% of participants to have an unsuccessful PTCA or							**Outcome 5** Major bleeding (after discharge)	0-365d Coumarin+ASA =5/530 ASA = 0/528	treated with ticlopidine versus 54% of the stented ASA patients. Moreover, there were no statistically significant differences in the stented study groups
							Outcome 6 Minor bleeding	0-365d Coumarin+ASA =21/530 ASA = 2/528	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
incomplete follow-up, a required total of 530 patients per group was calculated.									

Table 138: Van Es 2002[598]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author van Es RF, Jonker JJ, Verheugt FW, Deckers JW, Grobbee DE; Antithrombotics in the Secondary Preventionof Events in Coronary Thrombosis-2 (ASPECT-2) Research	RCT	N=999 Drop outs/no longer eligible. W+ASA = 69/333 (21%) ASA = 34/336 (10%) W = 67/330 (20%)	**Inclusion criteria** Men or women not pregnant, admitted for acute MI or unstable angina within the preceding 8 weeks. **Exclusion criteria** Established indications for treatment with oral	Warfarin (INR 3-4) + ASA (100mg/d)	ASA (100mg/d) Warfarin(INR 3-4)	26m (max)	**Outcome 1** All-cause mortality	W+ASA = 9/332 ASA = 15/336 W = 4/325	**Source of funding** Netherlands National Health Insurance Fund Council and Netherlands Heart foundation Limitations
							Outcome 2 Vascular death	W+ASA = 8/332 ASA = 12/336 W = 4/325	
							Outcome 3 Reinfarction	W+ASA = 10/332 ASA = 14/336	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Group. **Title** Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study): a randomised controlled trial. **Journal** Lancet. 2002 Jul 13;360(9327):109-13. Country: Netherlands Randomisation: Yes. Unclear methods. Allocation Concealment: Yes, central		Analysis: ITT	anticoagulants (AF, prosthetic heart vale, ventricular aneurysm) or platelet inhibitors, contraindications for study drug, planned revascularisation, serious comorbidity, increased risk of bleeding, abnormal blood platelets or erythrocytes, anaemia, history of stroke.					W = 13/325	
							Outcome 4 Stroke (all stroke)	W+ASA = 1/332 ASA = 5/336 W = 0/325	
							Outcome 5 Major bleeding (including intracranial)	W+ASA = 7/332 ASA = 3/336 W = 3/325	
							Outcome 6 Revascularisation	W+ASA = 32/332 ASA = 39/336 W = 34/325	
							Outcome 7		

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
telephone service. Blinding: No. Open label. Power Calculations: Assuming a rate of clinical endpoints of 12.5% in ASA in 2.5 yrs, a reduction of 20% for oral AntiC treatment, a power of 85%, and a two-sided alpha of 5%, 2900 patients/grp were needed over 3 yrs.									

Table 139: De Wilde 2013[150]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Dewilde WJ, Oirbans T, Verheugt FW, Kelder JC, De Smet BJ, Herrman JP, Adriaenssens T, Vrolix M, Heestermans AA, Vis MM, Tijsen JG, van 't Hof AW, Ten Berg JM; for the WOEST study investigators **Title** Use of clopidogrel with or without aspirin in patients taking oral anticoagulan	Parall el RCT	N=573 **Drop outs/no longer eligible.** 1.7% **Analysis:** ITT	**Inclusion criteria** Only patients scheduled for PCI can be included tough this intervention would also take place without this study. Patients is on oral anticoagulation therapy and this will be continued throughout the period of 1 year- and deployment of at least 1 coronary stent (bare metal stent (BMS) or drug eluting stent (DES)). –age of more than 18 years **Ages Eligible for Study**: 18 Years to 80 Years	Warfarin + clopidogrel 75mg/day + aspirin 80mg/day = 284	Warfarin + clopidogrel 75mg/day N=279	1 year	**Outcome 1** Incidence of bleeding (TIMI classification) Any TIMI bleeding	TT = 127/284 (44.9%) DT = 54/279 (19.5%) HR:0.36 (0.26-0.50) p<0.001	**Source of funding** Centre of platelet function research. Sint Antonius Hospital, Nieuwegein Netherlands Stichting Strect, Tilburg, The Netherlands **Limitations:** The study was powered to show superiority on the primary endpoint (bleeding), but not to show non-
							Outcome 2 All-cause mortality	TT = 18/284 (6.4%) DT = 7/279 (2.6%) HR:0.39 (0.16-0.93) p=0.027	
							Outcome 3 Reinfarction	TT =13/284 (4.7%) DT = 9/279 (3.3%)	
							Outcome 4 Stroke	TT = 8/284 (2.9%) DT = 3/279 (1.1%)	
							Outcome 5 Revascularisation	TT = 19/284 (6.8%) DT = 20/279 (7.3%)	
							Outcome 6 Stent thrombosis	TT = 9/284 (3.2%) DT = 4/279 (1.5%)	
							Outcome 7 Major bleeding	TT = 16/284 (5.8%) DT = 9/279 (3.3%)	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
t therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. **Journal** Lancet. 2013 Feb 12. pii: S0140-6736(12)62177-1. doi: 10.1016/S0140-6736(12)62177-1. **Country:** BELGIUM NETHERLANDS **Randomisation:**			**Genders Eligible for Study**: Both **Accepts Healthy Volunteers**: Yes **Exclusion criteria** •cardiogenic shock, •contra-indication for aspirin or clopidogrel •allergy to aspirin or clopidogrel, •documented peptic ulcer disease within the previous six months, •pregnancy and •previous intracerebral haemorrhage or •significant thrombocytopenia (platelet count < 50x10 9/L). •major bleeding				TIMI **Outcome 8** Minor bleeding TIMI	 TT = 77/284 (27.2%) DT = 3116/279 (11.2%)	inferiority on the secondary endpoint. Indirect population (not all ACS) Initiated treatment at different times in those with BMS vs DES Open label trial design with inherent bias Classificaion of smaller bleeding, although well defined and blindly adjudicate, may be

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Yes, patients were assigned in a 1:1 ratio, using a computer generated randomisation sequence. **Allocation concealment** Unclear. Patients allocation was given in a sequentially sealed **Blinding:** No, open label **Assessor of outcomes –** blinded **Power Calculations:**			according to timi criteria within the past 12 months •age > 80 years **Baseline characteristics** Matched. Yes. Double therapy n=279 Age: 70.3 (±7.3) Male: 214 (76.7%) BMI:27.5 (±4.3) Current smoker: 60 (21.5%) Diabetes: 68 (24.4%): Hypertension: 193 (69.2%) History of MI:96 (34.4.%) HF:71 (25.4%) Stroke:49 (17.6%) PCI:86 (30.8%) CABG:56 (20.1%) GI Bleeding:14 (5.0%)						subjective

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Based on large retrospective study by Karjalainen. They anticipated a 12% bleeding rate in the triple therapy group and a 5% bleeding rate in the double therapy group. Power was chosen to be 80% and a α level at 5%. The total patient number is estimated at n=496.			**Indication for OAC:** AF/A flutter:164 (69.5%) Mechanical valve:24 (10.2%) Other (pulmonary embolus, EF<30%, apical thrombus): 48 (20.3%) **ACS as baseline**: 69/279 (25.0%) **Procedural characteristics** LVEF ≤30%: 40 (21.1%) **Stent:** No: 5 (1.8%) BMS: 89 (32%) DES:181 (65.1%) BMS+DES:3 (1%) INR day of PCI: 1.86 (±0.9) Triple therapy n=284						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			Age:69.5 (±8.0) Male:234 (82.4%) BMI:27.9 (±4.2) Current smoker:42 (14.8%) Diabetes: 72 (25.4%) Hypertension: 193 (68%) **History of** MI:100 (35.2%) HF:70 (24.6%) Stroke:50 (17.6%) PCI:101 (35.6%) CABG: 74 (26.1%) GI Bleeding: 14 (4.9%) **Indication for OAC:** AF/A flutter: 162 (69.2%) Mechanical valve:25 (10.7%) Other (pulmonary embolus, EF<30%, apical thrombus): 47						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			(20.1%) **ACS as baseline:** 86 (30.6%) **Procedural characteristics** LVEF ≤30%: 37 (18.1%) **Stent:** No:4 (1.4%) BMS:86 (30.3%) DES:183 (64.4%) BMS+DES:11 (3.8%) INR day of PCI: 1.94 (±1.1)						

Table 140: Mattichak 2005[372]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author: Mattichak SJ, Reed PS,	Non-RCT. Retro	N=82 **Drop**	**Inclusion criteria** Consecutive patients with AMI	Warfarin + Clopidogrel + ASA	Clopidogrel + ASA	12 months	**Outcome 1** All-cause mortality	TT = 1/40 DT=0/42	**Source of funding** None

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Gallagher MJ, Boura JA, O'Neill WW, Kahn JK. **Title:**Evaluation of safety of warfarin in combination with antiplatelet therapy for patients treated with coronary stents for acute myocardial infarction **Journal:** J Interv Cardiol. 2005 Jun;18(3):163-6. **Country:** USA	spective	**outs/no longer eligible.** Not relevant **Analysis:** ITT	who underwent urgent coronary angiography, mechanical reperfusion, and coronary stenting for STEMI cineangiograms and discharge medications and survived to hospital discharge. Patients discharged with warfarin anticoagulation for clinical indications along with combination antiplatelet therapy (ASA and clopidogrel) were compared to patients discharged with combination therapy. **Exclusion criteria** Co-				**Outcome 2** Reinfarction	TT = 11/40 DT=4/42	provided. **Limitations** Patients in control arm did not have a prior indication for OAC
							Outcome 3 Cerebrovascular accident	TT=0/40 DT=3/42	
							Outcome 4 GI bleeding (Major bleeding)	TT=6/40 DT=0/42	
							Outcome 5 Transfusion	TT=8/40 DT=2/42	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Randomisation: No, retrospective study. **Blinding:** No. **Power Calculations:** None provided.			administration of thrombolytic agents for the index infarction, renal failure requiring dialysis, stroke during the preceding month, cardiogenic shock, and known contraindications to warfarin, ASA ticlopidin or clopidogrel						

G.4.8 Beta-blockers vs. placebo

This section was partially updated in 2020. See www.nice.org.uk/guidance/ng185 for the 2020 evidence review.

Table 141: Anon 1982[4]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Anon 1982A (BHAT)	RCT	N= 3,837	**Inclusion criteria** Age 30-69 years;	Propranolol 180mg (82% of	Placebo (n=1921)	Mean 25.1	**Outcome 1** Total death	138/1916 propranolol (7.2%)	**Source of funding**

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Journal JAMA 1982; 247: 1707-1714. Country: US/Canada Randomisation: not stated Allocation Concealment: not stated Blinding: double-blind Power Calculations: not stated		Drop outs study medication withdrawn from around 7% of patients in each group for reasons relating to adherence (e.g. lost interest, moved away) and in other patients because of symptoms / signs e.g. congestive heart failure (4% propranolol vs. 3.5% placebo, NS), hypotension (1.2% propranol	acute MI (symptoms, ECG and enzyme changes) **Exclusion criteria** contraindications to propranolol (e.g. marked bradycardia); history of severe congestive heart failure as asthma as an adult; life-threatening illness apart from CHD; had/likely to undergo cardiac surgery; already taking or likely to have beta-blockers prescribed to them **Baseline characteristics** Age: mean 54.7 years propranolol and 54.9 years placebo	cases) or 240mg daily (18% of cases); dose based on serum levels , started 5-21 days after MI (n=1916)		months; maximum 39 months		vs. 188/1921 (9.8%) placebo, nominal p<0.005; allowing for repeated testing p<0.01	National Heart, Lung, and Blood Institute Limitations study medication withdraw from a large proportion of both study groups. Trial not designed to answer the question of how long beta-blockers should continue Authors' conclusions Authors recommend the use of propranolol for at least
							Outcome 2 Cardiovascular mortality	127/1916 propranolol (6.6%) vs. 171/1921 (8.9%) placebo, p<0.01	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		ol vs. 0.3% placebo, p<0.005), tiredness (1.5% propranol ol vs. 1.0% placebo, NS). Vital status unknown for 4 in propranol ol group and 8 in placebo group (0.3%) Analysis: ITT	Gender: 83.8% male propranolol and 85.1% placebo MI: 100% Previous angina: 35.8% propranolol and 36.5% placebo Hypertension: 41.4% propranolol and 40.1% placebo Treatment Medical Concomitant medications: anti-arrhythmic 16.6% propranolol and 17.9% placebo; anticoagulant 13.9% and 15.1%; antiplatelet 7.1% and 6.8%; diuretic 16.1% and 18.0%; vasodilator 36.0% and 36.3%; digitalis 12.5%						three years after MI in patients with no contraindications to beta-blockade

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			and 13.0; oral hypoglycaemic 2.2% and 1.8% Groups matched at baseline? yes						

Table 142: Bbhartg 2012[59]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author BBHATRG2012 (BHAT 1983) **Journal** JAMA 1983; 250: 2814-2819 (same study as above). Country: US/Canada Randomisation: not stated	RCT	N= 3,837 Drop outs study medication withdrawn from around 7% of patients in each group for reasons relating to adherence	**Inclusion criteria** Age 30-69 years; acute MI (symptoms, ECG and enzyme changes) **Exclusion criteria** contraindications to propranolol (e.g. marked bradycardia); history of severe congestive heart failure as asthma	Propranolol 180mg (82% of cases) or 240mg daily (18% of cases); dose based on serum levels , started 5-21 days after MI (n=1916)	Placebo (n=1921)	mean 25 months ; minimum 12 months , maximum 40 months	**Outcome 1** Nonfatal reinfarction **Outcome 2** Death plus non-fatal reinfarction **Outcome 3** Congestive heart	85/1916 propranolol (4.4%) vs. 101/1921 (5.3%) placebo, relative risk 0.84 192/1916 propranolol (10%) vs. 249/1921 (13.0%) placebo, RR 0.77, p<0.01 129/1916 propranolol (6.7%)	Source of funding National Heart, Lung, and Blood Institute Limitations study medication withdrawn from a large proportion of both study

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Allocation Concealment: not stated Blinding: double-blind Power Calculations: not stated		(e.g. lost interest, moved away) and in other patients because of symptoms / signs e.g. congestive heart failure (4% propranolol vs. 3.5% placebo, NS), hypotension (1.2% propranolol vs. 0.3% placebo, p<0.005), tiredness (1.5% propranolol vs. 1.0% placebo, NS). Vital status unknown for 4 in propranol	as an adult; life-threatening illness apart from CHD; had/likely to undergo cardiac surgery; already taking or likely to have beta-blockers prescribed to them **Baseline characteristics** Age: mean 54.7 years propranolol and 54.9 years placebo Gender: 83.8% male propranolol and 85.1% placebo MI: 100% Previous angina: 35.8% propranolol and 36.5% placebo Hypertension: 41.4% propranolol and				failure **Outcome 4** Angina **Outcome 5** Intermittent claudication **Outcome 6** Stroke **Outcome 7** CABG	vs. 126/1921 (6.7%) placebo, RR 1.01 748/1916 propranolol (39.0%) vs. 733/1921 (38.2%) placebo, RR 1.01 217/1916 propranolol (11.3%) vs. 222/1921 (11.6%) placebo, RR 0.98 29/1916 propranolol (1.5%) vs. 30/1921 (1.6%) placebo, RR 0.97 174/1916 propranolol (9.1%) vs. 202/1921 (10.5%) placebo, RR 0.86	groups. Trial not designed to answer the question of how long beta-blockers should continue Authors' conclusions Authors recommend the use of propranolol for at least three years after MI in patients with no contraindications to beta-blockade

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		ol group and 8 in placebo group (0.3%) Analysis: ITT	40.1% placebo Treatment Medical Concomitant medications: anti-arrhythmic 16.6% propranolol and 17.9% placebo; anticoagulant 13.9% and 15.1%; antiplatelet 7.1% and 6.8%; diuretic 16.1% and 18.0%; vasodilator 36.0% and 36.3%; digitalis 12.5% and 13.0; oral hypoglycaemic 2.2% and 1.8% Groups matched at baseline? yes						

Table 143: Baber 1980[37]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Baber **Journal** Br Heart J 1980; 44: 96-100 Country: Multinational Randomisation: "random code" Allocation Concealment: not stated Blinding: double blind Power Calculations: yes: estimated that 1000 patients needed in each group to give adequate power to detect a reduction in 3-	RCT	N= 720 Drop outs 82/355 (23%) propranolol and 88/365 (24%) placebo withdrawn from trial for angina requiring treatment with beta-blocker; bradycardia <50/minute or heart block greater than first degree; other clinical indications (e.g. heart failure); or discontinu	**Inclusion criteria** anterior MI (ECG, symptoms, enzymes) **Exclusion criteria** bronchospasm, antrioventricular block greater than first degree; sinus bradycardia (<55/minute); persistent heart failure; beta blockade at time of infarction **Baseline characteristics** Age: mean 55 years propranolol and 54.8 years placebo Gender: 86% male propranolol and 83% placebo MI: 100% Previous angina: 35% propranolol and 40% placebo	Propranolol 40mg three times daily, started 2-14 days (mean 8.5 days) after MI	Placebo	mean around 170 days	**Outcome 1** Total deaths **Outcome 2** Cardiac deaths **Outcome 3** Non-fatal reinfarctions	28/355 (7.9%) propranolol vs. 27/365 (7.4%) placebo, NS 19/355 (5.4%) propranolol vs. 18/365 (4.9%) placebo 15/355 (4.2%) propranolol vs. 14/365 (3.8%) placebo	Source of funding not stated Limitations high number of withdrawals Authors' conclusions trial designed to detect a 50% reduction in mortality and this was not shown.

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
month mortality from 4% to 2%; trial terminated when reached statistical end-point of no difference		ation of treatment for >10 days, NS between groups Analysis: not stated	Hypertension: 13% propranolol and 15% placebo Treatment Medical Concomitant medications not stated Groups matched at baseline? yes						

Table 144: Barber 1967[43]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Barber **Title** Clinical trial of propranolol in acute myocardial infarction. P127-130	RCT	N= 107 Drop outs none stated Analysis: appropriat e	**Inclusion criteria** MI in previous 12 hours (clinical + ECG) **Exclusion criteria** heart rate <60 beats per minute (sinus bradycardia or atrio-	Propranolol 40mg 6-hourly for 28 days	Placebo	4 weeks	**Outcome 1** Death at 4 weeks **Outcome 2** Heart failure	Propranolol 10/52 (19.4%) died vs. placebo 12/47 (25.5%), NS 20/52 propranolol (38.5%) vs. 18/47	Source of funding Imperial Chemical Industries, Pharmaceut icals Division

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Country: Ireland Randomisation: "previously prepared plan" Allocation Concealment: not stated Blinding: not stated Power Calculations: yes, designed to have 95% probability of detecting (at 0.05) a critical difference of 15% in survival rate at 4 weeks (number required not stated) but trial			ventricular block); asthma, bronchospasm; systolic blood pressure <90mmHg **Baseline characteristics** Age: not stated Gender: not stated MI: 100% Angina: not stated Hypertension: not stated Treatment Medical Concomitant medications not stated Groups matched at baseline? unclear				**Outcome 3** Rhythm change **Outcome 4** Further attacks of heart pain	(38.3%) placebo, NS 7/52 (13.5%) propanolol vs. 10/47 (21.3%) placebo, NS 14/52 (26.9%) propranolol vs. 10/47 (21.3%) placebo, NS	Limitations underpowered; trial terminated due to no effect; unclear if blinded Authors' conclusions no significant difference in mortality between the drugs at 4 weeks

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
terminated due to no effect									

Table 145: Basu 1997[46]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Basu 1997 **Journal** Circulation 1997; 96: 183-191. Country: UK Randomisation: not stated Allocation Concealment: not stated Blinding: double blind	RCT	N= 151 Drop outs 4 excluded (2 from each group) due to no MI and 1 found to have renal failure and not given study medication; adverse events requiring withdrawal unrelated to cardiac endpoints: 4 on carvedilol and 3 on placebo Analysis: ITT	**Inclusion criteria** MI (chest pain, ECG changes, enzymes); 54 had heart failure (34 on carvedilol and 20 on placebo); 49 had left ventricular ejection fraction <45% (24 on carvedilol and 25 on placebo) **Exclusion criteria** already on alpha or beta blockers and calcium antagonists or had contraindications to alpha or beta blockers; Killip class	Carvedilol 2.5mg intra-venously, then oral 6.25mg at 4 hours, then 6.25mg bd for 2 days, 12.5mg bd for 6 months (or increased to 25mg bd if BP > 120/95mm Hg and heart rate >55 bpm	Placebo n=74	168 days	Cardiovascular endpoint: cardiac death, reinfarction, unstable angina, heart failure, emergency re-vascularisation, ventricular arrhythmia requiring intervention, stroke, additional cardiovascular therapy (other than sublingual nitrates for	Carvedilol 18/77 vs. placebo 31/74, p<0.02	Source of funding NPH Cardiac Research Fund, and Boehringer Mannheim GmbH Limitations Authors' conclusions Carvedilol is safe to use after

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Power Calculations: yes: calculated that 144 patients (72 per group) needed to demonstrate 20% difference between groups			IV heart failure or cardiogenic shock; severe bradycardia (<45 bpm), hypotension (systolic BP <90mmHg), second to third degree heart block, left bundle branch block, severe valvular disease, insulin-dependent diabetes, renal failure (creatinine >159 micromol/L), malignancy, other severe disease, pregnancy **Baseline characteristics** Age: not stated in text Gender: not stated in text MI: 100% Treatment Medical Concomitant medications: all had	on day 14, in 9% of patients) n=77			angina, diuretics for hypertension or continuation of pre-existing ACE inhibitors, digitalis, or antiarrhythmics); starting ACE inhibitors, digitalis, or antiarrhythmics Death or reinfarction Event-free survival curves (31 months) Dizziness	6/77 carvedilol vs. 11/74 placebo (NS) Curves started to converge after carvedilol withdrawn at 6 months 5/77 (6.5%) carvedilol vs. 1/74 (1.4%) placebo	acute MI with or without associate heart failure; after stopping carvedilol, 10 patients who had been on the drug subsequently had cardiac events, 8 of which were ischaemic (unstable angina and reinfarction), although not immediately after withdrawal

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			aspirin; 97% heparin; 95% streptokinase; 7 tissue plasminogen activator; 80% nitrates; none on calcium channel blockers, long-acting nitrates or ACE inhibitors (not shown separately by treatment group) Groups matched at baseline? yes						

Table 146: CAPRICORN 2001[576]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author CAPRICORN 2001 Country: Multinational Randomisation: permuted blocks stratified by	RCT	N= 1959 Drop outs: 192/975 (19.7%) carvedilol and 174/984 (17.7%) placebo Analysis: ITT	**Inclusion criteria** Acute MI and LVEF ≤40%; receiving ACE inhibitor for at least 48 hours prior to randomisation **Exclusion criteria** continued to need IV diuretics or inotropes;	Carvedilol (target dose 25mg twice daily, achieved by 692 (74%) of patients; 103 (11%) 12.5mg twice daily; 65 (7%)	placebo	mean 1.3 years	**Outcome 1** All-cause mortality	116/975 (12%) carvedilol and 151/984 (15%) placebo	Source of funding not stated
							Outcome 2 Cardiovascular death:	104/975 (11%) carvedilol and 139/984 (14%) placebo	Limitations details of methodology published
							Outcome 3	34/975 (3%)	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
centre Allocation Concealment: not stated Blinding: double blind Power Calculations: For 90% power, assuming hazard ratio of 0.77, minimum of 1850 patients needed (633 deaths) for primary endpoint of all cause mortality or cardiovascular hospital admission			uncontrolled heart failure, systolic BP <90mmHg; heart rate <60bpm; unstable angina; unstable insulin-dependent diabetes; clinical need for beta-blockers; therapy with inhaled beta-2 agonists or steroids **Baseline characteristics** Age: mean 63 (IQR 29-88) carvedilol and 63 (25-90) placebo Gender: 1440/1959 male (73.5%); 519 female MI: 100% Hypertension: 55% carvedilol and 52% placebo Treatment Thrombolytic therapy or primary coronary angioplasty: 45% carvedilol and 47% placebo	6.25mg twice daily)			Non-fatal MI	carvedilol and 57/984 (6%) placebo	in previous paper so few here Authors' conclusions In patients treated long-term after an acute MI with left ventricular systolic dysfunction, carvedilol reduced all-cause and cardiovascular mortality and recurrent non-fatal MI
							Outcome 4 Sudden death:	51/975 (5%) carvedilol and 69/984 (7%) placebo	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			Concomitant medications: aspirin 86% carvedilol and 86% placebo; ACE inhibitor: 98% carvedilol and 97% placebo; nitrates: 73% carvedilol and 73% placebo; IV heparin: 65% carvedilol and 63% placebo; subcutaneous heparin 49% carvedilol and 47% placebo; IV diuretics 33% carvedilol and 35% placebo Groups matched at baseline? yes						

Table 147: Chen 2005[107]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author	RCT	Total =	Metoprolol	Metoprolol up	Placebo:	Discharg	**Outcome1**	Metoprolol:	**Source of**

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Chen ZM;Jiang LX;Chen YP;Xie JX;Pan HC;Peto R;Collins R; **Title** Addition of clopidogrel to aspirin in 45852 patients with acute myocardial infarction:randomised placebo-controlled trial" **Journal** Lancet 2005;366:1607-21 China Randomization: Random allocation, unclear methods Allocation concealment: Yes, used	COMMIT-(STEMI) Analysis: ITT	45,852 Metoprolol=22,929 Placebo=22,923 Lost to follow-up Clopidogrel=2 Placebo=0 Inclusion criteria: Post MI recruited within 24 h of suspected acute MI onset (ST elevation Excluded: patients scheduled for PCI: small likelihood of worthwhile benefit, or high risk of AE.	Age: 61.4 ± 11.8 Female:6431 (28%) Time since onset (h):10.3±6.7 ECG abnormality at entry STelevation:19868 (86.7%) Bundle branch block:1431 (6.2%) STdepression (without ST elevation): 1630 (7.1%) Before admission: MI: 1925 (8.4%) Aspirin:4219(18.4%) BB:1484 (6.5%) Fibrinolytic before randomisation: 11407 (49.7%) Non-trial treatment during trial Anticoagulant: 17051 (75%) ACEi: 15397 (67.2%) Antiarrhythmic:5034 (22.0%) Calcium antagonist:2508 (10.9%) Placebo	to 15mg iv. Then 200mg oral daily Concomitant therapy:Fibrinolytic therapy (chiefly urokinase) was received by 50% of patients before or at or after randomisation. During hospital stay, 50% received antiplatelet and 75% received heparin.	Daily for up to 4 weeks (or, if earlier, until hospital discharge or death)	e or up to 4 weeks in hospital	Death from any cause **Outcome 2** Reinfarction (fatal+non-fatal) **Outcome 3**: Stroke (died+survived) - haemorrhagic; ishaemic or unknown **Outcome 4**: Adverse event – (non-cerebral bleeding, pulmonary embolus, AV block, other vascular, respiratory) **Outcome 5:** Bradycardia	1774 /22929 Placebo 1797/22923 Metoprolol: 464 /22929 Placebo 568/22923 Metoprolol: 247 /22929 Placebo 220/22923 Metoprolol: 1417 /22929 Placebo 1337/22923 Metoprolol: 1235 /22929 Placebo 500/22923	**funding:** Sanofi-Aventis, Bristol-Myers Squibb, Astra-Zeneca, MRC UK, BHF, Cancer Research UK. Sponsor: had no role in study design/data collection/data interpretation/or writing of the report Other outcomes Primary Composite of death, reinfarction, or stroke.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
sealed study treatment cases and assigned by removing allocated treatment from an opening at the bottom of the treatment case. Blinding: Unclear, single blind investigator assessing ECG's blind Power calculations: To have at least 95% power to detecte a reduction of one tenth with a two-sided pvalue of 0.05 at least 45,000 patients needed to be			Age: 61.3±11.8 Female:6328 (27.6%) Time since onset (h):10.3 ±6.7 ECG abnormality at entry STelevation:19887 (86.8%) Bundle branch block:1497 (6.5%) STdepression (without ST elevation): 1539 (6.7%) Before admission: MI:1893 (8.3%) Aspirin:4225 (18.4%) BB:1506 (6.6%) Fibrinolytic before randomisation:11387 (49.7%) Non-trial treatment during trial Anticoagulant:17128 (75%) ACEi: 15890 (69.3%) Antiarrhythmic:5209 (22.7%) Calcium antagonist:2898 (12.6%)						Subgroup analysis, including ECG at entry Cardiogenic shock;Heart failure;Cardiac rupture;VF; other cardiac arrest;pulmonary embolus infarction Stroke Cardiogenic shock Heart failure Presumed cardiac rupture Ventricular fibrillation Other cardiac arrest Pulmonary embolism

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
recruited									

Table 148: Fonarow 2007[194]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Fonarow 2007 (CAPRICORN) Country: Multinational Randomisation: not stated Allocation Concealment: not stated Blinding: double blind Power Calculations: not stated	RCT	N= 1959 Drop outs At 30 days: 75/975 on carvedilol and 67/984 on placebo withdrew; at end of study (mean 1.3 years): 117/881 on carvedilol and 107/884 on placebo withdrew; total: 192/975 (19.7%) carvedilol and 174/984	**Inclusion criteria** Acute MI and LVEF ≤40%; receiving ACE inhibitor for at least 48 hours prior to randomisation **Exclusion criteria** continued to need IV diuretics or inotropes; uncontrolled heart failure, systolic BP <90mmHg; heart rate <60bpm **Baseline characteristics** Age: mean 63 (IQR 29-88) carvedilol and 63 (25-90) placebo Gender: 1440/1959 male (73.5%) MI: 100% Hypertension: 55%	Carvedilol (target dose 25mg twice daily, achieved by 73% of patients; 13% on 12.5mg twice daily; rest not stated)	Placebo	mean 1.3 years; these outcome at <6 weeks	**Outcome 1** All-cause mortality **Outcome 2** fatal/non-fatal MI: **Outcome 3** non-fatal MI: bradycardia:	19/975 carvedilol and 33/984 placebo 13/975 (1.3%) carvedilol and 23/984 (2.3%) placebo 11/975 (1.1%) carvedilol and 21/984 (2.1%) placebo 1/975 (0.1%) carvedilol and 0/984 (0%) placebo	Source of funding not stated Limitations details of methodology published in previous paper so few here Authors' conclusions In clinically stabilised post-MI patients with LVD, there is an early

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		(17.7%) placebo Analysis: ITT	carvedilol and 52% placebo Treatment Thrombolytic therapy: 36% carvedilol and 37% placebo; primary coronary angioplasty 12% carvedilol and 13% placebo Concomitant medications: aspirin 86% carvedilol and 86% placebo; lipid-lowering drugs: 22% carvedilol and 24% placebo Groups matched at baseline? yes				hypotension:	15/975 (1.5%) carvedilol and 0/984 (0%) placebo	benefit with carvedilol similar to that seen in long-term therapy

Table 149: Hansteen 1982[259]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
AuthorHansteen 1982 **Journal** BMJ 1982; 284: 155-160.	RCT	N= 560 Drop outs withdrawals (severe angina,	**Inclusion criteria** acute MI; high risk group (increased risk of death: either treated for ventricular fibrillation, asystole or prolonged ventricular tachycardia, or	Propranolol 40mg four times daily, started 4-6 days after infarction, n=278	placebo, n=282	12 months	**Outcome 1** Sudden cardiac death **Outcome 2**	11 propranolol vs. 23 placebo, p=0.038 11 propranolol	Source of funding Norwegian Council fo Cardiovascular Diseases and the

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Country: Norway Randomisation: not stated Allocation Concealment: not stated Blinding: double blind Power Calculations: yes: 700 calculated but premature cessation of recruitment at 2.5 years "to keep up the interest and enthusiasm of the participating centres"		serious arrhythmias, heart failure, sinus bradycardia, stopping treatment >10 days, reinfarction, atrioventricular or sinoatrial block): total 70 (25.2%) propranolol vs. 72 (25.5%) placebo Analysis: ITT	VT of short duration, complicated ventricular asystoles, atrial fibrillation or flutter not previously diagnosed, sinus tachycardia >120 bpm for >3 hours, left ventricular failure) **Exclusion criteria** severe heart failure (i.e. cardiogenic shock or pulmonary oedema) or still having heart failure at randomisation despite treatment with digitalis and frusemide **Baseline characteristics** Age: mean around 58 years (no. of pts 35-64 years: propranolol 218, placebo 203; no. of pts 65-69 years: propranolol 60 and placebo 79) Gender: propranolol 235 (84.5%) and placebo 241 (85.5%) male MI: 100% Previous angina: 85 (30.6%) propranolol and				Fatal reinfarction **Outcome 3** Other cardiac deaths **Outcome 4** Total cardiac deaths **Outcome 5** Total death **Outcome 6** Non-fatal reinfarction **Outcome 7** Total cardiac events (sudden cardiac death, fatal and non-	vs. 10 placebo, NS 0 propranolol vs. 2 placebo, NS 22 propranolol vs. 35 placebo, p=0.079 25 propranolol vs. 37 placebo, NS 16 propranolol vs. 21 placebo, NS 38 propranolol vs. 56 placebo, NS	National Centre for Medical Products Control Limitations underpowered; premature cessation of recruitment; large number of withdrawals Authors' conclusions Propranolol significantly reduced sudden death

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			90 (31.9%) placebo Hypertension: 62 (22.3%) propranolol and 51 (18.1%) placebo Treatment Medical Concomitant medications not stated Groups matched at baseline? yes				fatal reinfarctions, other cardiac deaths) Adverse effects: sinus bradycardia	88 mild + 7 severe propranolol vs. 13 mild + 1 severe on placebo, p<0.05	

Table 150: Hansen 1984[255]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Hansen DA, Jürgensen HJ, Pedersen-Bjergaard O **Title** Effect of acute and long-term beta-adrenergic blockade with alprenolol in	RCT	N=480	Study population: Little detail was provided. The mean age of trial patients is higher than the Danish population. A large proportion were >65 yrs, in this group the mean age was 74 yrs. Mean age: 63. Inclusion criteria All	Alprenolol, 200mg 2x day AM and PM. N=238 Asap after admission	Placebo, N=242	28 days and 12 month follow-up	**Outcome 1** Mortality 12 months. Combined age groups + cumulative total	Alprenolol: 62/238 Placebo: 65/242	**Source of funding** Danish heart foundation No power calculations, so unclear if enough power to detect differences
							Outcome 2 Mortality 28 days Combined age	Alprenolol: 41/140 (238) Placebo: 37/142 (242)	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
definite or suspected myocardial infarction. Causes of death and post-mortem findings with special reference to early deaths. **Journal** Acta Med Scand Suppl. 1984;680:50-8 DENMARK Randomisation : Stratification of patient o risk groups prior to randomisation was done in order to decrease different baseline characteristic.			patients with a suspected or definite acute MI were considered. Patients were eligible regardless of age and duration of the qualifying symptoms. Pre-entry exclusion: Cardiogenic shock, pulmonary oedema >2hrs of treatment, AV block, bradycardia <40 b/min, COPD, labile diabetes mellitus. Death after admission, non-resident in area, treatment with BB on admission, refusal to participate, terminal or other disease.				groups		bw groups. Groups were not matched at baseline. No clear recording of AE
							Outcome 3 Bradychardia	T: 56/238 23.6% P: 36/242 15.2%	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Patients were stratified into 12 risk groups according to age, HR and degree of consciouness. Strata: <50 yrs vs. 51-65 yrs vs.>65. HR on admission <100bpm vs. >100bpm and disturbance of consciousness on admission. Allocation concealment: unclear Blinding Double blind. Power calculations: No, unclear									

Table 151: Norris 1968[429]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Norris **Journal** BMJ 1968; 2: 398-400 Country: New Zealand Randomisation: not stated Allocation Concealment: not stated Blinding: double blind Power Calculations: not stated	RCT	N= 454 with certain or probable MI Drop outs 36 withdrawn (21/226 [9%] propranolol, 15/228 [7%] control) for heart failure (3 vs. 5), hypotension (7 vs. 4), heart block (2 vs. 3), sinus bradycardia (6 vs. 0) or other reasons (3 vs. 3) Analysis: not stated	**Inclusion criteria** MI (criteria: clinical, ECG, enzymes): certain=3 criteria or probable=2 criteria, in last 3 days **Exclusion criteria** initial criteria: shock (BP <90mmHg), heart failure (significant breathlessness at rest or jugular venous congestion >5cm from sterna angle at 45°), heart block, sinus bradycardia (heart rate < 50 per minute); at 6 months, redefined to: acute pulmonary oedema or systolic BP <80mmHg **Baseline characteristics** Age: not stated Gender: not stated MI: 100% Treatment Medical Concomitant medications: anticoagulation at physician's discretion	Propranolol 20mg four times a day, n=226	placebo, n=228	3 weeks	**Outcome 1** Death **Outcome 2** Arrhythmia **Outcome 3** Heart failure **Outcome 4** Hypotension (<90mmHg systolic) **Outcome 5** Further chest pain	31/226 propranolol vs. 24/228 placebo, NS 45/226 (20%) propranolol vs. 75/228 (33%) placebo, p<0.01 38/226 (17%) propranolol vs. 43/228 (19%) placebo, NS 25/226 (11%) propranolol vs. 18/228 (8%) placebo, NS 104/226 (46%) propranolol vs. 119/228 (52%) placebo, NS	**Source of funding** ICI Ltd Limitations short follow up of only 3 weeks Authors' conclusions Propranolol has no place in the routine management of myocardial infarction

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			Groups matched at baseline? stated as yes but no data shown						

Table 152: Pedersen 1983[459]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Pedersen TR. **Title** A multicentre study on timolol in secondary prevention after myocardial infarction" **Journal** Acta Med Scand 1983. Suppl:674:129 Randomisation: block randomisation	RCT ITT analysis. Part of ANON_Norweign 100% patients folllowed-up Withdrew: Timolol: 275/945 (29%)	N=1884 Group I n=247 Group II n=720 Group III n=115	Patients were grouped into 3 Risk Groups: I - recurrent MI II – first MI + transient left ventricular failure III – remaining patients. Inclusion criteria: Diagnosis of AMI within the first 4 days of symptoms..max 6 days. All patients ranging from 20 to 75 years considered eligible. Exclusion criteria: contraindications to BB, serious disease impeding follow-up; need for BB; need for other	Timolol 10mg 2xday. N=945 Treatment was started 7-28 days after onset of symptoms Concomitant therapy, 6-12m Timolol Digitalis:206 BB:1 Anticoagulants:23 Diuretics:190 Antiarrhythmic agents:15	Placebo – similar shape, size and colour but less bitter in taste N=939 Concomitant therapy, 6-12m Placebo Digitalis: 226 BB:5 Anticoagulants:33 Diuretics:234 Antiarrhythmi	Up to 33 months	**Outcome 1** All-cause mortality	Placebo: total n=152/939 Timolol: total n=98/945 Deaths 1-6m: P=71 T=50 7-12m:P=35 T=22 13-24m:P=34 T=18 25-34m:P=12 T=8	High drop out >20% Not matched at baseline for 12 characteristics. Funding: Merch Sharp&Dohme Research Lab, USA.
							Outcome 2 Reinfarction (fatal)	Placebo: total n=22/939 Timolol: total n=13/945	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Blinding: Double blind Allocation concealment: yes, allocation was made by giving the next bottle in numbered sequence to the patient. Power calculation: Sample size was based on sudden cardiac death as the end point, and not All-cause mortality which would have required a more "generous" sample estimate. However,	Placebo: 219/939 (23%)		concomitant therapy; alternative reasons including patient refusal. Placebo M:F: 78:22 % Age:61.4 Angina: 362 (38.6%) Treated hypertension: 203 (21.6%) Diabetes: 46 (4.6%) Risk factors: Pulmonary rales:291 (31%) Third hear sound: 42 (4.5%) Pulmonary congestion: 54 (5.8%) Enlarged heart: 218 (23.2%) SBP: 238 (25.3%) AF: 96 (10.2%) Aflutter:32 (3.4%) Time of MI to start of medication: mean 11.6 days Timolol	Salicylates: 1	c agents:17 Salicylates:3				
							Outcome 3 Cardiac mortality	Placebo: total n=142/939 Timolol: total n=83/945	
							Outcome 4 Sudden death	Placebo: total n=44/939 Timolol: total n=18/945	
							Outcome 5 HR <40 BPM (Brachycardia)	Placebo: n=3/939 Timolol: n=47/945	
							Outcome 6 Dizziness:	Placebo: n=34/939 Timolol: n=53/945	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
estimate were made for each of the Risk Groups I and II, to have the possibility to reach a conclusion in one group of patients even if the other Risk Group turned out to behave differently and the study had to be stopped for a particular group. The power for the entire study with respect to All-cause mortality with the given alpha and the postulated treatment effect was larger than			M:F: 80:20% Age: 60.3 yrs Angina: 364 (38.5%) Treated hypertension: 172 (18.2%) Diabetes: 53 (5.6%) Risk factors: Pulmonary rales:282 (29.8%) Third hear sound:33(3.5%) Pulmonary congestion:58 (6.1%) Enlarged heart: 202 (21.4%) SBP:213 (22.5%) AF:87 (9.2%) Aflutter:33 (3.5%) Time of MI to start of medication:11.4 days						

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
for each Risk Group and large enough to warrant an investment in resources									

Table 153: Poulsen 2000[483]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Poulsen 2000 Country: Denmark Randomisation: not stated Allocation Concealment: not stated Blinding: double blind Power Calculations:	RCT	N= 59 Drop outs none Analysis: appropriate	**Inclusion criteria** acute MI (enzymes, ECG and chest pain); in sinus rhythm; aged 40-75 years **Exclusion criteria** ongoing treatment with beta-blockers, systolic BP <100mmHg; heart rate <50 bpm; LV ejection fraction <25%, intermittent claudication, significant valvular heart disease, severe obstructive lung disease, 2nd or 3rd degree heart block, uncontrolled diabetes	Metoprolol XL 200mg	Placebo	Planned: 12 months; data at 3 months in this paper	**Outcome 1** Peak exercise capacity **Outcome 2** Residual myocardial ischaemia **Outcome 3** Time to 1mm ST-segment depression	135+/-29W metoprolol vs. 126+/-34 W placebo (p<0.01) 15/29 metoprolol patients and 13/30 placebo 430+/-100sec metoprolol vs. 333+/-130sec placebo (p<0.02)	Source of funding not stated Limitations No routine angiographic studies performed; results may not be generalisable to older patients Authors' conclusions Metoprolol increases

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
not stated			mellitus, severe uncontrolled congestive ehart failure, other life-threatening disease **Baseline characteristics** Age: metoprolol 62 +/-9 years; placebo 61+/-9 years Gender: 46 men, 13 women MI: 100% Hypertension: 6/29 (21%) metoprolol and 7/30 (23%) placebo Treatment Medical; thrombolysis: 19/29 (66%) metoprolol and 21/30 (70%) placebo Concomitant medications aspirin: 27/29 (93%) metoprolol and 29/30 (97%) placebo; nitrates6/29 (21%) metoprolol and 7/30 (23%) placebo; calcium antagonist: 3/29 (10%) metoprolol and 5/30 (17%) placebo;				**Outcome 4** Ejection fraction	50+/-10% metoprolol vs. 48+/-9% placebo	exercise capacity after 3 months and this change seems related to improvement of LV diastolic filling after acute MI

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			diuretics 6/29 (21%) metoprolol and 5/30 (17%) placebo; ACE inhibitor: 10/29 (35%) metoprolol and 9/30 (30%) placebo Groups matched at baseline? yes						

Table 154: Roque 1987[509]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Roque 1987 **Journal** Circulation 1987; 76: 610-617. Country: Multinational Randomisation: not stated Allocation	RCT	N= 200 Drop outs treatment discontinued in 13/102 (13%) timolol vs. 17/98 (17%) placebo, NS (e.g. for systolic arterial hypotension <90mmHg,	**Inclusion criteria** acute MI (pain 30 minutes or more, onset < 6 hours previously, enzymes, consent); no ECG criteria used **Exclusion criteria** evolution > 6 hours; on beta-blockers, amiodarone, calcium channel blockers or digitalis at entry; left ventricular failure, insulin dependent	Timolol, total dose 5.5mg (1mg initial dose, 1.5mg at 10 mins; 1.5mg at 1 hour and 1.5mg at 2 hours) intravenously, started within 6 hours of onset of pain, then 2 hours after last IV dose, 10mg orally every 12	Placebo, n=98	1 month during treatment + 2 years after (mean 24 months; range 6-35 months)	**Outcome 1** Cumulative total creatine kinase release (reflecting amount of cardiac necrosis) at 4 days **Outcome 2**No. of patients with ≥1 episode of	1274 +/- 73 IU/L timolol (n=81) vs. 1677 +/- 132 IU/L placebo (n=83), p<0.01 7/82 (8.5%) timolol vs. 16/80 (20%) placebo,	**Source of funding** Merck Sharp and Dohme Limitations study not powered to assess mortality Authors' conclusions early treatment

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Concealment: not stated Blinding: double blind Power Calculations: yes: sample size selected to detect a 30% difference in cumulative creatine kinase (CK) release between groups with power 80% and significance 0.05 (number required not stated)		bradycardia <45 bpm that was symptomatic or lasted > 1 hour, second or third degree atrioventricular block, left ventricular failure, bronchospasm requiring treatment, stroke or need for coronary artery surgery Analysis: appropriate	diabetes, bradycardia, hypotension, bronchospasm, severe concomitant disease, nonischaemic heart disease, intermittent claudication, previous cardiac surgery Baseline characteristics Age: mean 53+/- 1 years timolol and 52 +/- 1 years placebo Gender: timolol: 86 men (84.0%), 16 women; placebo: 89 men (91.0%) and 9 women MI: 100% Hypertension: 32.4% timolol and 29.6% placebo Treatment Medical Concomitant medications not stated Groups matched at baseline? yes	hours for 1 month, n=102			ventricular tachycardia on Holter readings days 7, 14, 21 and 28 **Outcome 3** Death within first month (during treatment) **Outcome 4** Death by 24 months (after treatment stopped)	p=0.05 3/102 timolol (2.9%) vs. 7/98 (7.1%) placebo 7/102 (6.9%) timolol vs. 12/98 (12.2%) placebo, NS	of patients with MI with IV timolol followed by oral timolol reduced infarct size and decreased the number of patients with ventricular tachycardia in the first month; this therapy should be considered in patients without contraindication to timolol admitted soon after the onset of pain.

Table 155: Taylor 1982[573]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Taylor 1982 Country: UK Randomisation: not stated Allocation Concealment: not stated Blinding: double blind Power Calculations: sample size based on 25% reduction in cardiac events at 0.05, predicted total event rate	RCT	N= 1103 Drop outs 183/632 (29%) withdrawn from oxprenolol and 141/471 (30%) from placebo Analysis: ITT	**Inclusion criteria** male; 1 or more confirmed MIs (2 or more of pain, ECG changes and enzymes); < 65 years **Exclusion criteria** heart failure, pulmonary venous congestion, heart rate < 50/min; any grade heart block; symptomatic obstructive airways disease or history of bronchial asthma; diabetes mellitus requiring medication; hypertension (diastolic > 100mmHg); treatment with antidysrhythmics, beta-blockers, salicylates, anticoagulants, antiplatelet drugs, positive inotropic agents; other serious	Oxprenolol 40mg twice a day, n=632	Placebo, n=471	Mean 48 months (range 6-84 months)	**Outcome 1** Death	60/632 (9.5%) oxprenolol vs. 48/471 placebo (10.2%)	**Source of funding** Ciba-Geigy, Yorkshire Regional Hospital Board, West Riding Medical Research Trust Limitations randomisation and allocation concealment not stated; large number of withdrawals in both groups Authors' conclusions

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
10%/year, drop out 8% per year			systemic illnesses, valvular or non-ischaemic heart disease; administrative difficulties (e.g. living far from centre, language problems, antisocial activities, unreliability) Baseline characteristics Age: mean 51 years Gender: all male MI: 100% Treatment Medical Concomitant medications not stated Groups matched at baseline? yes				All-cause mortality MI <1 y MI>1 yr	BB = 22/388 P = 32/285 BB = 38/244 Placebo = 11/168	overall no difference in mortality or cardiac events between groups; benefit of oxprenolol if started within 4 months of MI; same mortality rate if started 5-12 months; oxprenolol group had higher mortality after starting 1-7.5 years after MI
							CV mortality MI < 1yr MI >1 yr	BB = 44/388 P = 62/285 BB = 32/244 P = 10/168	
							Reinfarction MI < 1yr MI>1yr	BB = 39/388 P = 34/285 BB=28/244 P = 24/168	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
							Hypotension	2/632 oxprenolol vs. 1/471 placebo	
							Fatigue	3/632 oxprenolol vs. 3/471 placebo	

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments

Table 156: Wilcox 1980[618]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Wilcox 1980 **Journal** BMJ 1980; 885-888. Country: UK Randomisation: predetermined code Allocation Concealment: not stated Blinding: double blind Power Calculations: not stated	RCT	N=388 Drop outs withdrawn at 6 weeks: 44/132 (33%) on propranolol, 51/127 (40%) on atenolol and 40/129 (31%) on placebo (due to heart failure, heart block, bradycardia, hypotension, dysrhythmia requiring beta-	**Inclusion criteria** MI in last 24 hours (clinical, ECG, enzyme) **Exclusion criteria** Already on beta-blocker; severe heart failure (breathlessness, elevated jugular venous pressure, crepitations); sinus bradycardia <40 bpm, second or third degree heart block; systolic BP <90mmHg; history of asthma or diabetes mellitus; not a resident of Nottingham; already in another study **Baseline characteristics** Age: Propranolol: <35 years: 5; 35-45: 17; 45-55: 44; 55-65: 43; >65:	Propranolol 40mg three times daily (n=132) or atenolol 50mg twice daily plus midday placebo (n=127); at 6 weeks, changed to propranolol 80mg twice daily or atenolol 50mg twice daily, within 12 hours of onset of pain	placebo three times daily, n=129	1 year	**Outcome 1** Death at 6 weeks **Outcome 2** Further deaths between 6 weeks and 1 year **Outcome 3** Total deaths at 1 year **Outcome 4** Cold hands and feet	10/132 (7.5%) propranolol, 11/127 (8.5%) atenolol and 15/129 (11.6%) placebo, NS 7 propranolol, 8 atenolol, 4 placebo 17 propranolol, 19 atenolol, 19 placebo 78/259 (30%)	Source of funding Imperial Chemical Industries Limitations unclear if adequately powered; high withdrawal rate Authors' conclusions immediate prophylactic treatment with a beta-blocker is unlikely to be helpful

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		blocker, angina not controlled with glyceryl trinitrate, not MI or non-compliance) and between 6 weeks and 1 year a further 17 (13%) propranolol, 9 (7%) atenolol and 10 (8%) placebo withdrawn Analysis: ITT	23. Atenolol: <35 years: 5; 35-45: 13; 45-55: 45; 55-65: 35; >65: 29. Placebo: <35 years: 3; 35-45: 21; 45-55: 40; 55-65: 40; >65: 25 Gender: Propranolol: 111 men, 21 women Atenolol: 113 men, 14 women Placebo: 104 men, 25 women MI: 100% Previous angina: Propranolol: 36/132 (27%); Atenolol: 40/127 (31%); Placebo: 31/129 (24%) Hypertension: Propranolol: 15/132 (11%); Atenolol: 13/127 (10%); Placebo: 20/129 (16%) Treatment Medical Concomitant medications not stated Groups matched at baseline? yes				**Outcome 5** Muscle fatigue **Outcome 6** Bowel upsets **Outcome 7** Angina	on beta-blockers vs. 9/129 (7%) placebo, p<0.001 57/259 (22%) on beta-blockers vs. 17/129 (13%) placebo, p<0.005 49/259 (19%) on beta-blockers vs. 5/129 (4%) placebo, p<0.001 26/259 (10%) on beta-blockers vs. 25/129 (19%) placebo, p<0.05	because the 1-year survival rates did not differ between groups.

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments

Table 157: Yoshitomi 2000[629]

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Author Yoshitomi 2000 **Journal** Am Heart J 2000; 140: e27 Country: Japan Randomisation: not stated Allocation Concealment: sealed envelopes Blinding: double blind Power Calculations: none	RCT	N= 60 Drop outs none Analysis: appropriate	**Inclusion criteria** MI (pain >30 minutes starting <4 hours previously; ECG; enzymes); 17/60 (28%) patients with congestive heart failure (Bisoprolol 6 [30%], Imidapril 4 [20%], Placebo:7 [35%]) **Exclusion criteria** cardiogenic shock, failed reperfusion therapy, re-occlusion of the infarct-related artery during 1-year follow-up, significant valvular heart disease or cardiomyopathy **Baseline characteristics** Age: Bisoprolol: mean 61 +/-9 years, Imidapril: 61+/-12 years, Placebo: 59 +/-11 years	Bisoprolol 2.5mg (dose titration on day 3 if BP > 110/80mmHg and heart rate >55bpm; target maintenance dose 5mg once daily, reached by all patients), n=20 started within 24 hours of pain and continued for 1 year	Imidapril 2.5mg (dose titration on day 3 if BP > 110/80mmHg and heart rate >55bpm; target maintenance dose 5mg once daily, reached by all patients), n=20 or placebo n=20	1 year	**Outcome 1** Mean pulmonary capillary wedge pressure at 1 year **Outcome 2** Left ventricular end diastolic pressure at 1 year	Bisoprolol 12+/-7mmHg; imidapril 8+/-2mmHg, placebo 9+/-4mmHg, p<0.01 between bisoprolol and imidapril; all p<0.01 vs. baseline Bisoprolol 17+/-8mmHg; imidapril 11+/-4mmHg, placebo 15+/-6mmHg, p<0.01 between bisoprolol and imidapril; imidapril and	Source of funding not stated Limitations small number of patients; underpowered; not designed to assess the effects of early beta-blockers on long-term mortality or morbidity rates after MI Authors' conclusions early treatment

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			Gender: Bisoprolol: 12 men, 8 women; Imidapril: 19 men, 1 woman; Placebo: 17 men, 3 women MI: 100% Hypertension: Bisoprolol 12 (60%); Imidapril 13 (65%); Placebo: 12 (60%) Treatment All patients had reperfusion therapy (direct percutaneous transluminal coronary angioplasty, primary stent implantation or percutaneous transluminal coronary recanalization by means of intra-coronary infusion of prourokinase; successful reperfusion defined as coronary blood flow improved to TIMI grade 3 Concomitant medications All patients had aspirin and long-acting nitrates; diuretics used in 8 patients with congestive heart failure;				**Outcome 3** Mean change (%) in left ventricular function baseline to 3 months **Outcome 4** Mean change (%) in left ventricular function baseline to 12 months **Outcome 5** Major adverse cardiac events (AMI, CABG or death)	placebo p<0.01 vs. baseline but bisoprolol NS Bisoprolol 5+/-8%; imidapril 6+/-9%, placebo 4+/-10%, NS Bisoprolol 5+/-7%; imidapril 6+/-7%, placebo 2+/-8%, NS none	with beta-blockers shows less decline in the indicators of preload and increases left ventricular volume in AMI; this treatment cannot prevent ventricular remodelling. Early treatment with ACE inhibitors attenuates ventricular remodelling.

Reference	Study type	Number of patients	Patient Characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			45/60 (75%) calcium channel antagonists Groups matched at baseline? yes except sex distribution (bisoprolol M 12/ F 8, imidapril 19/1, placebo 17/3), p<0.01						

G.4.9 Antiplatelets

G.4.10 Beta-blocker initiation

Table 158: Califf 2009[91]

Reference	Study type	No. of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Author Califf et al 2009 **Journal** (VALIANT trial) **Title** Usefulness of beta blockers in high-risk patients after myocardial	RCT of valsartan vs. captopril vs. valsartan plus captopril (beta-blockers not	N= 14,703 Drop outs 30 patients died Analysis: observational analysis of RCT data	Inclusion criteria Patients with MI (direct population) and left ventricular systolic dysfunction or heart failure or both Exclusion criteria not stated	Beta-blocker initiated for acute MI before randomisation (mean of 4.9 days after MI): group 1 (n=9851) patients who were still on beta-blockers at	Beta-blocker initiated for acute MI after randomisation (mean of 4.9 days after MI) but before hospital discharge:	Around 1050 days	**Outcome 1** Survival (excluding first 45 days after MI)	Hazard ratio (HR) 0.88 (95% CI 0.79 to 0.98) group 1 vs. group 4 (i.e. use at both time points better than no use of beta-blocker)	Source of funding not stated Limitations patients not randomly assigned to beta-
								HR 0.84 (0.73	

infarction in conjunction with captopril and/or valsartan (from the VALsartan In Acute Myocardial Infarction [VALIANT] trial). **Journal** Am J Cardiol 2009; 104: 151-157 Country: Multi-national Randomisation: Not stated Allocation Concealment: Not stated Blinding: Not stated Power Calculations: Not stated	randomised)		Baseline characteristics Age: median (25th, 75th percentiles) group 1: 64.1 (54.3, 72.9); group 2 67.7 (58.7, 75.0); group 3 67.6 (59.1, 73.8); group 4:69.8 (61.9, 76.4), p<0.001; Gender number of males (%): group 1: 6954/9851 (70.6%); group 2: 947/1402 (67.5%); group 3: 513/786 (65.3%); group 4: 1657/2576 (64.3%), p<0.001; MI: 100% Total angina: group 1: 3758/9851 (31.1%); group 2: 578/1402 (41.2%); group 3: 331/786 (42.1%); group 4: 1146/2576 (44.5%), p<0.001; Hypertension: group 1: 5442/9851 (55.3%); group 2: 755/1402 (53.9%); group 3: 443/786 (56.4%); group 4: 1435/2576 (55.7%), NS Treatment for acute MI: PCI group 1: 1669/9851 (16.9%); group 2 188/1402 (13.4%); group	discharge and group 2 (n=1402) who had stopped beta-blockers by discharge. Timing of discharge not stated	group 3 (n=786) or group 4 (n=2576) no beta-blocker use at all. Timing of discharge not stated			to 0.96) group 1 vs. group 2 (i.e. continuing beta-blocker better than stopping)	blockers and major differences between groups receiving or not receiving treatment; specific drug used, dose and adherence not recorded
								HR 0.86 (0.72 to 1.03) group 1 vs. group 3 (i.e. no difference between early initiation and later initiation)	
								HR 1.05 (0.91 to 1.22) group 2 vs. group 4 (i.e. stopping before discharge no better than no use of beta-blocker)	
								HR 1.02 (0.85 to 1.24) group 3 vs. group 4 (i.e. later start of beta-blocker no better than no use of beta-blocker)	
								HR 1.03 (0.83 - 1.27) group 2 vs. group 3	

			3 80/786 (10.2%); group 4: 226/2576 (8.8%), p<0.001; CABG group 1: 193/9837 (2.0%); group 2 63/1398 (4.5%); group 3 8/784 (1.0%); group 4: 48/2571 (1.9%), p<0.001 Concomitant medications (for the acute MI): aspirin group 1: 8899/9851 (90.3%); group 2: 1275/1402 (90.9%); group 3: 679/786 (86.4%); group 4: 2159/2576 (83.8%), p<0.001; ACE inhibitor group 1: 4165/9851 (42.3%); group 2: 619/1402 (44.2%); group 3: 300/786 (38.2%); group 4: 1050/2576 (40.8%), p=0.025; glycoprotein IIb/IIIa inhibitor group 1: 1484/9851 (15.1%); group 2: 158/1402 (11.3%); group 3: 59/786 (7.5%); group 4: 207/2576 (8.0%), p<0.001; angiotensin receptor blocker group 1: 120/9851 (1.2%); group 2: 23/1402 (1.6%); group 3: 7/786 (0.9%); group 4: 35/2576 (1.4%),					(i.e. before randomisation vs. discharge only)	

			NS; thrombolytic group 1: 3739/9851 (38.0%); group 2: 493/1402 (35.2%); group 3: 232/786 (29.5%); group 4: 673/2576 (26.1%), p<0.001 Groups matched at baseline? No						

Table 159: Roberts 1991[502]

Reference	Study type	No. of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Author Roberts et al 1991 (TIMI II-B study) **Title** "Immediate versus deferred beta-blockade following thrombolytic therapy in patients with acute myocardial infarction. Results of the	RCT	N= 1434 eligible for beta-blocker substudy Drop outs data on the primary end point available for 84% of patients (similar in the two groups) Analysis: intention	**Inclusion criteria** Patients with acute MI (direct population); ≤75 years of age; treated ≤4 hours after onset of chest pain **Exclusion criteria** history of CVA, BP ≥180mmHg systolic or >110mmHg diastolic, bleeding disorder, surgery in previous 2 weeks, recent prolonged CPR, PTCA or severe trauma within 6 months, previous CABG, prosthetic heart valve replacement, left bundle branch block, dilated cardiomyopathy, other serious illness; implanted pacemaker, resting	Immediate (as soon as possible after initiating recombinant tissue-type plasminogen activator (rt-PA) beta-blocker (intravenous then oral metoprolol, 50mg every 12 hours for first 24 hours, then 100mg every 12 hours) n=720	delayed (6-8 days) beta-blocker therapy (metoprolol 50mg every 12 hours for first 24 hours, then 100mg every 12 hours) n=714	1 year	**Outcome 1** Global left ventricular ejection fraction	Around 50%, no difference between groups prior to discharge or at follow up	**Source of funding** National Heart, Lung, and Blood Institute, National Institutes of Health Limitations Inadequately powered to investigate subgroups (e.g. high and low risk patients)
							Outcome 2 Death	At 6 days: immediate: 17/720 (2.4%) vs. delayed 17/714 (2.4%), NS; at 6 weeks: 26/720 (3.6%) immediate vs. 25/714 (3.5%) deferred, NS; at 1 year 34/720 (4.8%) vs. 35/714 (5.0%), NS	
							Outcome 3 Death or reinfarction	At 6 days: immediate: 34/720 (4.7%) vs. delayed 50/714 (7.0%),	

Reference	Study type	No. of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
Thrombolysis in Myocardial Infarction (TIMI) II-B Study" **Journal** Circulation 1991; 83: 422-437 "Immediate versus deferred beta-blockade following thrombolytic therapy in patients with acute myocardial infarction. Results of the Thrombolysis in Myocardial Infarction (TIMI) II-B Study" Country:		to treat	ventricular rate <55 beats per minute, systolic BP < 100mmHg, moist rales that did not clear with coughing extending above the lower third of the lung fields or pulmonary oedema on chest x-ray, advanced first-degree or more heart block, history of asthma, wheezing on examination, COPD requiring chronic corticosteroids or beta-2 stimulants, beta-blocker, verapamil or diltiazem on admission Baseline characteristics Age: mean immediate beta-blocker: 54.8 years; deferred beta-blocker: 55.2 years, NS Gender number male (%): immediate beta-blocker: 620/720 (86.1); deferred beta-blocker: 603/714 (84.4%), NS MI: 100% Hypertension: immediate beta-blocker: 216/720 (30.0%); deferred beta-blocker: 219/714 (30.7%)	IV rt-PA was initiated at a mean of 2.6 hrs after onset of chest pain. 90.4% received iv metroprolol at a mean of 42 minutes after initiation of rt-PA				p=0.07; at 6 weeks: 52/720 (7.2%) immediate vs. 69/714 (9.7%) deferred, NS; at 1 year 84/720 (11.8%) vs. 93/714 (13.1%), NS	reliably
							Outcome 4 Fatal or non-fatal reinfarction	At 6 days: 19/720 (2.7%) immediate vs. 36/714 (5.1%) deferred (p=0.02); at 6 weeks: 32/720 (4.5%) vs. 51/714 (7.3%) ,p=0.03; at 1 year 60/720 (8.6%) vs. 67/714 (9.6%), NS	
							Outcome 5 Non-fatal reinfarction	At 6 days: 17/720 (2.4%) immediate vs. 33/714 (4.7%) deferred (p=0.02); at 6 weeks: 28/720 (4.0%) vs. 46/714 (6.6%) ,p=0.03; at 1 year 54/720 (7.8%) vs. 61/714 (8.8%), NS	
							Outcome 6 Fatal	At 6 days: 2/720 (0.3%) immediate vs. 3/714 (0.4%) deferred, NS; at 6 weeks: 5/720	

Reference	Study type	No. of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
USA Randomisation: not stated Allocation Concealment: not stated Blinding: not stated Power Calculations: yes: study goal of 340 patients in each of the four treatment groups (invasive or conservative strategy; immediate or delayed beta-blockers) had 80%			Treatment: all treated with rt-PA Concomitant medications: all patients received lidocaine, heparin and aspirin Groups matched at baseline? yes				reinfarction	(0.7%) vs.7/714 (1.0%), NS; at 1 year 9/720 (1.3%) vs. 8/714 (1.2%), NS	
							Outcome 7 Severe ischaemic event	At 6 weeks: 92/720 (13.0%) immediate vs. 102/714 (14.5%) deferred, NS; at 1 year 170/720 (24.4%) vs. 170/714 (24.5%), NS	

Reference	Study type	No. of patients	Patient Characteristics	Intervention	Comparison	Follow-up	Outcome measures	Effect sizes	Comments
power to detect differences of 3 units in mean resting ejection fraction between groups.									

Appendix H: Economic evidence tables

H.1 Cardiac rehabilitation

H.1.1 Interventions to increase uptake of and adherence to cardiac rehabilitation

Table 160: Jolly 2009[296]

Jolly K, Lip GYH, Taylor RS, Raftery J, Mant J, Lane D et al. The Birmingham rehabilitation uptake maximisation study (BRUM): a randomised controlled trial comparing home-based with centre-based cardiac rehabilitation. Heart. 2009; 95(1):36-42.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CCA ‡ **Study design:** Within RCT (BRUM, 2009 [296]) analysis **Approach to analysis:** the base-case analysis was the comparison between home and hospital rehabilitation, costed as in the trial, plus other cardiac-related NHS costs and inclusion of patients' travel costs in the hospital (societal perspective). Sensitivity analysis scenarios included a pro-hospital one based on direct costs to the	**Population:** 525 patients referred to four hospitals for cardiac rehabilitation following myocardial infarction or coronary revascularisation. **Cohort settings:** Start age = 61 M = 76-77% **Intervention 1:** Centre based programmes that varied in length, including 9 sessions at weekly intervals, 12 sessions over 8 weeks and 24 individualised sessions over 12 weeks. **Intervention 2:**	**Total costs (mean per patient):** Intvn 1: £157 Intvn 2: £198 Incremental (2-1): £41 (95% CI NR; p=NR) **Currency & cost year:** UK pounds (cost year NR). **Cost components incorporated:** Costs included in the study account for patients use of rehabilitation services and from participants on their use of general practice and hospital services and drug use for secondary prevention and staff costs. Direct cost per patient in the home arm: cost of each home visit and	**EQ5D (mean per patient)** Intvn 1: NR Intvn 2: NR Incremental (2-1): NR (95% CI NR; p>0.05‡) The change in EQ5D from baseline to 12 months was slightly higher in the centre-based arm but was not statistically significant. Note: Effect sizes will be added from clinical review.	**ICER (Intvn 2 vs Intvn 1):** Intervention 1 is dominant **Analysis of uncertainty**: When all costs including those to patients of travel to centres was included (societal cost per patient), the hospital arm became more costly than the home intervention arm, but with overlapping confidence intervals. The mean cost per patient was sensitive to how the service was organised. If telephone consultations were assumed to replace all the nurse visits in the home arm, the cost per patient would have fallen below that for the centre-based arm and vice versa if hospital staff required estra time to prepare for rehabilitation sessions.

Jolly K, Lip GYH, Taylor RS, Raftery J, Mant J, Lane D et al. The Birmingham rehabilitation uptake maximisation study (BRUM): a randomised controlled trial comparing home-based with centre-based cardiac rehabilitation. Heart. 2009; 95(1):36-42.				
NHS and one pro-home in which the costs of home visits were replaced by hypothetical telephone consultations. Intervention to increase adherence. **Perspective:** UK NHS **Time horizon:** 12 months **Discounting:** n/a	The home based programme consisted of a manual, three home visits and telephone contact at 3 weeks. Patients who had had an MI were discharged home with the Heart Manual.	associated telephone calls, nurse's travel and travel time and cost of the Heart Manual (including training). Direct cost in the hospital arm: cost per rehabilitation session in each hospital multiplied per the number attended.		
Data sources				
Health outcomes: Within-RCT (BRUM, 1999 [296]) analysis. **Quality-of-life weights:** EQ-5D UK tariff. Within RCT analysis (BRUM). **Cost sources:** resource use was collected by hospital staff during the BRUM trial. Unit costs were based on national costs.				
Comments				
Source of funding: UK Department of Health through its Health Technology Assessment Programme. National Heart Association funded the development of the Heart Manual for patients following a revascularisation procedure. **Limitations:** Analysis only includes one of a number of interventions to increase adherence identified by clinical review (TBC following GDG discussion). Cost year unclear. While change in EQ5D utility was described, full cost effectiveness results are not reported in terms of ICERs and the joint distribution of costs and effects. EQ5D tariff used not stated. Baseline health outcome and estimates of resource use were not stated as identified by a systematic review but seemed reasonable (within RCT analysis). EQ5D described narratively only – no figures. Limited sensitivity analysis.				
Overall applicability*: Potentially applicable Overall quality: Potentially serious limitations**				

Abbreviations: CI = Confidence interval; CCA = cost-consequence analysis; EQ-5D = Euroqol five dimensions (scale: 0.0 [death] to 1.0 [full health]; <0.0 = worse than death); HDL = High density lipoprotein; ICER = incremental cost-effectiveness ratio; MI = Myocardial infarction; NR = not reported; QALYs = quality-adjusted life years

‡ It is not clear if QALYs were calculated. Change from baseline EQ5D was discussed but numerical values not reported. Directly applicable / partially applicable / Not applicable; ** Minor limitations /potentially serious limitations / Very serious limitations*

H.2 Drug therapy

H.2.1 ACE inhibitor vs. placebo and optimal duration of treatment

Table 161: Briggs [78]2007

A. Briggs, B. Mihaylova, M. Sculpher, A. Hall, J. Wolstenholme, M. Simoons, J. Deckers, R. Ferrari, W. J. Remme, M. Bertrand, and K. et al Fox. Cost effectiveness of perindopril in reducing cardiovascular events in patients with stable coronary artery disease using data from the EUROPA study. Heart 93 (9):1081-1086, 2007.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome = QALYs) **Study design:** Markov state transition model based on the EUROPA study.[195] **Approach to analysis:** Probabilistic Markov model. Health states: trial entry state, cardiovascular death, non-cardiovascular death, non-fatal event history 1 (NFE1), non-fatal event history 2 (NF2). People could only remain in the NFE1 state for one year after which they	**Population‡:** Patients with stable coronary artery disease (CAD). SUBGROUP A: patients with a 5-year risk of events = 29% SUBGROUP B: patients with a 5-year risk of events = 14% SUBGROUP C: patients with a 5-year risk of events = 8% SUBGROUP D: patients with a 5-year risk of events = 7%	**Incremental costs (mean per patient) – Intvn 2 – Intvn 1: ¥** SUBGROUP A: £390 SUBGROUP B: £346 SUBGROUP C: £478 SUBGROUP D: £443 SUBGROUP E: £499 **Currency & cost year:** 2005 UK pounds **Cost components incorporated:** Perindopril, concomitant	**Incremental QALYs (mean per patient) – Intvn 2 – Intvn 1: ¥** SUBGROUP A: 0.104 SUBGROUP B: 0.054 SUBGROUP C: 0.049 SUBGROUP D: 0.031 SUBGROUP E: 0.016	**ICER (Intvn 2 vs Intvn 1):** £9,700 per QALY gained (median of the distribution) Probability Intvn 2 cost-effective (£20K/30K threshold): 88%/97% SUBGROUP A: = £3,729 per QALY gained 95% CI: £2,400/QALY - £9,000/QALY Probability Intvn 2 cost-effective (£20K/30K threshold): 100%/100% SUBGROUP B: £6,408 per QALY gained 95% CI: £3,200/QALY - £17,000/QALY Probability Intvn 2 cost-effective (£20K/30K threshold): 99%/100% SUBGROUP C: ££9,700 per QALY gained CI: £5,500/QALY; £24,000/QALY Probability Intvn 2 cost-effective (£20K/30K threshold): 94%/99%

A. Briggs, B. Mihaylova, M. Sculpher, A. Hall, J. Wolstenholme, M. Simoons, J. Deckers, R. Ferrari, W. J. Remme, M. Bertrand, and K. et al Fox. Cost effectiveness of perindopril in reducing cardiovascular events in patients with stable coronary artery disease using data from the EUROPA study. Heart 93 (9):1081-1086, 2007.				
moved to the NF2 or they had an event. At the NF2 the probability of event was lower and they could also stay in that health state. **Perspective:** UK NHS **Time horizon:** 50 years **Treatment effect duration:** Lifetime treatment effect. **Discounting**: Costs = 3.5%; Outcomes = 3.5%	SUBGROUP E: patients with a 5-year risk of events = 3% **Cohort settings:** Start age = 60 M = 85.4% **Intervention 1:** Placebo. **Intervention 2:** Perindopril; 8 mg daily; 3.7 years of median treatment duration with a mean follow up of 4.2 years.	cardiac drugs, inpatient days in hospital by speciality, costs for the different health states adjusted for some covariates (age, diabetes mellitus, angina or heart failure, creatinine clearance, use of nitrates at baseline, use of calcium channel blockers at baseline, use of lipid lowering drugs at baseline, treated in UK).		SUBGROUP D: £14,163 per QALY gained CI: £6,800/QALY; £40,000/QALY Probability Intvn 2 cost-effective (£20K/30K threshold): 75%/93% SUBGROUP E: £31,195 per QALY gained CI: £17,200/QALY; £83,000/QALY Probability Intvn 2 cost-effective (£20K/30K threshold): 8%/41% **Analysis of uncertainty:** Results did not change under the following scenarios: the treatment effect was assumed to be limited to the treatment duration perindopril was assumed not to have any protective effect on events subsequent to a first event
Data sources				
Health outcomes: Probabilities of secondary cardiovascular events and relative treatment effects were estimated from risk equations based on the EUROPA study [195]. Non-cardiovascular mortality by age and sex taken from the life tables for England and Wales and for Scotland [218,434], mid-2003 population estimates by age and sex [435] and deaths by age and sex and underlying cause for 2003 obtained from the General Register Office, Edinburgh [219] **Quality-of-life weights:** SF-36 data was used to calculate SF-6D. They assigned quality of life weights obtained from the Welsh Health Survey (1998) to each of the model states. **Cost sources:** Drug costs and hospitalisation costs based on standard doses with national unit costs; health state costs estimated from observed costs in the EUROPA study.				
Comments				
Source of funding: Servier Laboratories, manufacturers of perindopril. **Limitations:** Changes in HRQoL not reported specifically from post MI patients and/or carers but from a cross-section of the population with a range of illnesses or disabilities and on similar groups of healthy people. The changes in HRQoL were not estimated by using EQ-5D but SF-36. Estimates of resource use and relative treatment effects were based on one of 40 trials included in our clinical review. Transition probabilities were estimated using risk equations that were based on a composite primary end point from the EUROPA trial. The same limitation in the EUROPA trial was identified				

A. Briggs, B. Mihaylova, M. Sculpher, A. Hall, J. Wolstenholme, M. Simoons, J. Deckers, R. Ferrari, W. J. Remme, M. Bertrand, and K. et al Fox. Cost effectiveness of perindopril in reducing cardiovascular events in patients with stable coronary artery disease using data from the EUROPA study. Heart 93 (9):1081-1086, 2007.
in the clinical review.
Overall applicability*: Partially applicable Overall quality: Potentially serious limitations**

Abbreviations: CUA = cost-utility analysis; da = deterministic analysis; EQ-5D = Euroqol five dimensions (scale: 0.0 [death] to 1.0 [full health]; <0.0 = worse than death); HRQoL = Health related quality of life; ICER = incremental cost-effectiveness ratio; NR = not reported; pa = probabilistic analysis; QALYs = quality-adjusted life years; SF-36 = The Short Form Health Survey; SF-6D = instrument composed of six multilevel dimensions used to derive a single utility index from the SF-36 Health Survey.
** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*
‡ Subgroups were defined on the basis of 5 centiles (2.5th, 25th, 50th, 75th and 97.5th) of risk of cardiovascular event in the population.
¥Only incremental cost and incremental effectiveness of perindopril were reported.

Table 162: Taylor 2009[571]

Taylor M, Scuffham PA, Chaplin S, Papo NL. An economic evaluation of valsartan for post-MI patients in the UK who are not suitable for treatment with ACE inhibitors. Value in Health. 2009; 12(4):459-465.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome = QALYs) **Study design:** Decision analytic model. **Approach to analysis:** Probabilistic Markov model with 3 month cycles. Health states included no complications (after first MI), post heart failure, post stroke, post subsequent MI and death. **Perspective:** UK NHS perspective. **Time horizon:** 10 years. **Treatment effect duration:** in the model it is populated for the first 3 months and for	**Population:** Post MI patients with left ventricular systolic dysfunction, heart failure, or both, who are not suitable for treatment with ACE inhibitors. **Cohort settings:** Start age = NR (between 0 and 10 days after their MI). M = NR. **Intervention 1:** Placebo. **Intervention 2:** Valsartan.	**Total costs (mean per patient):** Intvn 1: £6198 Intvn 2: £8878 Incremental (2-1): £2680 **Currency & cost year: a**ll costs presented in 2008 UK pounds. **Cost components incorporated:** Costs considered in the study included cost of death, non-fatal MI, stroke, heart failure, GP visit, cardiologist visit, nurse visit, exercise tolerance test, angiography, PCI, CABG, drug costs (valsartan).	**QALYs (mean per patient)** Intvn 1: 4.519 Intvn 2: 5.021 Incremental (2-1): 0.502 (95% CI NR; p=NR).	**ICER (Intvn 2 vs Intvn 1)** £ per QALY gained = 5338. CI: NR. Probability Intvn 2 cost-effective (£20K/30K threshold): tends to 100% in both cases. **Analysis of uncertainty:** One way sensitivity analyses were performed to assess the impact of key parameters in the results of the model including parameters of costs, QALYs, event rates and discount rates.

subsequent 3-month periods. **Discounting:** Costs = 3.5%; Outcomes = 3.5%.				
Data sources				
Health outcomes: these were obtained from the valsartan for acute myocardial infarction (VALIANT) study [473] for the treatment arm. For the placebo one these were obtained from a meta-analysis [191] of the AIRE [12], SAVE [470] and TRACE [316] trials. **Quality-of-life weights:** from two different studies: one using a trade-off instrument, the other was a review of 20 articles. **Cost sources:** From standard or published UK sources.				
Comments				
Source of funding: Novartis Pharmaceuticals. **Limitations:** Whether all the sources used for the HRQoL data was reported directly from patients and/or carers and whether it was obtained from a representative sample of the public is unclear. The estimates of baseline health outcomes are not stated in the study. Estimates of relative treatment effects were obtained from different studies for the treatment and the placebo arms and there is therefore a break of randomization. Estimates of resource use needed the use of assumptions and expert clinical opinion. There is a potential conflict of interests. **Other:** None.				
Overall applicability*: Partially applicable **Overall quality**:** Very serious limitations				

Abbreviations: CI = 95% confidence interval; CUA = cost-utility analysis; HRQoL = Health Related Quality of Life; ICER = incremental cost-effectiveness ratio; NR = not reported; QALYs = quality-adjusted life years

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

Table 163: Lamy 2011[331]

Lamy A, Wang X, Gao P, Tong W, Gafni A, Dans A et al. The cost implications of the use of telmisartan or ramipril in patients at high risk for vascular events: The ONTARGET study. Journal of Medical Economics. 2011; 14(6):792-797.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**

Lamy A, Wang X, Gao P, Tong W, Gafni A, Dans A et al. The cost implications of the use of telmisartan or ramipril in patients at high risk for vascular events: The ONTARGET study. Journal of Medical Economics. 2011; 14(6):792-797.				
Economic analysis: CCA **Study design:** multi-center RCT (ONTARGET trial) [577] **Perspective:** USA healthcare system **Follow-up:** 56 months **Discounting:** Costs = 3%; Outcomes = N/A	**Population:** patients with coronary artery, peripheral vascular, or cerebrovascular disease or high risk diabetes mellitus with end-organ damage. **Patient characteristics:** N=17,118 **Intervention 1:** Ramipril (ACE inhibitor), 10 mg daily, for 56 months. N=8,542 **Intervention 2:** Telmisartan (ARB), 80 mg daily, for 56 months. N=8,576	**Total costs (mean per patient):** Intvn 1: £7,172 Intvn 2: £7,629 Incremental (2-1): £458 (95% CI: £136-£779; p = 0.005) **Currency & cost year:** 2008 US dollars (presented here as 2008 UK pounds‡) **Cost components incorporated:** Hospitalisations, procedures, and study and non-study drugs. The only significant cost difference was on the study drug (p<0.001).	No significant difference between the two groups for: • Primary outcome (CV death, MI, stroke or hospitalisation for heart failure) • Death from CV causes, MI, or stroke • Cardiovascular death • MI • Stroke • Hospitalisation for heart failure • Death from any cause Based on the results of the ONTARGET study.	**NR** **Analysis of uncertainty:** Unit costs for new diagnosis of TIA, stroke, and renal failure with or without dialysis were selected for the sensitivity analysis as variations were potentially more significant than other variables. Varying those unit costs by ±25% had limited impact on total costs measured per patient either individually or grouped.
Data sources				
Health outcomes: N/A. **Quality-of-life weights:** N/A. **Cost sources:** healthcare utilisation for each patient was extracted from the ONTARGET's case report forms. Country specific unit costs were then assigned to arrive at a cost per patient.				
Comments				
Source of funding: this work was supported by an unrestricted grant from Boehringer Ingelheim as part of the ONTARGET study. **Limitations:** It is not a UK study. Discount rate was 3% instead of the 3.5% recommended by NICE. Health effects were expressed in terms of QALYs. Potential conflict of interest (see source of funding).				
Overall applicability*: Partially applicable **Overall quality**:** Potentially serious limitations				

Abbreviations: CCA = Cost consequence analysis; CI = 95% confidence interval; EQ-5D = Euroqol five dimensions (scale: 0.0 [death] to 1.0 [full health]; <0.0 = worse than death); ICER = incremental cost-effectiveness ratio; N/A = not applicable; NR = not reported; pa = probabilistic analysis; QALYs = quality-adjusted life years; TIA = Transient ischemic attack. ‡ Converted using 2008 Purchasing Power Parities

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

H.2.2 Late initiation of antiplatelet therapy

Table 164: Chen 2011[105]

Chen J, Shi C, Mahoney EM, Dunn ES, Rinfret S, Caro JJ et al. Economic evaluation of clopidogrel plus aspirin for secondary prevention of cardiovascular events in Canada for patients with established cardiovascular disease: Results from the CHARISMA trial. Canadian Journal of Cardiology. 2011; 27(2):222-231.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA/CEA (health outcome = QALYs/LYG) **Study design:**Within-RCT analysis (CHARISMA established CVD subgroup) with extrapolation. **Approach to analysis:** Costs based on analysis of patient-level resource use with Canadian unit costs applied. Health outcomes calculated by attributing different lost life expectancy attributed to different clinical outcomes (death, MI, stroke, no event). Different QOL weights applied to LYs for MI, mild stroke and moderate/severe stroke. Short term QOL decrement applied for major bleeding. Bootstrapping used to estimate joint distribution of costs and LYs. **Perspective:** Canadian healthcare system **Time horizon:**Lifetime **Treatment effect duration:**28 months	**Population:** People with established CVD • Prior MI subgroup reported **Patient characteristics:** <u>Established CVD</u> N = 12,153 Setting = 32 countries Mean age =64 years M = 73% MI = 41% <u>Prior MI subgroup</u> N = 3023 Mean age = NR M = NR **Intervention 1:** Clopidogrel 75 mg daily plus 75 to 162 mg of aspirin daily **Intervention 2:** Placebo plus 75 to 162 mg of aspirin daily	**Established CVD** <u>Total costs (mean per patient):</u> Intvn 1: £3730 Intvn 2: £2946 Incremental (2-1): £785 (CI £617 to £952; p < 0.001) **Prior MI subgroup** <u>Total costs (mean per patient):</u> Intvn 1: NR Intvn 2: NR Incremental (2-1): £684 (CI NR; p = NR) **Currency & cost year:** 2008 Canadian dollars (presented here as 2008 UK pounds‡) **Cost components incorporated:** Cardiovascular hospitalisations and procedures; medications; post-acute care associated with different clinical endpoints (rehabilitation, nursing home and longterm care, home	**Established CVD** <u>QALYs (mean per patient):</u> Intvn 1:NR Intvn 2: NR Incremental (2-1): 0.07 (CI NR; p = NR) <u>LY (mean per patient):</u> Intvn 1: NR Intvn 2: NR Incremental (2-1): 0.057 (CI NR; p = NR) **Prior MI subgroup** <u>LY (mean per patient):</u> Intvn 1: NR Intvn 2: NR Incremental (2-1): 0.106 (CI NR; p = NR)	**Established CVD** <u>ICER (Intvn 2 vs Intvn 1):</u> £11,362 per QALY gained CI:NR; probability Intvn 2 cost-effective (£20K/30K threshold): NR £13,754.38 per LY gained CI:NR; probability Intvn 2 cost-effective (~£26K (CAD 50K) threshold): 76% **Prior MI subgroup** <u>ICER (Intvn 2 vs Intvn 1):</u> £6467 per LY gained CI:NR; probability Intvn 2 cost-effective (£20K/30K threshold): NR **Other subgroups:**Results available but not reported here for age <65yrs, ≥65yrs, male, female, white, non-white, diabetes, no diabetes, prior stroke, documented PAD, no prior MI, stroke or PAD. **Analysis of uncertainty:** Sensitivity analyses in the CVD population included discount rates, lost life years

Discounting: Costs = 5%; Outcomes =5%		healthcare services, outpatient office visits, laboratory services, diagnostic testing, durable medical equipment, day care).		applied, and varying clopidogrel, post-acute care, bleeding and hospital costs. ICERs remained < £20,000 except when LYs lost per event were reduced by 50% (ICER = £29,557) and when clopidogrel cost increased by 50% (ICER = £21,495). A 50% reduction in clopidogrel cost reduced the ICER to £5,891.
Data sources				
Health outcomes: Event rates for cardiovascular events, bleeding events and death from within trial analysis. Lost life expectancy was calculated using the 'Saskatchewan Health databases'. **Quality-of-life weights:** Utilities from published sources; methods unclear.**Cost sources:** Resource use: within-trial analysis for medication, hospitalisations and procedures. Post-acute care for different clinical events from external sources. Unit costs: Canadian national sources or adjusted to reflect national costs; inflated as required.				
Comments				
Source of funding: Sanofi-Aventis Canada Inc. and Bristol-Myers Squibb Canada. **Limitations:** CVD analysis: indirect population (~40% MI). Some uncertainty about applicability of Canadian costs and multinational resource use. Cost of clopidogrel higher than current UK context (£485 per year). Discount rate not in line with NICE reference case. MI subgroup only: QALYs not used therefore interpretation limited. CVD subgroup only: Some uncertainty about applicability of utility data as methods unclear. MI subgroup Based on analysis of MI subgroup of CHARISMA established CVD subgroup. CVD subgroup: Based on analysis of CHARISMA established CVD subgroup (defined as pre-existing coronary artery disease [angina, MI, PCI, or coronary artery bypass surgery], cerebrovascular disease [ischemic stroke, transient ischemic attack], or symptomatic peripheral arterial disease [PAD]) – clinical review excluded this subgroup analysis in favour of CHARISMA high risk CVD (defined as MI, stroke or symptomatic PAD) subgroup analysis considered more relevant.Study funded by Sanofi-aventis Canada Inc. and Bristol-Myers Squibb Canada (manufacture clopidogrel).**Other:** none.				
Overall applicability*: Partially applicable**Overall quality**:**Potentially serious limitations				

Abbreviations: CUA = cost–utility analysis; CVD = cardiovascular disease; ICER = incremental cost-effectiveness ratio; LY = life years; NR = not reported; QALYs = quality-adjusted life years.
‡ Converted using 2008 Purchasing Power Parities
** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

Table 165: Heeg 2007[266]

Heeg B, Damen J, van HB. Oral Antiplatelet Therapy in Secondary Prevention of Cardiovascular Events: An Assessment from the Payer's Perspective. Pharmacoeconomics. 2007; 25(12):1063-1082.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome = QALYs) **Study design:** Decision analytic model with multiple analyses based single RCTs (reported here: CHARISMA[64]†; PCI-CURE; CREDO) **Approach to analysis:** Probabilistic Markov model with 6 month cycles. Health states included no event, myocardial infarction, stroke and death and also took account of up to three events. It distinguished between 3 time phases: 0-6 months, 6-12 months and post 12 months. Difference in bleeding rate was incorporated on the cost side. **Perspective:** UK NHS perspective **Time horizon:** Lifetime time **Treatment effect duration:** same as treatment duration – see intervention desscriptions **Discounting:** Costs = 3.5%; Outcomes = 3.5%	CHARISMA **Population:** Established CVD or multiple CV risk factors **Cohort setting:** Start age = 64 yrs M = 70% **Intervention 1:** Clopidogrel 75mg/day + aspirin 300mg/day **Intervention 2:** Aspirin 300mg/day PCI-CURE **Population:** NSTE ACS (NSTEMI & unstable angina) **Cohort setting:** Start age = 64 yrs M = 70% **Intervention 1:** 1 month clopidogrel 75mg/day + lifetime aspirin 300mg/day **Intervention 2:** 1 year clopidogrel 75mg/day + lifetime aspirin 300mg/day	**Total costs (mean per patient):** CHARISMA Intvn 1: NR Intvn 2: NR Incremental (2-1): £772 (CI NR; p = NR) PCI-CURE Intvn 1: NR Intvn 2: NR Incremental (2-1): £772 (CI NR; p = NR) CREDO Intvn 1: NR Intvn 2: NR Incremental (2-1): £772 (CI NR; p = NR) **Currency & cost year:** 2006 UK pounds **Cost components incorporated:** Aspirin, clopidogrel, MI first 6 months after event, MI second 6 months after event, MI first year(per 6 months), fatal MI, stroke first 6 months after event, stroke second 6 months after event, stroke after the first year (per 6 months), Fatal stroke, other	**LY (mean per patient):** CHARISMA Intvn 1: NR Intvn 2: NR Incremental (2-1): 0.0054 (CI NR; p = NR) PCI-CURE Intvn 1: NR Intvn 2: NR Incremental (2-1): 0.0293 (CI NR; p = NR) CREDO Intvn 1: NR Intvn 2: NR Incremental (2-1): 0.1068 (CI NR; p = NR)	**ICER (Intvn 2 vs Intvn 1):** CHARISMA £143,071 per LY gained (pa) CI: NR; probability Intvn 2 cost-effective (£20K/30K threshold): ~15%/27% PCI-CURE Intvn 2 dominant CI: NR; probability Intvn 2 cost-effective (£20K/30K threshold): ~73%/70% CREDO Intvn 2 dominant CI: NR; probability Intvn 2 cost-effective (£20K/30K threshold): ~100%/100% **Analysis of uncertainty:** None reported

	CREDO **Population:** PCI **Cohort setting:** Start age = 64 yrs M = 70% **Intervention 1:** 1 month clopidogrel 75mg/day + lifetime aspirin 300mg/day **Intervention 2:** 1 year clopidogrel 75mg/day + lifetime aspirin 300mg/day	cardiovascular death, other non-cardiovascular death and haemorrhage.		
Data sources				
Health outcomes: Event probabilities based on CHARISMA trial - probabilities for second and third events were adjusted to reflect fact that previous event increases risk of subsequent event based on published data. Assumed cardiovascular death was split evenly between fatal MI, stroke and other vascular events. Age-specific increases in event rates based on the 'Rotterdam study' and UK life tables. **Quality-of-life weights:** n/a **Cost sources:** Costs were obtained from national or published UK sources (PRAIS-UK; NHAR; NHS reference costs; BNF) and previous cost-effectiveness publications; inflated as required.				
Comments				
Source of funding: Pharmerit International. **Limitations:** CHARISMA only: Indirect population (~35% MI). CREDO only: PCI population (indirect MI<75%). Some uncertainty about applicability of multinational resource use. Cost of clopidogrel higher than current UK context (£460 per year). QALYs not used therefore interpretation limited. CHARISMA only: Event probabilities based on analysis of CHARISMA full study population (established CVD and multiple CVD risk factors) – clinical review excluded this analysis in favour of CHARISMA high risk CVD (defined as MI, stroke or symptomatic PAD) subgroup analysis considered more relevant. Some methodological limitations with probabilistic methods. No other sensitivity analysis reported. **Other:** none.				
Overall applicability*: Partially applicable **Overall quality**:** Potentially serious limitations				

Abbreviations: ASA = aspirin; CUA = cost-utility analysis; ICER = incremental cost-effectiveness ratio; LYG = life-years gained; MI = myocardial infarction; NR = not reported; QALYs = quality-adjusted life years

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

Table 166: Karnon 2010[309]

Karnon J, Holmes MW, Williams R, Bakhai A, Brennan A. A cost-utility analysis of clopidogrel in patients with ST elevation acute coronary syndromes in the UK. International Journal of Cardiology. 2010; 140(3):315-322.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome = QALYs) **Study design:** Decision analytic model **Approach to analysis:** Probabilistic Markov model. Health states: initial STEMI, new MI, post-new MI, stroke and death. People could only remain in the stroke state for one year after which they had a new-MI, died or moved back to the STEMI state. Separate transition probabilities for month 1, months 2-12 and year 1 onwards. **Perspective:** UK NHS **Time horizon:** Lifetime horizon **Treatment effect duration:** same as treatment duration (see intervention descriptions) **Discounting:** Costs = NR ; Outcomes = NR	**Population:** People with STEMI **Cohort settings:** Start age = 60 years **Intervention 1:** Aspirin 300mg/day for lifetime **Intervention 2:** Clopidogrel 75 mg/day (with/without 300 mg loading dose for CLARITY/COMMIT respectively) + aspirin 300mg/day for 1 month, followed by aspirin alone for remaining lifetime **Intervention 3:** Clopidogrel 75 mg/day (with/without 300 mg loading dose for CLARITY/COMMIT respectively) + aspirin 300mg/day for 1 year, followed by aspirin alone for remaining lifetime Note that publication reports separate 1 month and 1 year clopidogrel+aspirin vs aspirin alone comparisons but here results have been recalculated to incorporate different durations into same incremental analysis as this is most appropriate.	**Total costs (mean per patient):** COMMIT/CCS-2 analysis Intvn 1: £14,840 Intvn 2: £14,960 Intvn 3: £15,570 Incremental (2-1) = £120 (CI NR; p = NR) Incremental (3-2) = £610 (CI NR; p = NR) CLARITY-TIMI analysis Intvn 1: £15,350 Intvn 2: £15,710 Intvn 3: £16,340 Incremental (2-1) = £360 (CI NR; p = NR) Incremental (3-2) = £630 (CI NR; p = NR) **Currency & cost year:** 2006 UK pounds **Cost components incorporated:** Aspirin, clopidogrel, ongoing hospital resource use for those remaining event-free or have a new MI, primary and secondary care costs for stroke.	**QALYs (mean per patient)** COMMIT/CCS-2 analysis Intvn 1: 7.931 Intvn 2: 7.984 Intvn 3: 8.117 Incremental (2-1) = 0.053 Incremental (3-2) = 0.133 CLARITY-TIMI analysis Intvn 1: 8.214 Intvn 2: 8.411 Intvn 3: 8.553 Incremental (2-1) = 0.197 Incremental (3-2) = 0.142	**ICERs** COMMIT/CCS-2 analysis 2 vs 1: £2284 per QALY gained 3 vs 2: £4586 per QALY gained Probability cost-effective (£20K/30K threshold): Note: only reported for pairwise comparisons not full incremental analysis of 3 intvns 2 vs 1: 100%/100% 3 vs 1: 100%/100% CLARITY-TIMI analysis 2 vs 1: £1857 per QALY gained 3 vs 2: £4437 per QALY gained Probability cost-effective (£20K/30K threshold): Note: only reported for pairwise comparisons (1 vs 2 or 3) not full incremental analysis of 3 intvns 2 vs 1: 100%/100% 3 vs 1: 100%/100%

				Analysis of uncertainty: Univariate sensitivity analyses for: RRs, baseline event rates, costs, utilities, age at entry and discount rates. Results for pairwise comparisons did not change but full incremental analysis not undertaken and results provided do not allow assessment of impact.

Data sources

Health outcomes: Baseline probabilities (aspirin alone group): Month 1 and 2-12: death probabilities were based on UK GRACE (Global Registry of Acute Coronary Events) data, non-fatal MI and stroke probabilities were based on a German observational study and adapted to the UK context using GRACE data. Year 1 onwards: primary based on Nottingham Heart Attack Registry (NHAR) data. Relative treatment effects: Month 1: composite endpoint RR (non-fatal MI, non-fatal stroke or death) from CLARITY-TIMI or COMMIT/CCS-2 trials (depending on analysis) (SA used separate RRs for each outcome); months 2-12: composite endpoint RR for months 2-12 in CURE trial (NSTEMI and unstable angina) (SA used separate RRs for each outcome although specific 2-12 month individual outcome data not available). **Quality-of-life weights:** Utilities from published sources; methods unclear. **Cost sources:** Drug costs based on standard doses with national unit costs; health state costs from published studies.

Comments

Source of funding: BMS/Sanofi-Aventis (manufacture clopidogrel). **Limitations:** Some uncertainty about applicability of health state costs based on resource use from over 10 years ago. Cost of clopidogrel higher than current UK context (~£460 per year). Basecase discount rate not reported. Some uncertainty about applicability of utility data as methods unclear. Patients can only remain in stroke health state for 1 year - this may not capture full health outcome or cost impact. Bleeding not incorporated. Only hospital resource use incorporated into no new event and new MI health states. Baseline event probabilities based on studies published 2005/6, data therefore likely to be from some years before – may relate to old acute MI management strategies. Relative risks with clopidogrel + aspirin treatment months 2-12 based on NSTEMI trial as no STEMI data available. Funded by BMS/Sanofi-Aventis (manufacture clopidogrel). **Other:** None.

Overall applicability*: Partially applicable **Overall quality**:** Potentially serious limitations

Abbreviations: CI = confidence interval; CUA = cost-utility analysis; ICER = incremental cost-effectiveness ratio; MI = myocardial infarction; NR = not reported; PSA = probabilistic sensitivity analysis; QALYs = quality-adjusted life years; RR = relative risk; STEMI = ST-segment elevation myocardial infarction.

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

Table 167: Rogowski 2009[507]

Rogowski W, Burch J, Palmer S, Craigs C, Golder S, Woolacott N. The effect of different treatment durations of clopidogrel in patients with non-ST-segment elevation acute coronary syndromes: A systematic review and value of information analysis. Health Technology Assessment. 2009; 13(31):1-77.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome = QALYs) **Study design:** probabilistic decision analystic model based on single RCT (CURE[637]) **Approach to analysis:** Update of Main et al model used for TA80.[360] Short-term decision tree (12 months) used to model differences between treatment options - three mutually exclusive health outcomes: new non-fatal MI, death and no new event (ischemic heart disease [IHD] without new non-fatal MI) . A four state Markov model with 1 year cycles extrapolated these outcomes to the long term. Health states were IHD, MI, post-MI and dead. • Scenario 1 = constant treatment effect for the different durations of clopidogrel – for all	**Population:** Patients with NSTE-ACS **Cohort settings:** Start age = n/a M = n/a **Intervention 1:** Lifetime treatment with standard therapy alone (including aspirin) **Intervention 2:** Clopidogrel for 1 month + standard therapy **Intervention 3:** Clopidogrel for 3 months + standard therapy **Intervention 4:** Clopidogrel for 6 months + standard therapy **Intervention 5:** Clopidogrel for 12 months + standard therapy Note the study reported clopidogrel for 12 months versus no clopidogrel as it's base-case analysis	**Total costs scenario 1 (mean per patient):** All patients Intvn 1: £19,141 Intvn 2: £19,233 (2-1: £92) Intvn 3: £19,347 (3-2: £114) Intvn 4: £19,493 (4-3: £146) Intvn 5: £19,758 (5-4: £265) High-risk patients† Intvn 1: £18,487 Intvn 2: £18,604 (2-1: £117) Intvn 3: £18,744 (3-2: £140) Intvn 4: £18,900 (4-3: £156) Intvn 5: £19,187 (5-4: £287) Low-risk patients‡ Intvn 1: £20,731 Intvn 2: £20,786 (2-1: £55) Intvn 3: £20,886 (3-2: £100) Intvn 4: £21,005 (4-3: £119) Intvn 5: £21,244 (5-4: £239) **Total costs scenario 2 (mean per patient):** All patients Intvn 1: £19,250 Intvn 2: £19,449 (2-1: £119)	**QALYs scenario 1 (mean per patient):** All patients Intvn 1: 8.0642 Intvn 2: 8.0835 (2-1: 0.0193) Intvn 3: 8.0954 (3-2: 0.0119) Intvn 4: 8.1094 (4-3: 0.0140) Intvn 5: 8.1236 (5-4: 0.0142) High-risk patients† Intvn 1: 7.6882 Intvn 2: 7.7123 (2-1: 0.0241) Intvn 3: 7.7300 (3-2: 0.0177) Intvn 4: 7.7496 (4-3: 0.0196) Intvn 5: 7.7710 (5-4: 0.0214) Low-risk patients‡ Intvn 1: 8.6600 Intvn 2: 8.6713 (2-1: 0.0113) Intvn 3: 8.6769 (3-2: 0.0056) Intvn 4: 8.6802 (4-3: 0.0033) Intvn 5: 8.6850 (5-4: 0.0048) **QALYs scenario 2 (mean per patient):** All patients Intvn 1: 8.0686 Intvn 2: 8.1236 (2-1: 0.0550)	**ICERs scenario 1 (probability most cost effective option at £20K/£30K):** All patients 1: NA (15.7%/16.8%) 2 vs 1: £4790 per QALY gained (7.5%/5.0%) 3 vs 2: £9489 per QALY gained (2.0%/0.7%) 4 vs 3: £10,482 per QALY gained (18.9%/9.9%) 5 vs 4: £18,712 per QALY gained (51.7%/67.5%) High-risk patients† 1: NA (16.5%/17.3%) 2 vs 1: £ 4846 per QALY gained (4.8%/3.2%) 3 vs 2: £ 7930 per QALY gained (0.7%/0.2%) 4 vs 3: £7971 per QALY gained (9.3%/4.2%) 5 vs 4: £13,380 per QALY gained (65.8%/75.1%) Low-risk patients‡ 1: NA (11.1%/13.0%) 2 vs 1: £4891 per QALY gained (31.6%/20.2%) 3 vs 2: £17,826 per QALY gained (31.3%/30.0%) 4 vs 3: £36,226 per QALY gained (14.8%/20.2%) 5 vs 4: £49,436 per QALY gained (4.9%/16.7%) **ICERs scenario 2 (probability most cost effective option at £20K/£30K):** All patients 1: NA (0.0%/0.0%) 2 vs 1: £3632 per QALY gained (0.1%/0.0%) 3 vs 2: £4095 per QALY gained (24.6%/17.1%)

patients • Scenario 2 = separate treatment effects for the different durations of clopidogrel Major bleeding and stroke were also included on the cost side only. **Perspective:** UK NHS **Time horizon:** 40 years **Treatment effect duration:** up to 12 months – see intervention descriptions **Discounting:** Costs = 3.5%; Outcomes = 3.5%	and explored different durations as a sensitivity analysis – this is presented here as most relevant to guideline review.	Intvn 3: £19,661 (3-2: £212) Intvn 4: £19,820 (4-3: £159) Intvn 5: £20,094 (5-4: £274) High-risk patients† Intvn 1: £18,643 Intvn 2: £18,913 (2-1: £270) Intvn 3: £19,197 (3-2: £284) Intvn 4: £19,368 (4-3: £171) Intvn 5: £19,664 (5-4: £296) Low-risk patients‡ Intvn 1: £20,471 Intvn 2: £20,564 (2-1: £93) Intvn 3: £20,695 (3-2: £131) Intvn 4: £20,821 (4-3: £126) Intvn 5: £21,065 (5-4: £244) **Currency & cost year:** 2005-2006 UK pounds **Cost components incorporated:** Costs derived from non-fatal MI, mean annual costs of IHD and post-MI states, costs of adverse events related to major bleeding and stroke, drugs costs and costs related to the death of patients.	Intvn 3: 8.1753 (3-2: 0.0517) Intvn 4: 8.1887 (4-3: 0.0134) Intvn 5: 8.2019 (5-4: 0.0132) High-risk patients† Intvn 1: 7.6906 Intvn 2: 7.7653 (2-1: 0.0747) Intvn 3: 7.8400 (3-2: 0.0747) Intvn 4: 7.8586 (4-3: 0.0186) Intvn 5: 7.8783 (5-4: 0.0186) Low-risk patients‡ Intvn 1: 8.6589 Intvn 2: 8.6825 (2-1: 0.0236) Intvn 3: 8.7018 (3-2: 0.0193) Intvn 4: 8.7037 (4-3: 0.0019) Intvn 5: 8.7079 (5-4: 0.0042)	4 vs 3: £11,917 per QALY gained (32.5%/26.6%) 5 vs 4: £20,661 per QALY gained (42.9%/56.3%) High-risk patients† 1: NA (0.0%/0.0%) 2 vs 1: £3615 per QALY gained (0.1%/0.1%) 3 vs 2: £3809 per QALY gained (28.7%/24.4%) 4 vs 3: £9144 per QALY gained (11.9%/6.4%) 5 vs 4: £15,063 per QALY gained (59.3%/69.2%) Low-risk patients‡ 1: NA (0.2%/0.4%) 2 vs 1: £3936 per QALY gained (6.1%/2.3%) 3 vs 2: £6780 per QALY gained (81.9%/74.8%) 4: ED (6.0%/8.7%) 5 vs 3: £58,691 per QALY gained (4.6%/13.8%) **Analysis of uncertainty:** Results for different risk groups and different assumptions about relative risks presented above. VOI analysis was also undertaken and EVPI reported at WTP of £20,000, £30,000 and £40,000 while on patent and while off patent for scenarios 1 and 2.
Data sources				
Health outcomes: Baseline probabilities (aspirin alone group): Short-term decision tree: Death, non-fatal MI and revascularisation probabilities based on PRAIS-UK 6 month data extrapolated to 12 month probabilities using the observed relationship between these periods in the CURE trial, stratified by risk group. Stroke rate also from PRAIS-UK. Major bleeding rate source not reported. Long-term model: Nottingham Heart Attack Register (NHAR) from 1992 (n = 979) and 1998 (n = 300). Relative				

treatment effects: Scenario 1: constant RR over time from CURE trial for individual outcomes applied for duration of clopidogrel treatment only; Scenario 2: varying RR over time from analysis of CURE trial data. Only composite outcome (cardiovascular death, non-fatal MI and stroke) RR available so applied across events. The intervals reported in the analysis did not match up completely with the time intervals in the model. The SIGN guidance after three months (interventions 4 and 5) reports only one time interval of between 3 and 12 months. Therefore it was decided to pool the time intervals after 3 months to estimate one single treatment effect to be applied to these separate intervals. As bleeding events were not part of the composite end point, a separate analysis was undertaken, assuming that the risk of these particular events remained constant over the period of treatment being evaluated. **Quality-of-life weights:** Utility values from published studies – source methods unclear. **Cost sources:** Resource use and costs were obtained from national or published sources [PRAIS-UK; NHAR; NHS reference costs; BNF].

Comments

Source of funding: UK Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR). **Limitations:** Some uncertainty about applicability of health state costs based on resource use from over 10 years ago. Cost of clopidogrel higher than current UK context (~£460 per year). Some uncertainty about applicability of utility data as source methods unclear. Stroke and major bleeding not incorporated into health outcomes only costs. Stroke and major bleeding not incorporated into health outcomes only costs. Baseline event probabilities based on UK cohort from 1998-99 (PRAIS-UK) - may therefore relate to old acute management strategies. **Other:** none.

Overall applicability*: Partially applicable **Overall quality**:** Potentially serious limitations

Abbreviations: CUA = cost-utility analysis; EVPI = expected value of information analysis; ICER = incremental cost-effectiveness ratio; IHD = ischemic heart disease; MI = myocardial infarction; NA = not applicable; NR = not reported; NSTE-ACS = Non-ST elevation acute heart failure; QALYs = quality-adjusted life year; VOI = value of information analysis.

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

†High-risk patients are defined as by age≥70, ST depression or diabetes (58% of all patients belonged to this group).

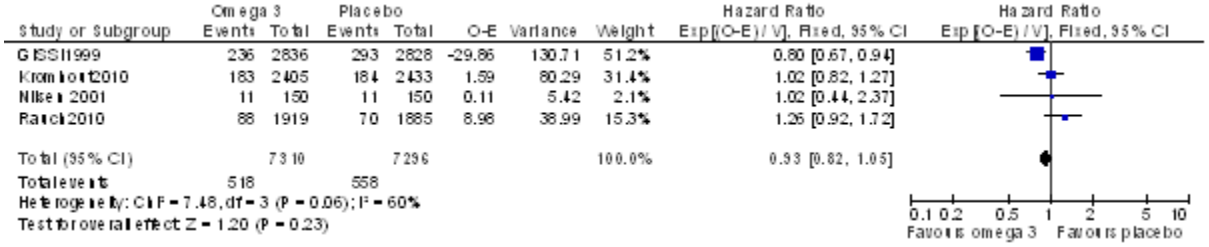
‡Low-risk patients are defined as the absence of all the previous conditions that define the high-risks.

Appendix I: Forest plots

I.1 Lifestyle

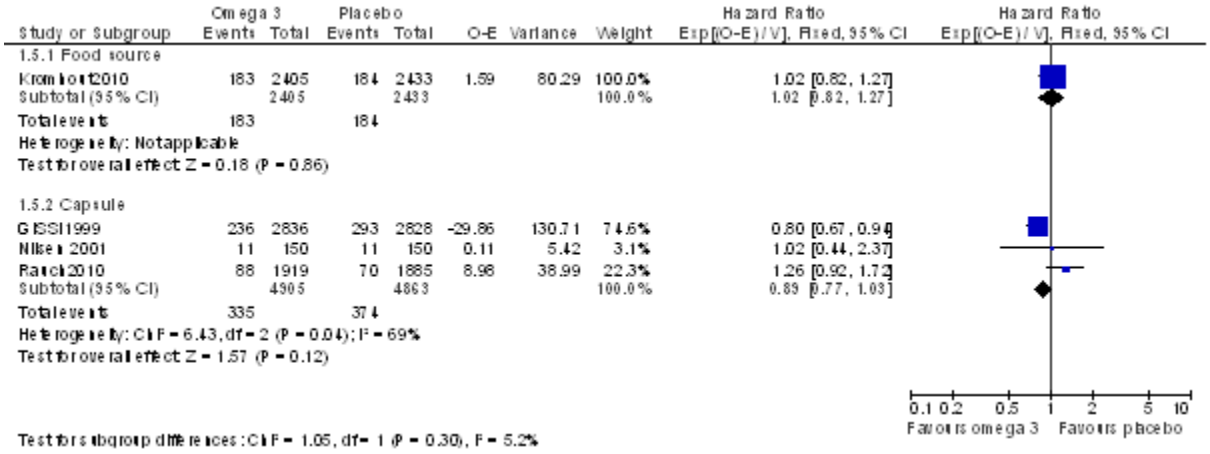
I.1.1 Omega-3 fatty acids

Figure 15: Omega-3 fatty acids vs. placebo (post MI 100%) - all-cause mortality (hazard ratio)



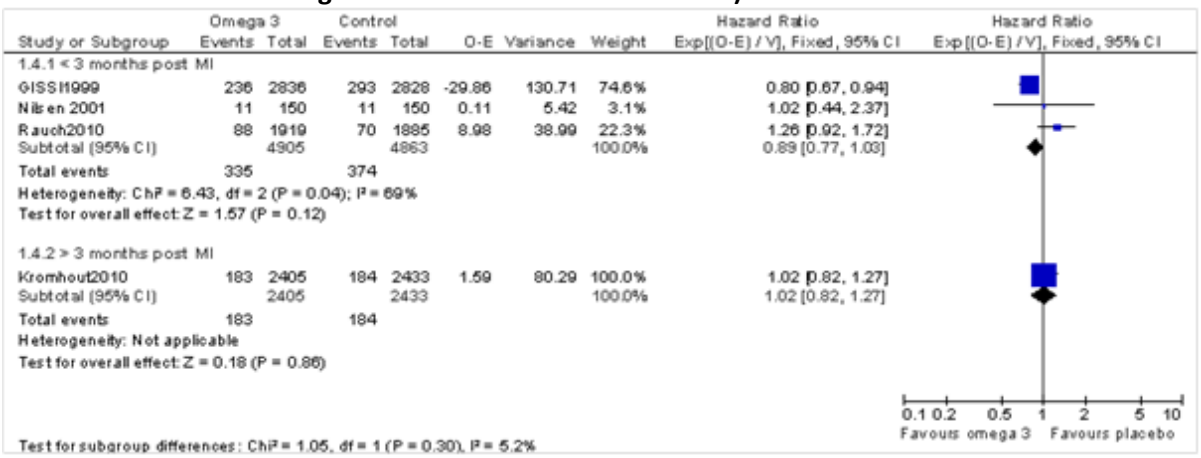
Heterogeneity was detected at I^2=60%. To investigate this, the papers were separated according to whether they used food or a capsule form of omega-3 fatty acids and the timing of the onset of treatment less than 3months vs. greater than 3 months following an MI. Relative risk data for all-cause mortality is also provided since only presenting HR meant excluding a key paper in the field (GISSI-P) that has influenced current practice.[228]

Figure 16: Omega-3 fatty acids vs. placebo – all-cause mortality (subgroup analysis of people provided with a food or capsule form of treatment(hazard ratio))



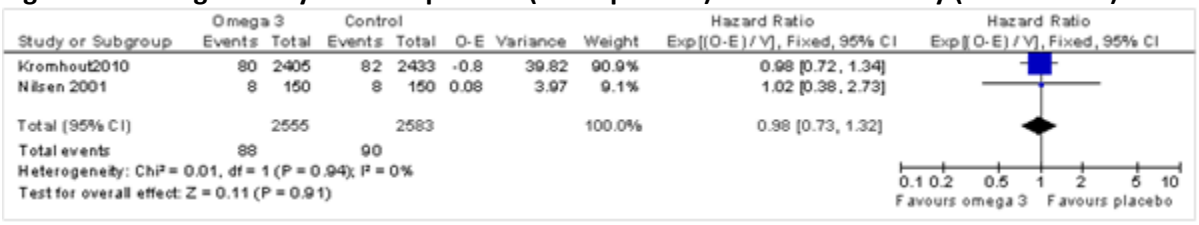
The subgroup analysis shows it is unclear whether capsule form of omega-3 fatty acids reduces the risk of all-cause mortality, while the food source of omega-3 fatty acids does not.

Figure 17: Omega-3 fatty acids vs. placebo – all cause mortality (hazard ratio) (less than3 months after an MI vs. greater than 3 months after an MI)



The subgroup analysis showed that initiating treatment within 3 months of having an MI may reduce the risk of all-cause mortality but after 3 months the benefit is lost.

Figure 18: Omega-3 fatty acids vs. placebo (100% post MI) – cardiac mortality (hazard ratio)



Heterogeneity was not present in cardiac mortality but subgroup analysis was performed on food vs. capsule form of omega-3-acid ethyl esters since the GDG expressed an interesting in exploring these groups.

Figure 19: Omega-3 fatty acids vs. placebo - cardiac mortality (subgroup analysis of people who received food or capsule source of omega-3 fatty acids) (hazard ratio))

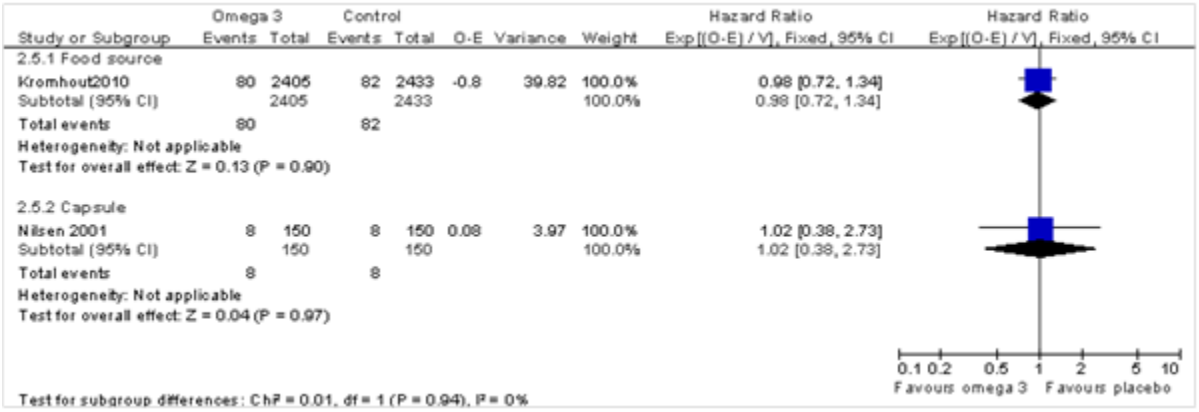


Figure 20: Omega-3 fatty acids vs. placebo – cardiac mortality (hazard ratio) (less than three months 3 after MI vs. greater than 3 months after MI) (100% post MI)

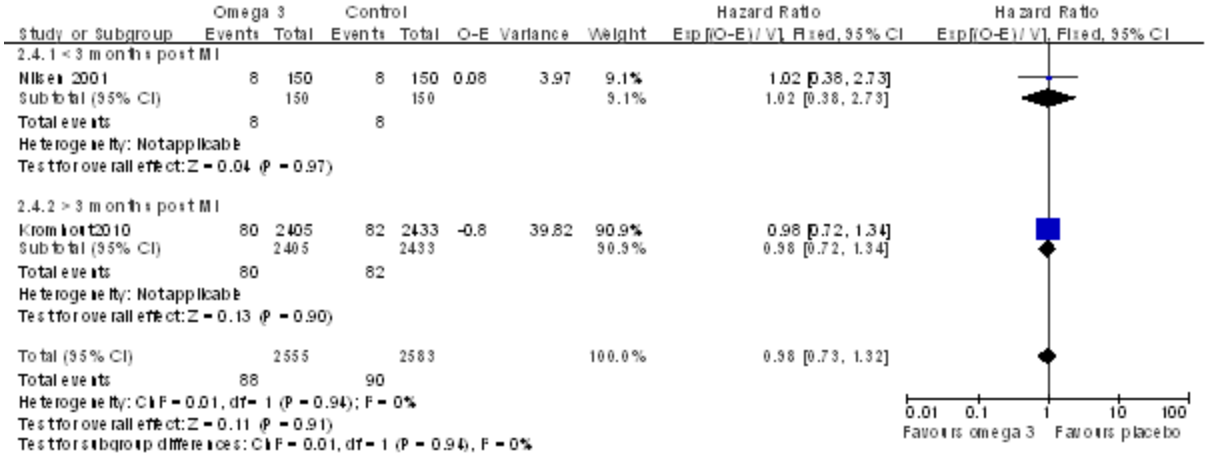


Figure 21: Omega-3 fatty acids vs. placebo (100% post MI) - cardiac mortality (relative risk)

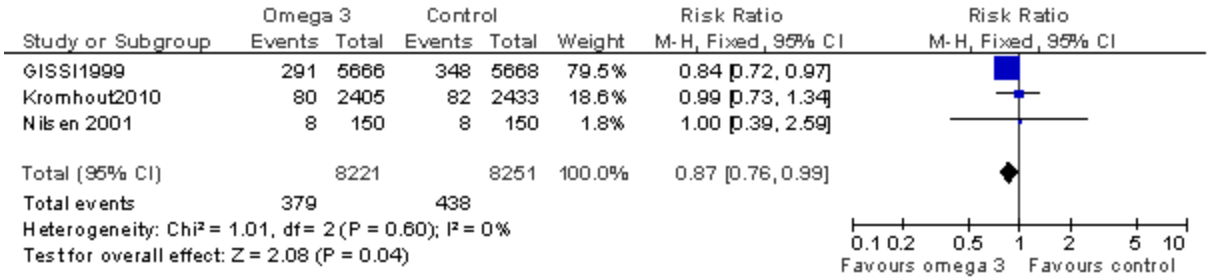


Figure 22: Omega-3 fatty acids vs. placebo (100% post MI) - cardiac mortality (relative risk) (subgroup analysis of food vs. capsule form of omega-3 fatty acids)

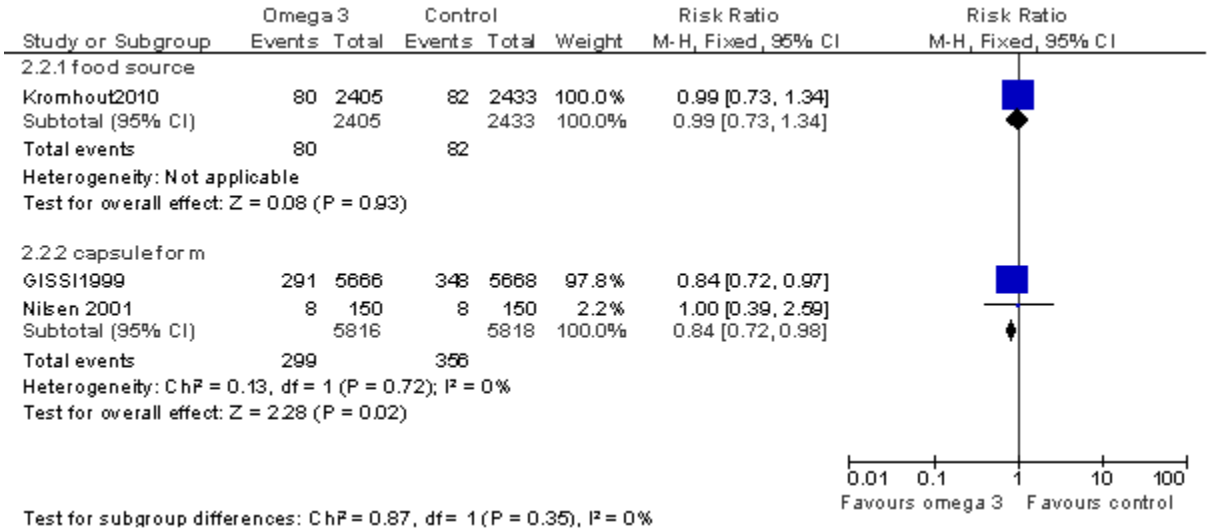


Figure 23: Omega-3 fatty acids vs. placebo (mixed population) - sudden death (hazard ratio)

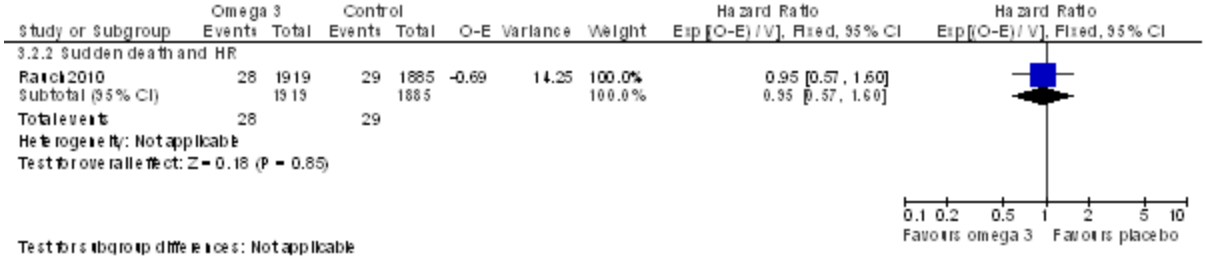


Figure 24: Omega-3 fatty acids vs. placebo (mixed population) - sudden death (relative risk)

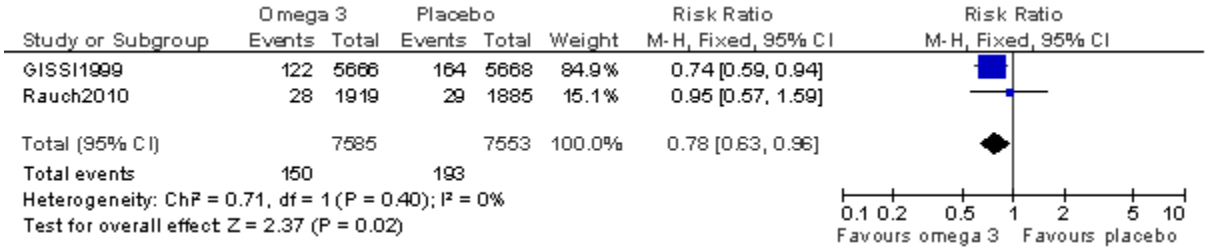


Figure 25: Omega-3 fatty acids vs. placebo (mixed population) -myocardial infarction (hazard ratio)

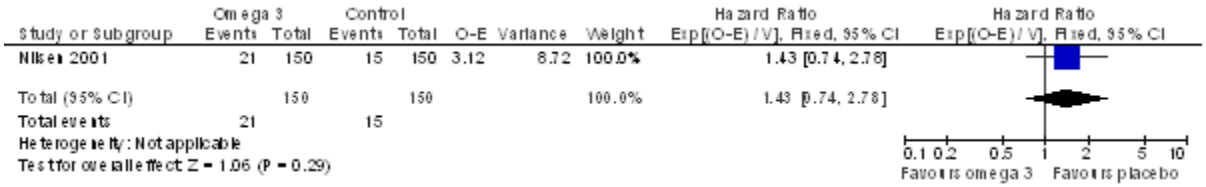


Figure 26: Omega-3 fatty acids vs. placebo (mixed population) - myocardial infarction (relative risk)

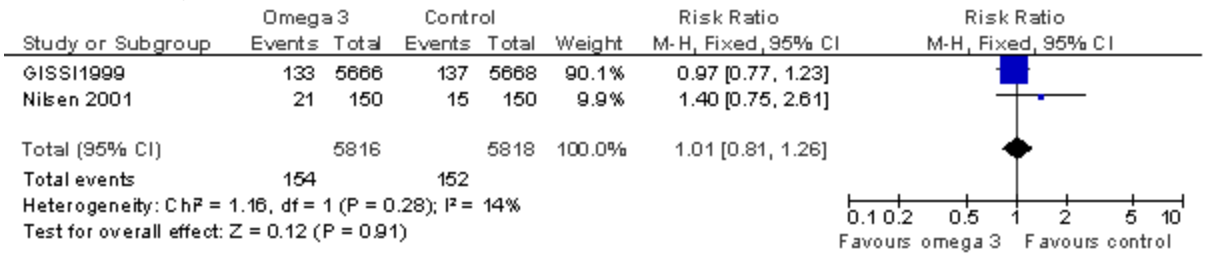


Figure 27: Omega-3 fatty acids vs. placebo (100% post MI) - revascularisation (hazard ratio)

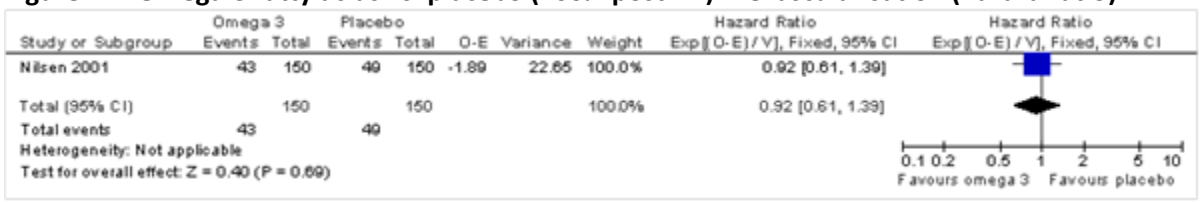


Figure 28: Omega-3 fatty acids vs. placebo (100% post MI) - revascularisation (relative risk)

Figure 29: Omega-3 fatty acids vs. placebo (mixed population) -stroke (hazard ratio)

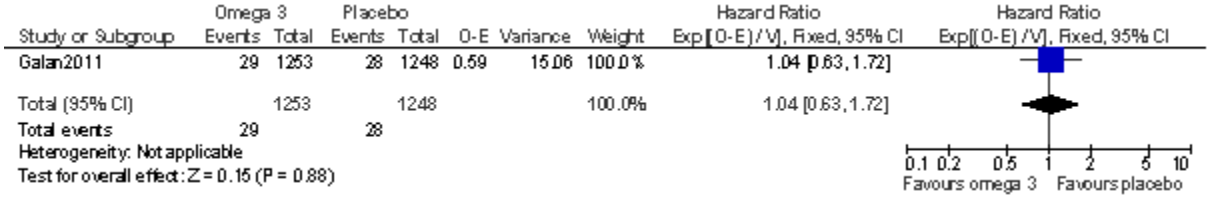


Figure 30: Omega-3 fatty acids vs. placebo (mixed population) -stroke (relative risk)

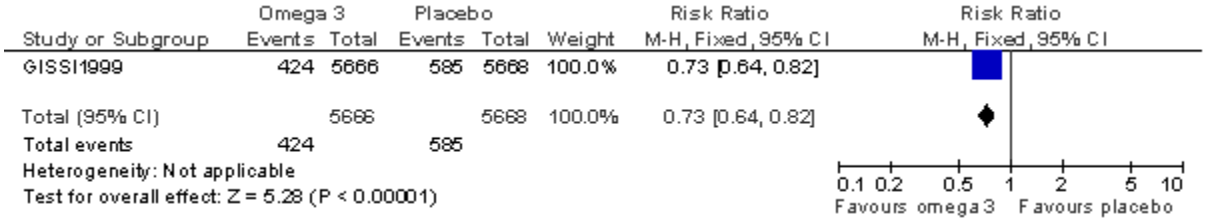
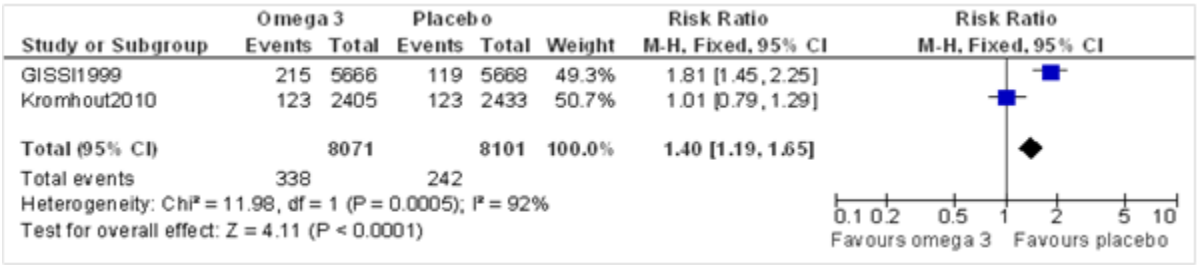


Figure 31: Omega-3 fatty acids vs. placebo (100% post MI) - adverse events



Heterogeneity in adverse events (I^2=92%) was investigated by separating the results into: 1) timing of initiating treatment less than 3 months vs. greater than 3 months post MI; and 2) food vs. capsule form of omega 3-fatty acids. Onset of treatment less than 3 months after an MI appeared to increase the risk of adverse events compared with no difference in starting treatment greater than 3 months post MI. Capsule form of omega-3 fatty acids also appeared to increase the risk of adverse events, whilst the food source did not.

Figure 32: Omega-3 fatty acids vs. placebo – adverse events (subgroup analysis of adverse events in patients who initiated treatment less than 3 or greater than 3 months after an MI MI)

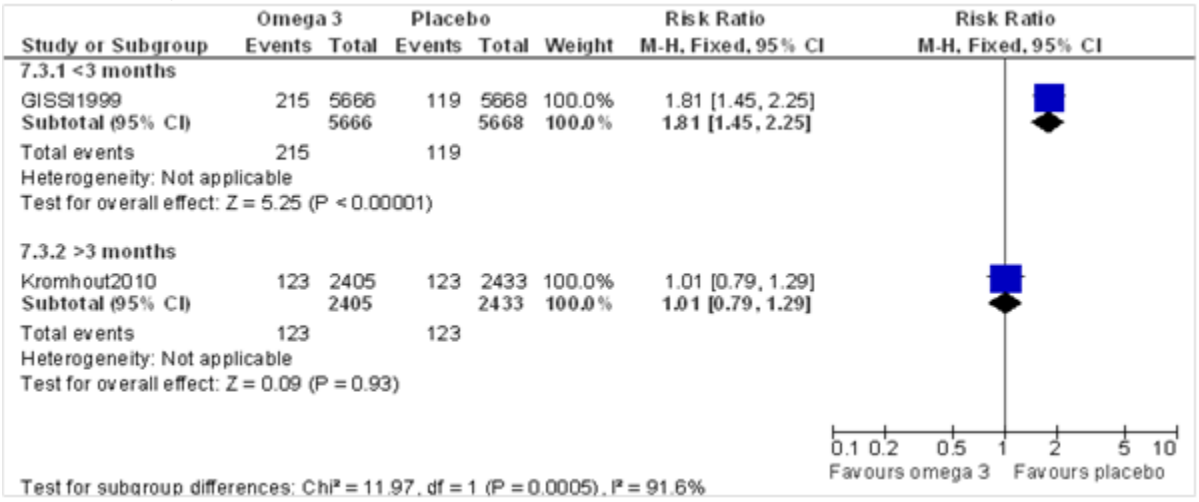


Figure 33: Omega-3 fatty acids vs. placebo (subgroup analysis of adverse events in people who were treated with either a food or capsule source of omega-3 fatty acids)

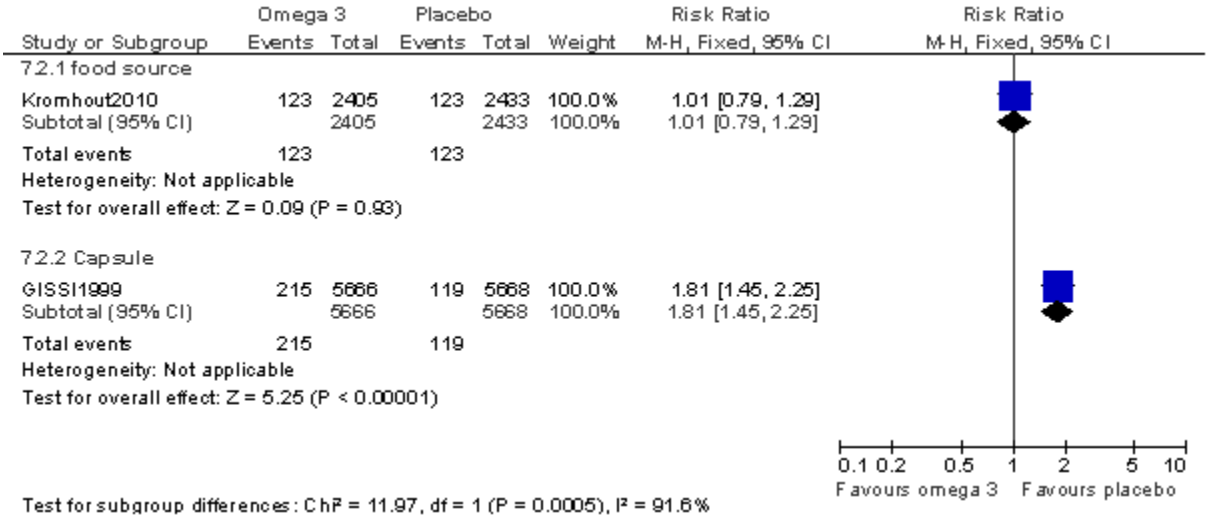
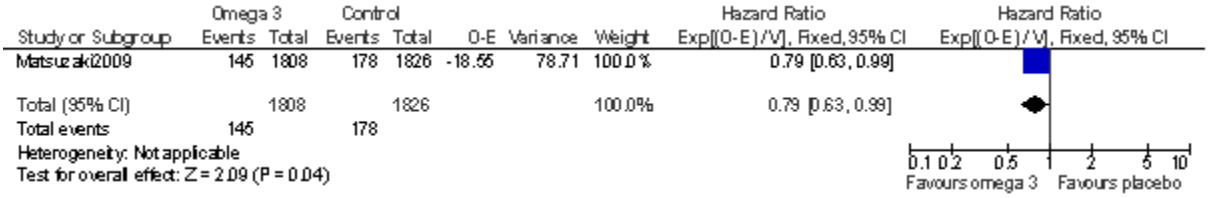


Figure 34: Omega-3 fatty acids vs. placebo -hospitalisation (hazard ratio)



I.1.2 Oily fish consumption

Figure 35: Oily fish vs. control diet in patients post MI -all-cause mortality (hazard ratio)

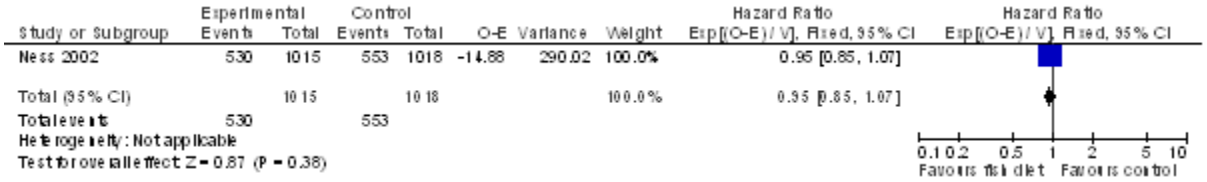


Figure 36: Oily fish vs. control diet in patients post MI - cardiac mortality (hazard ratio)

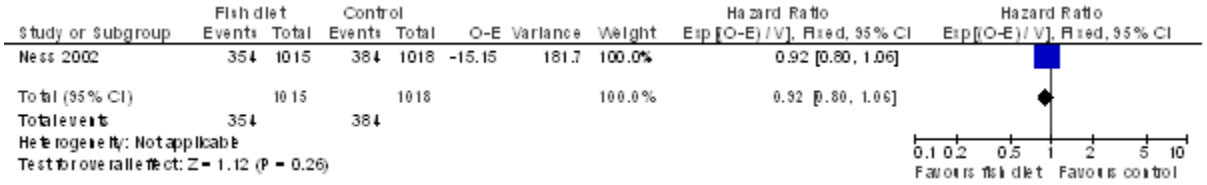


Figure 37: Oily fish vs. control diet in patients post MI - sudden death(hazard ratio)

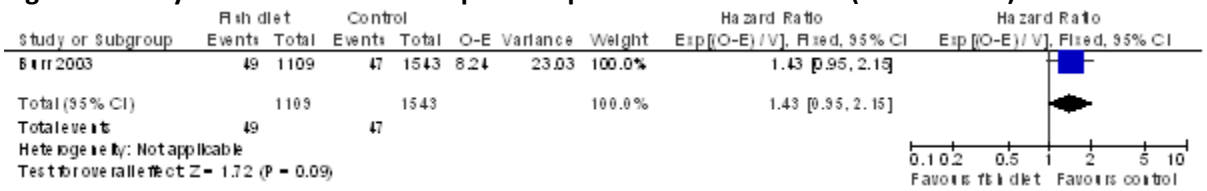


Figure 38: Oily fish vs. control diet in patients post MI - reinfarction(relative risk)

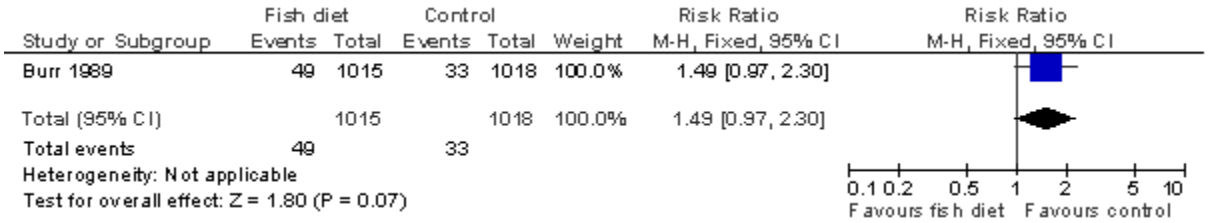
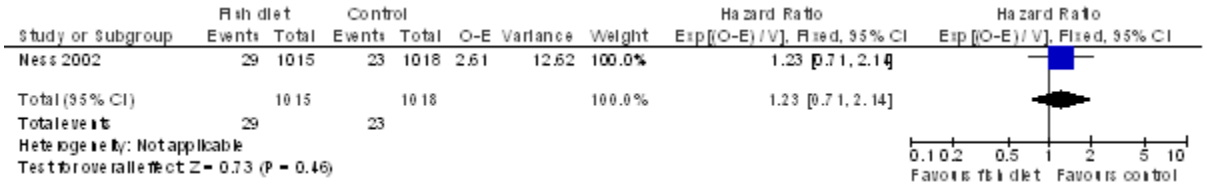


Figure 39: Oily fish vs. control diet in patients post MI - stroke(hazard ratio)



I.2 Cardiac rehabilitation

I.2.1 Interventions to increase uptake of and adherence to a cardiac rehabilitation programme

Figure 40: Early vs. late onset of cardiac rehabilitation programme - uptake

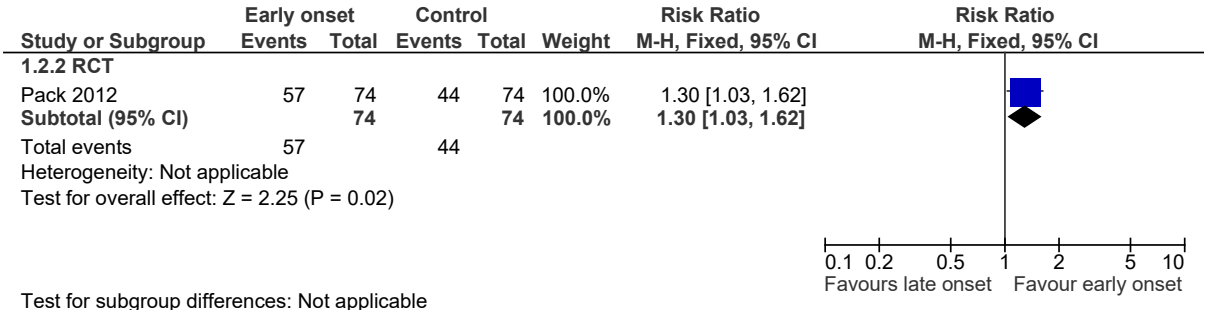


Figure 41: Early vs. late onset of cardiac rehabilitation programme - adherence

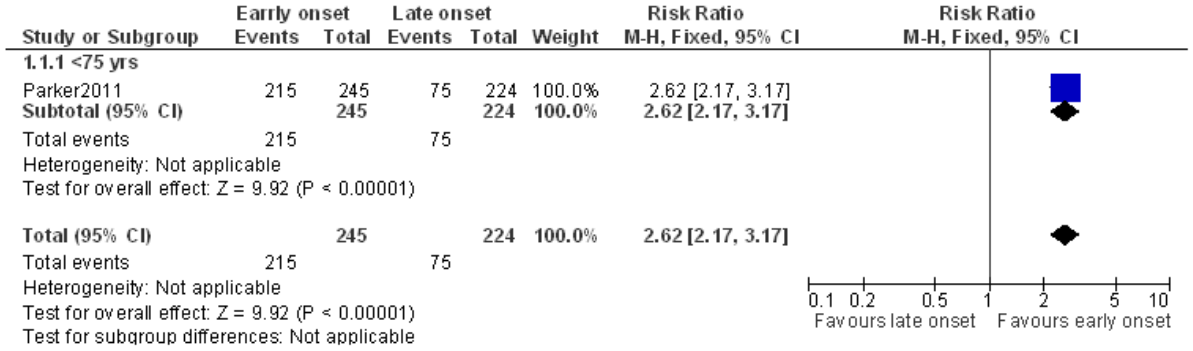


Figure 42: Gender tailored vs. traditional cardiac rehabilitation programme - adherence

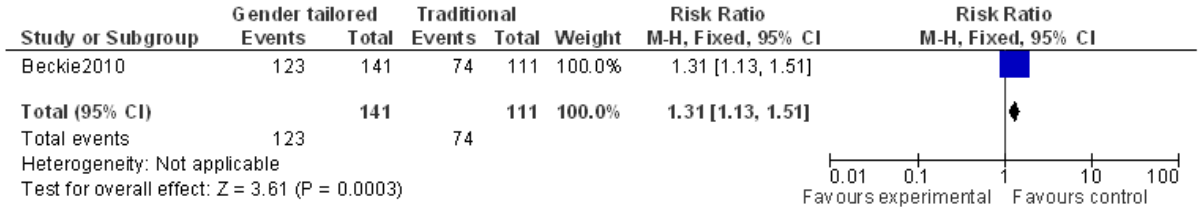


Figure 43: Goal setting vs. usual care – uptake

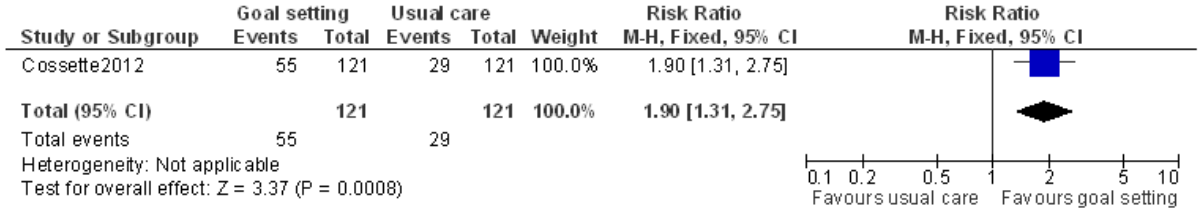


Figure 44: Planning and goal setting vs. usual care - adherence

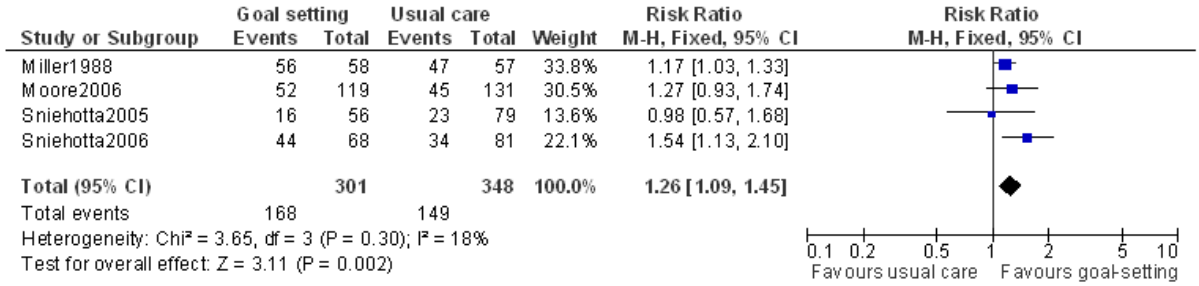


Figure 45: Planning, goal setting and diary vs. usual care - adherence

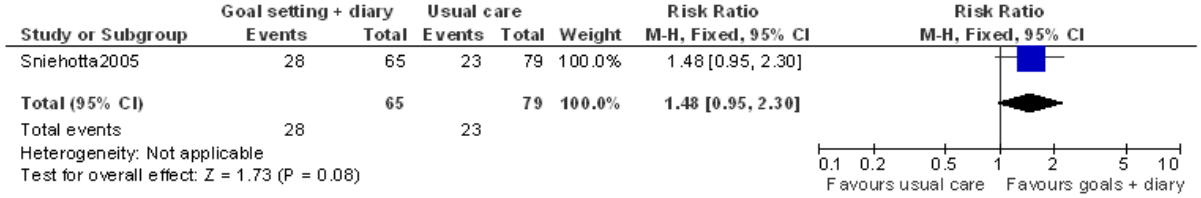


Figure 46: Planning, goal setting and signed diary - adherence

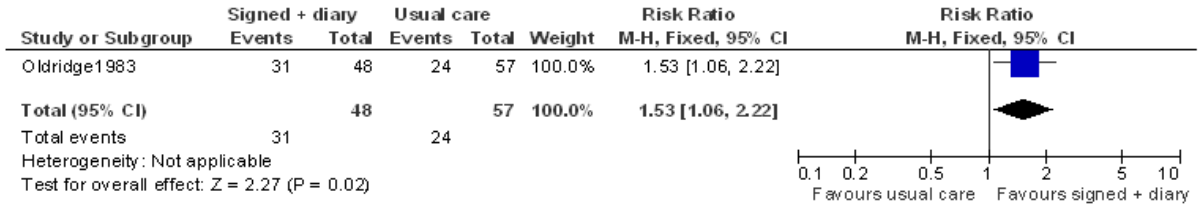


Figure 47: Liaison referral vs. usual referral to cardiac rehabilitation programme - uptake

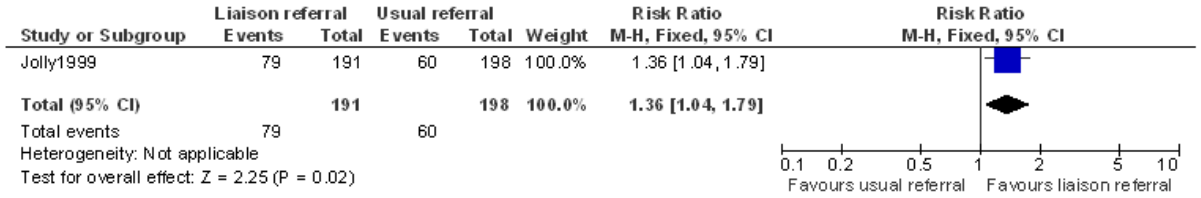


Figure 48: Liaison vs. usual referral to cardiac rehabilitation programme - percentage of classes attended

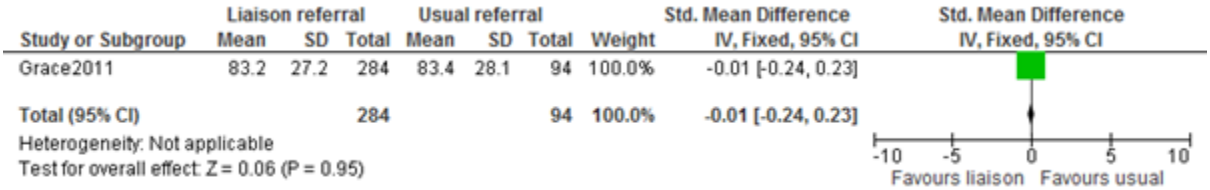


Figure 49: Automatic referral vs. usual referral to cardiac rehabilitation programme - uptake

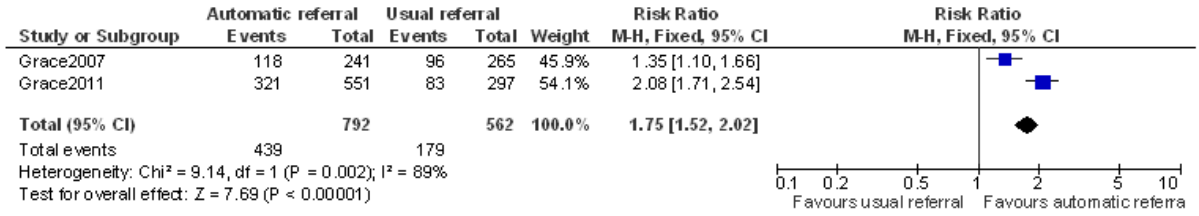


Figure 50: Automatic referral vs. usual referral to cardiac rehabilitation programme - adherence

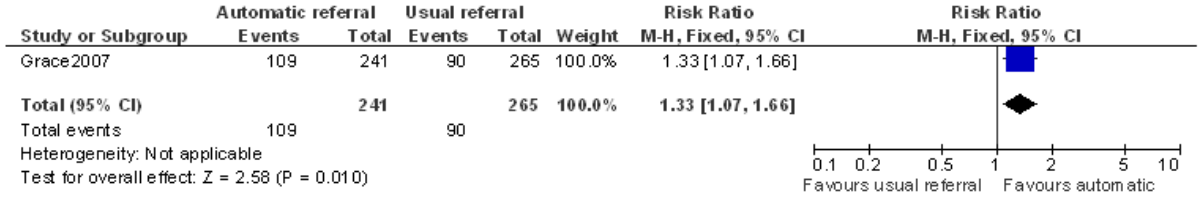


Figure 51: Automatic referral vs. usual referral to cardiac rehabilitation programme - percentage of classes attended

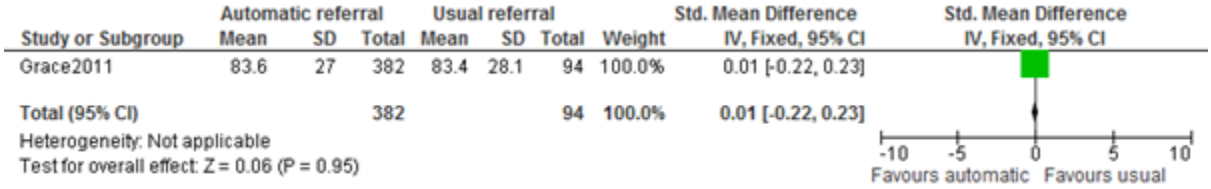


Figure 52: Automatic and liaison referral vs. usual referral to cardiac rehabilitation programme - uptake

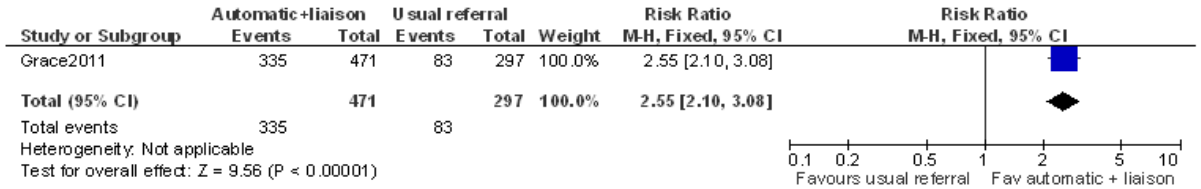


Figure 53: Automatic and liaison referral vs. usual referral to cardiac rehabilitation programme - percentage of classes attended

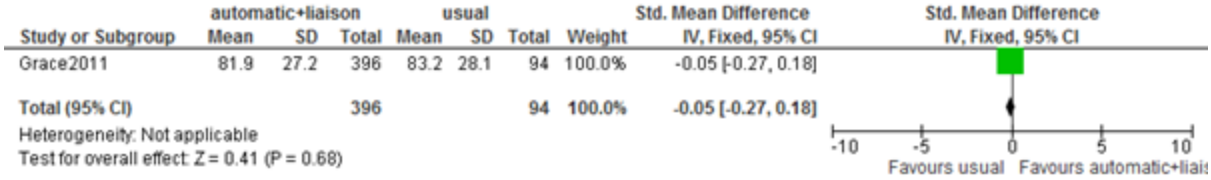


Figure 54: Short vs. long sessions - adherence

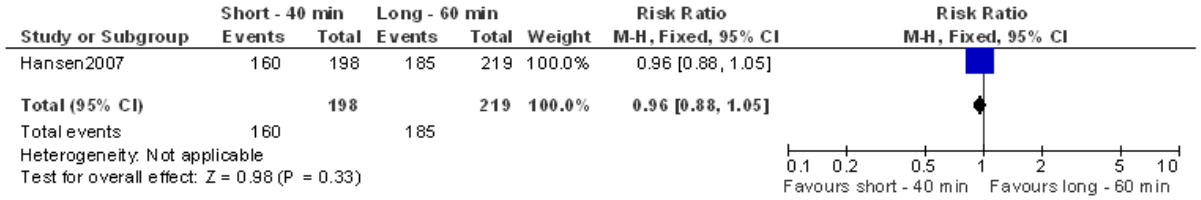


Figure 55: Home vs. centre based cardiac rehabilitation - adherence

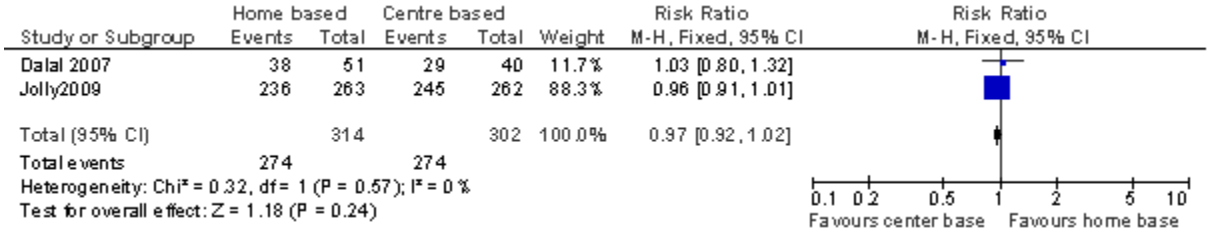


Figure 56: Behavioural letters vs. usual communication - uptake

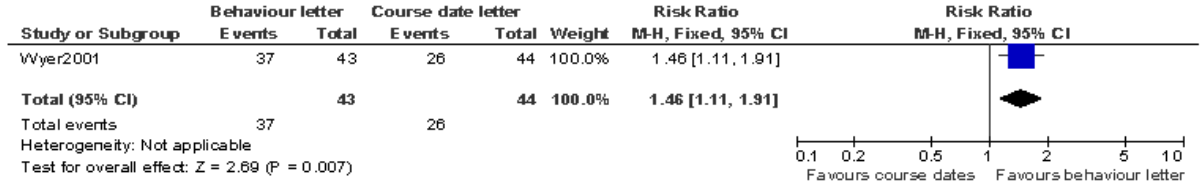
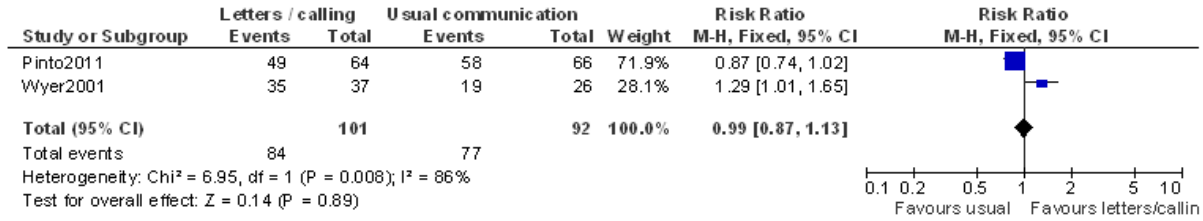


Figure 57: Letters and telephone calls vs. usual communication - adherence



Heterogeneity:

The results from this meta-analysis show heterogeneity is present, I^2=86% p =0.008. The protocol states that the following parameters should be investigated if heterogeneity is detected: type of MI (STEMI, NSTEMI), country (UK vs. non-UK), treatment (PCI, CABG, medical treatment) and co-morbidity. Of these factors, the only parameter the papers provided sufficient data was the country in which they were conducted. Wyer was conducted in the UK and Pinto in the USA. Whether this explains the variations in the results it is not clear.

Figure 58: Home visit vs. telephone calls – uptake

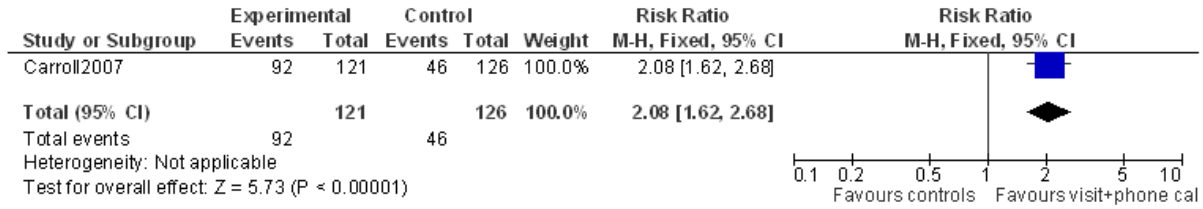


Figure 59: Education of staff vs. usual care - uptake

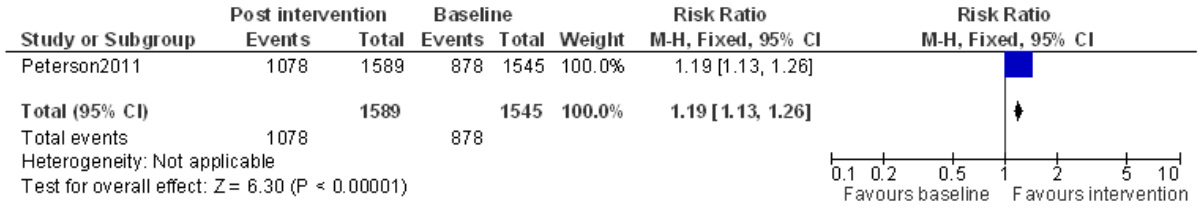


Figure 60: Telephone calls vs. usual care - uptake

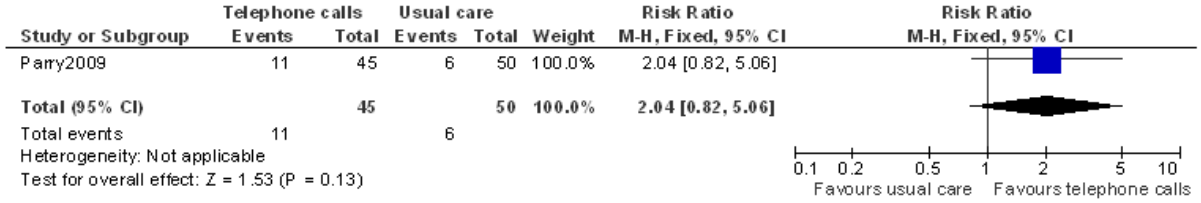


Figure 61: Letters and telephone calls vs. letters – mean attendance

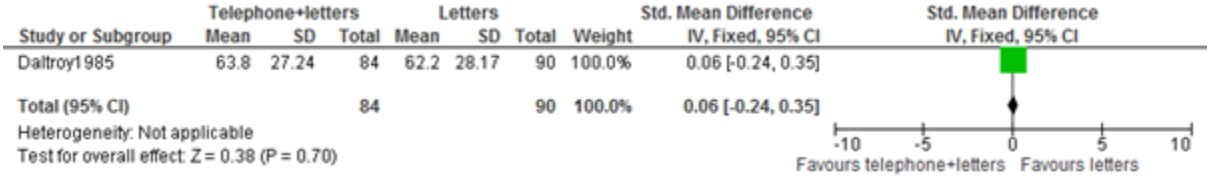


Figure 62: Pre-approved referral strategy vs. usual referral to cardiac rehabilitation programme-uptake

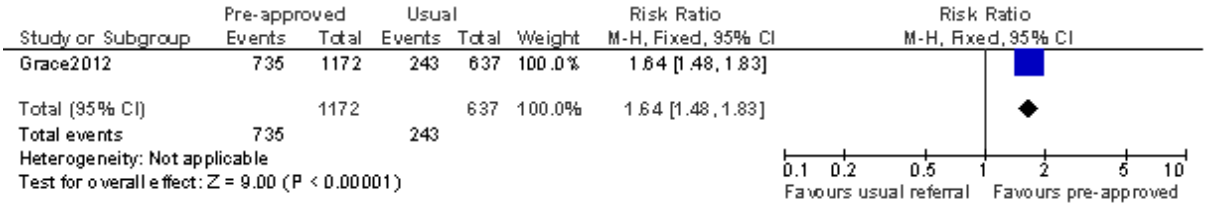


Figure 63: Pre-approved referral strategy vs. usual referral to cardiac rehabilitation programme – mean attendance

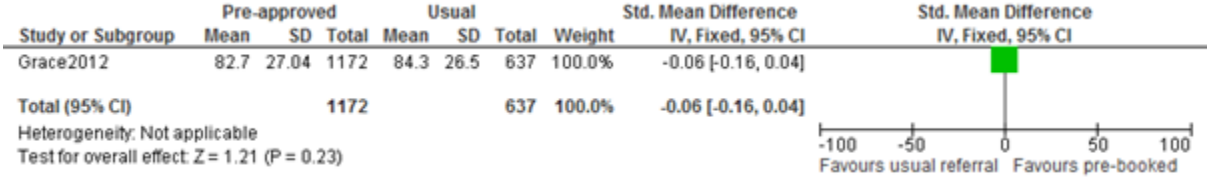


Figure 64: Pre-booked referral strategy vs. usual referral to cardiac rehabilitation programme - uptake

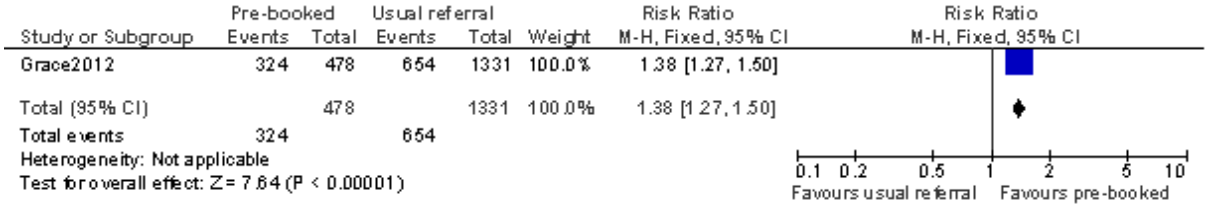


Figure 65: Pre-booked referral strategy vs. usual referral to cardiac rehabilitation programme – mean attendance

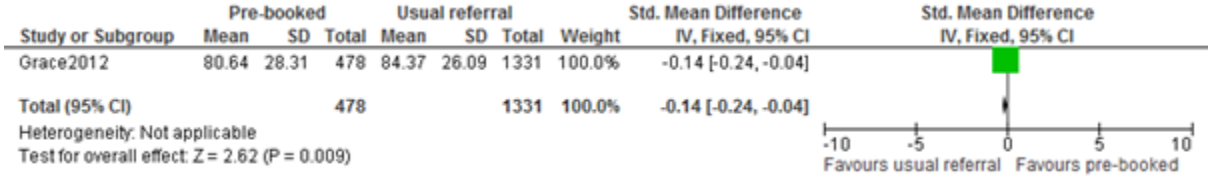


Figure 66: Early education vs. usual referral to cardiac rehabilitation programme - uptake

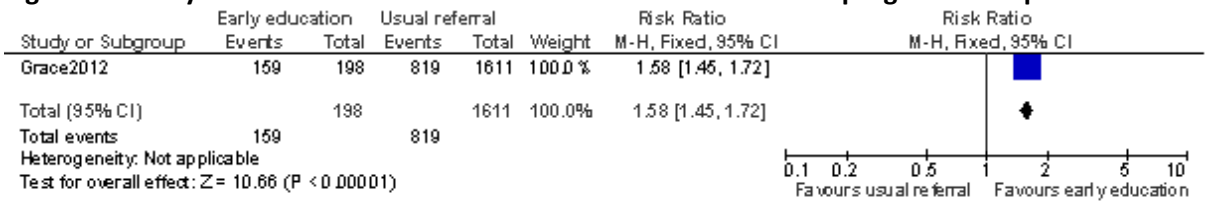
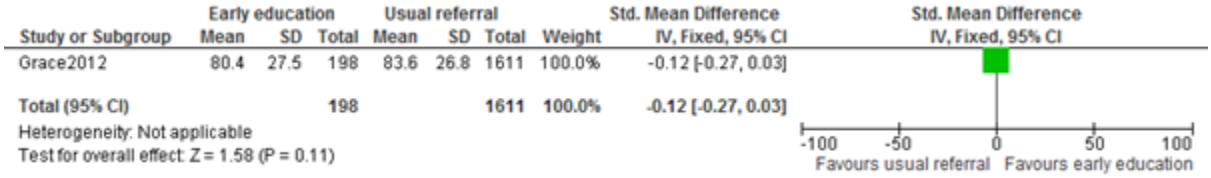


Figure 67: Early education vs. usual referral to cardiac rehabilitation programme – mean attendance



I.3 Drug therapy

I.3.1 ACE inhibitor vs. placebo and optimal duration of ACE inhibitor therapy

I.3.1.1 People who have had an MI with LVSD

Figure 68: ACE inhibitor vs. placebo in people who have had an MI with LVSD – all-cause mortality

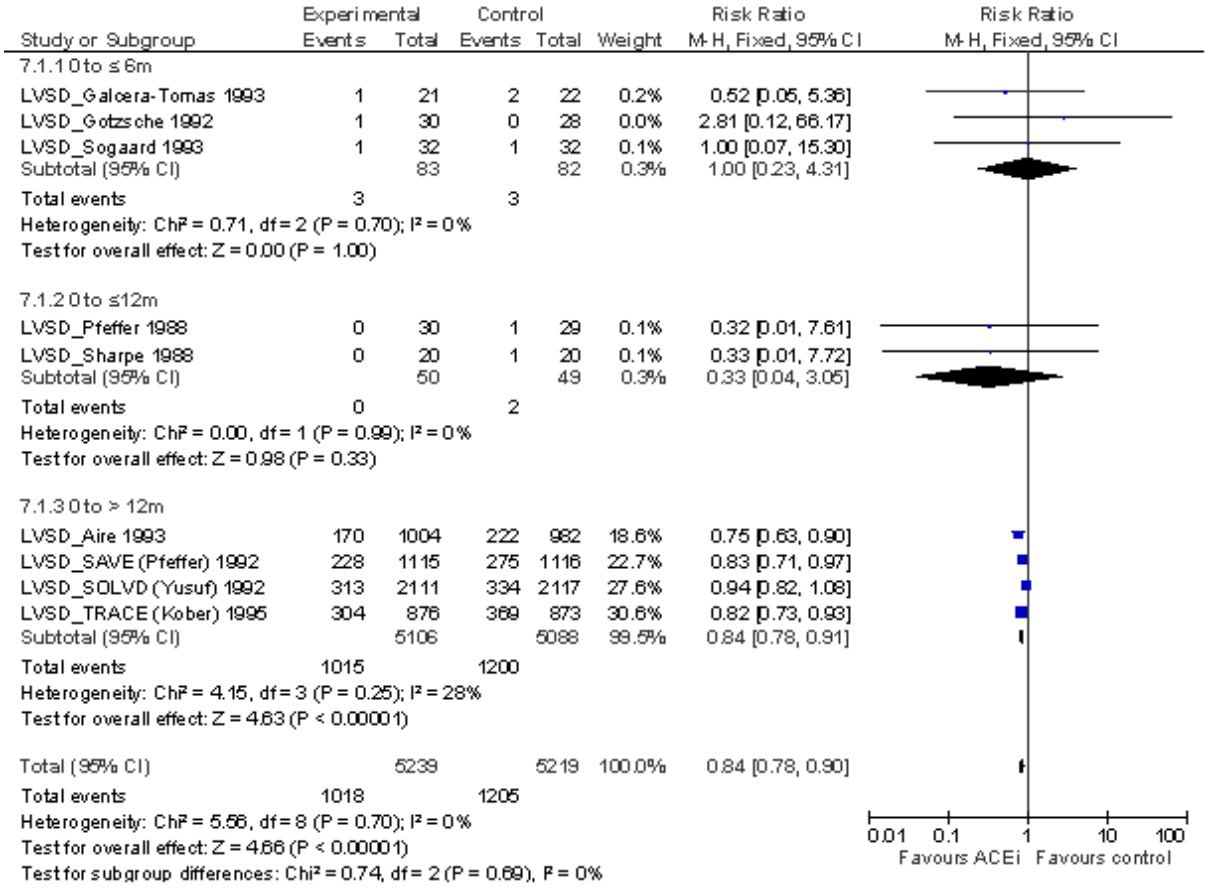
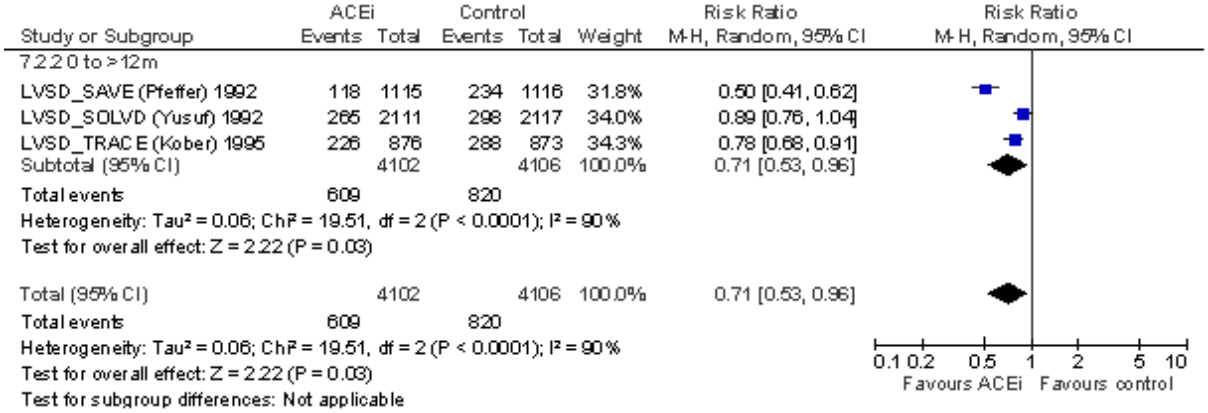


Figure 69: ACE inhibitor vs. placebo in people who have had an MI with LVSD – cardiac mortality



Heterogeneity

Heterogeneity was detected (I^2=90%, p<0.0001) for the effects of ACE inhibitors on the risk of cardiac mortality in post MI patients for the first 12 months of treatment. The results show the same trend for all three papers, but one paper shows a much larger effect than the other two paper and if this is

removed heterogeneity is also removed. However, there is no justification to remove this paper nor do any of the subgroups explain any differences. For this reason the results are presented as random effects rather than fixed effects.

Figure 70: ACE inhibitor vs. placebo in people who have had an MI with LVSD – sudden death

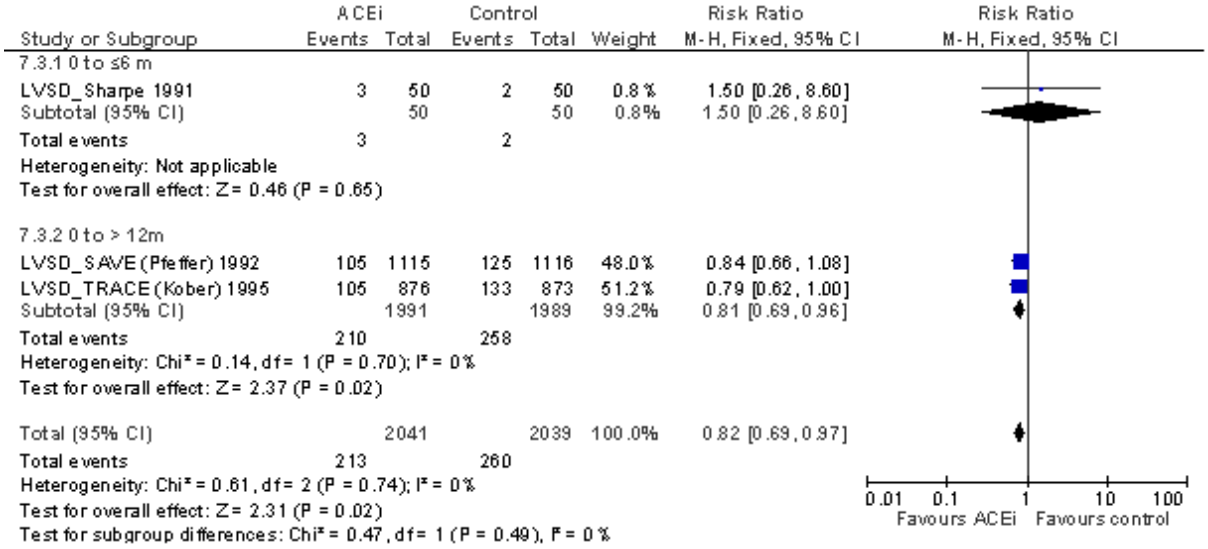
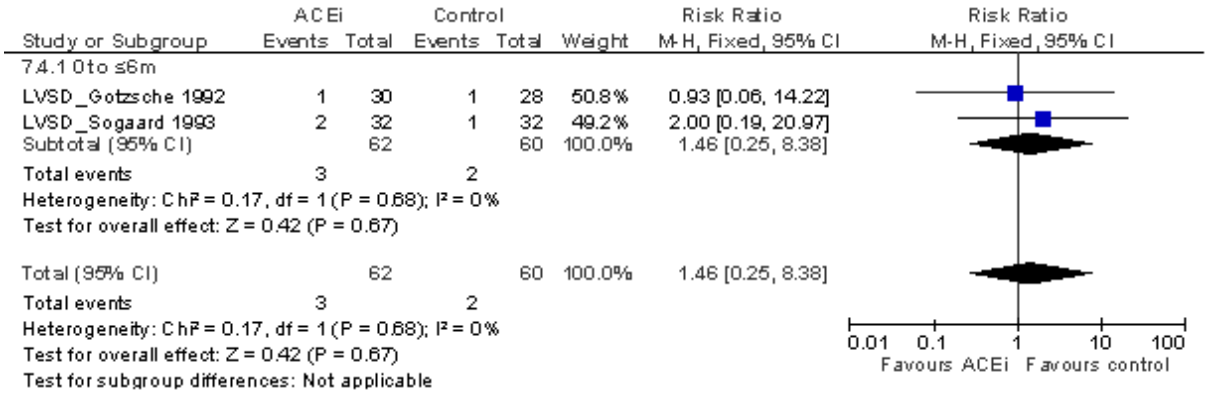


Figure 71: ACE inhibitor vs. placebo in people who have had an MI with LVSD - revascularisation



<Insert Note here>

Figure 72: ACE inhibitor vs. placebo in people who have had an MI patients with LVSD - reinfarction

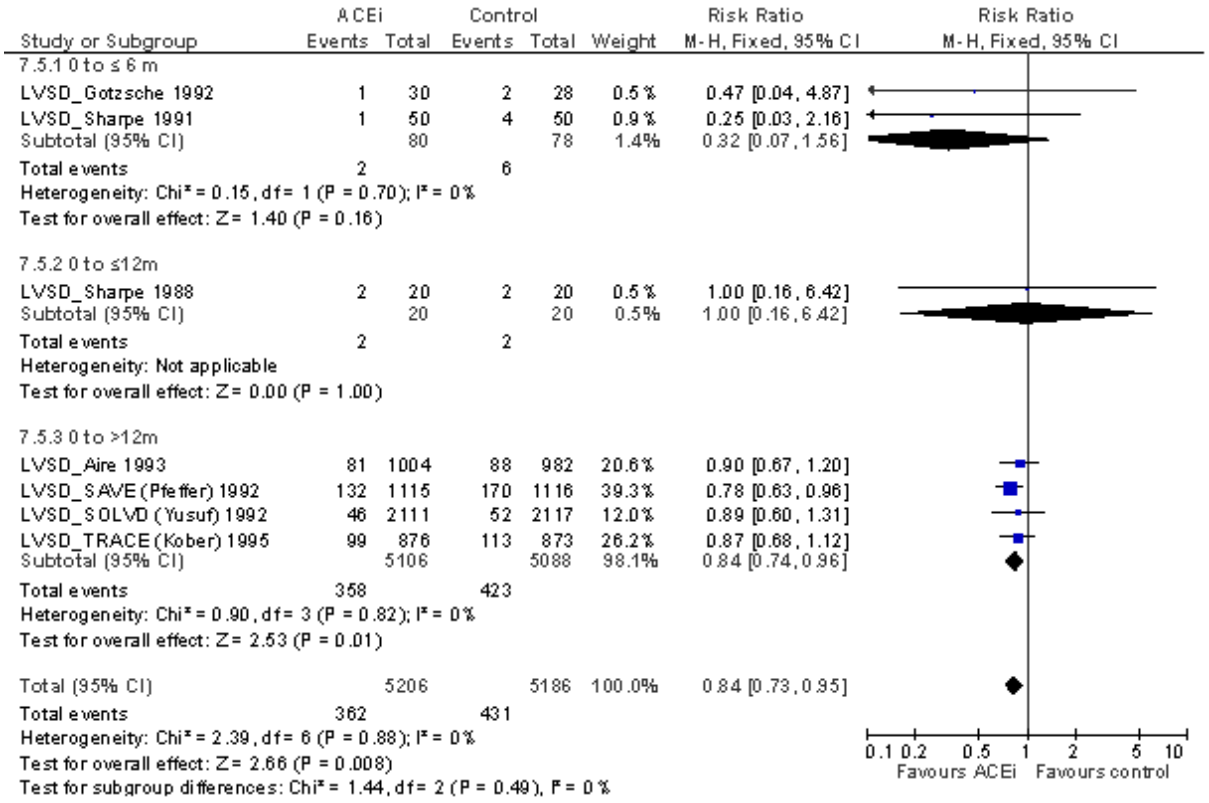
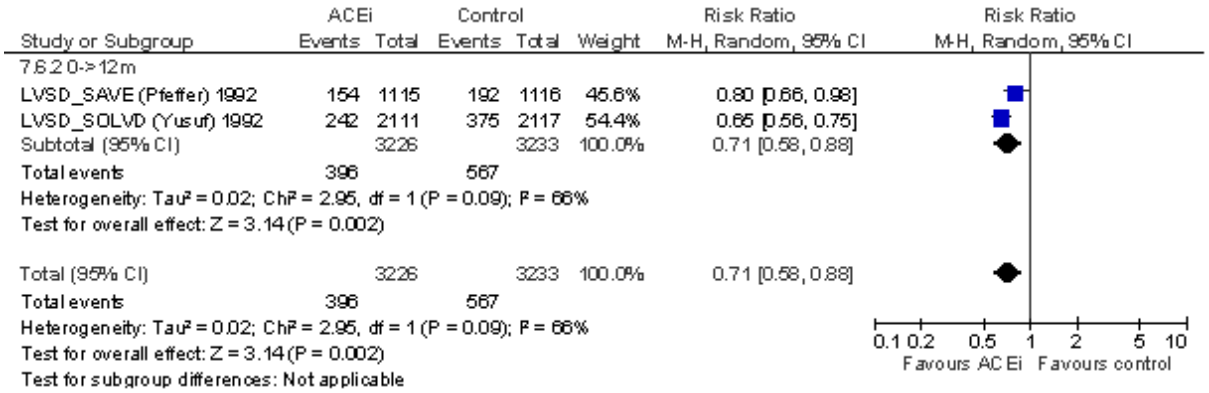


Figure 73: ACE inhibitor vs. placebo in people who have had an MI patients with LVSD - hospitalisation



Heterogeneity

Heterogeneity was detected (I^2=66%, p<0.09) for the effects of ACE inhibitors on the risk of rehospitalisation in post MI patients for the first 12 months of treatment. The results show the same trend for the two papers, but one paper shows a much larger effect than the other and if this is removed heterogeneity is also removed. However, there is no justification to remove this paper nor do any of the subgroups explain any differences. For this reason the results are presented as random effects rather than fixed effects.

Figure 74: ACE inhibitor vs. placebo in people who have had an MI patients with LVSD - stroke

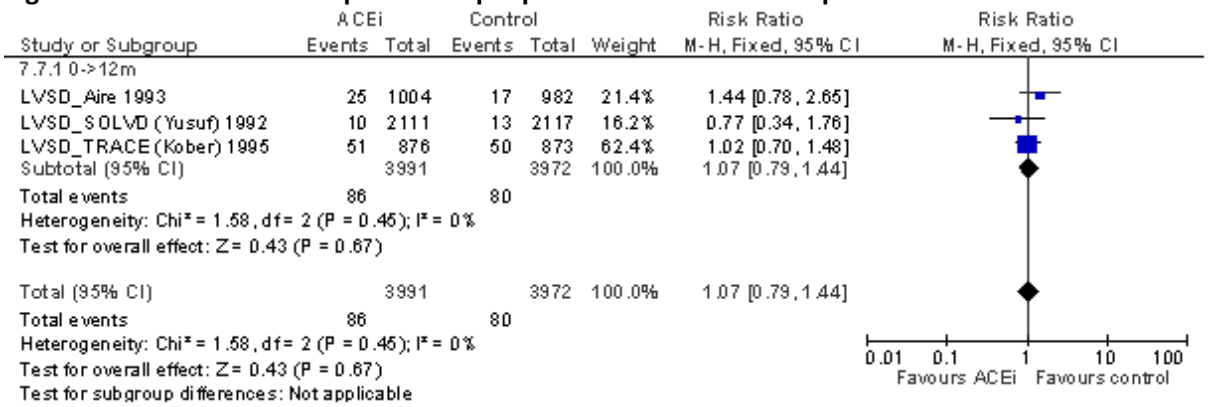


Figure 75: ACE inhibitor vs. placebo in people who have had an MI patients with LVSD – adverse events

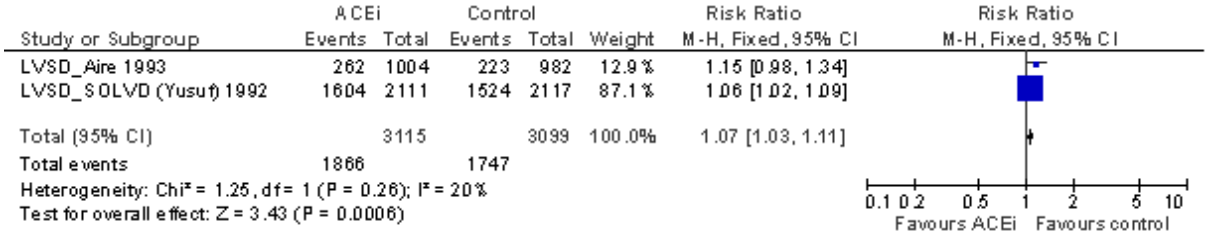


Figure 76: ACE inhibitor vs. placebo in people who have had an MI patients with LVSD – renal dysfunction

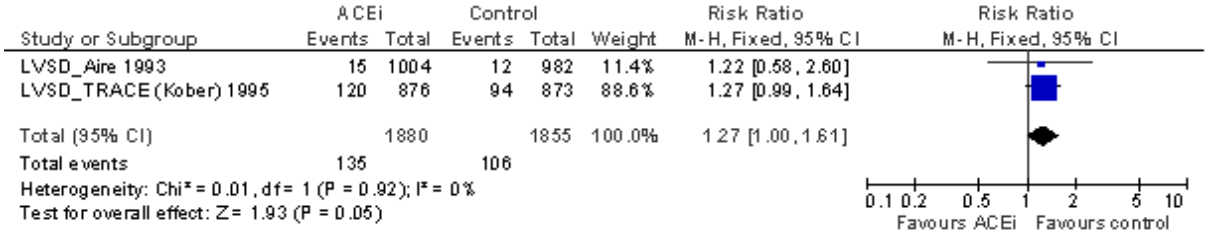


Figure 77: ACE inhibitor vs. placebo in people who have had an MI patients with LVSD – hypotension

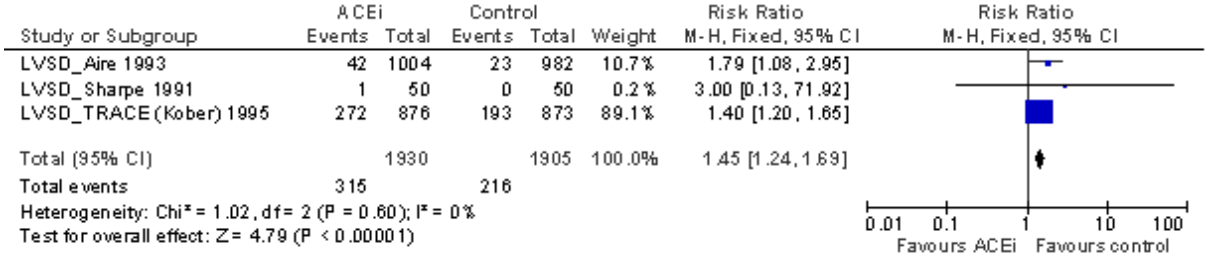
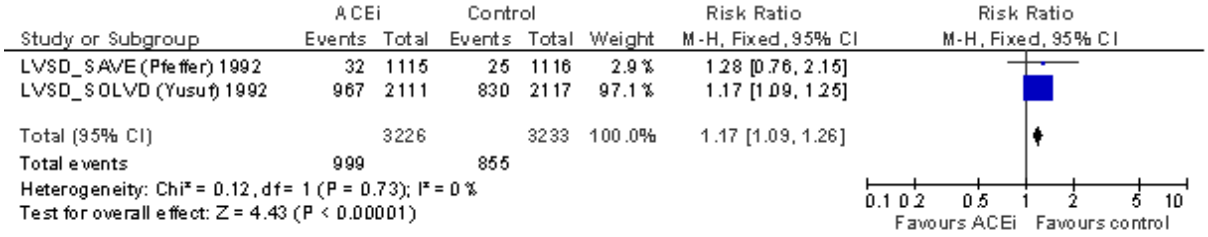


Figure 78: ACE inhibitor vs. placebo in people who have had an MI patients with LVSD – dizziness/fainting



I.3.1.2 People who have had an MI without heart failure

Figure 79: ACE inhibitor vs. placebo in people who have had an MI patients without heart failure– all-cause mortality

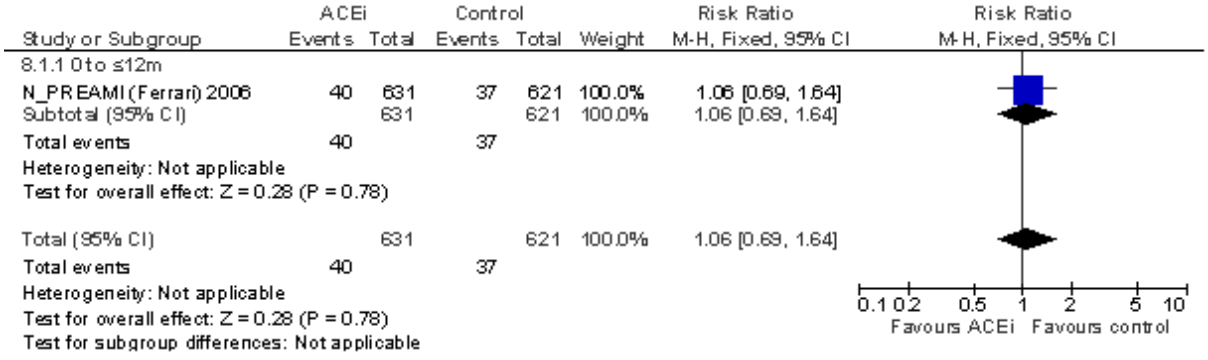


Figure 80: ACE inhibitor vs. placebo in people who have had an MI without heart failure - reinfarction

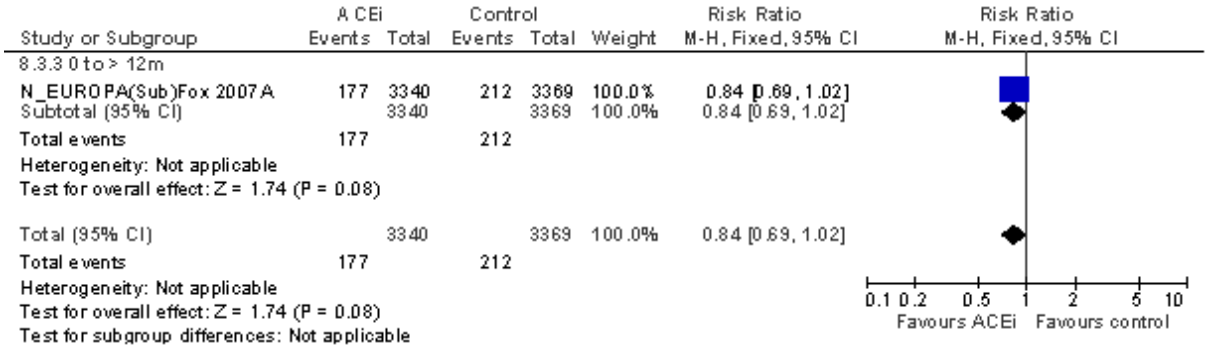


Figure 81: ACE inhibitor vs. placebo in people who have had an MI without heart failure - hospitalisation

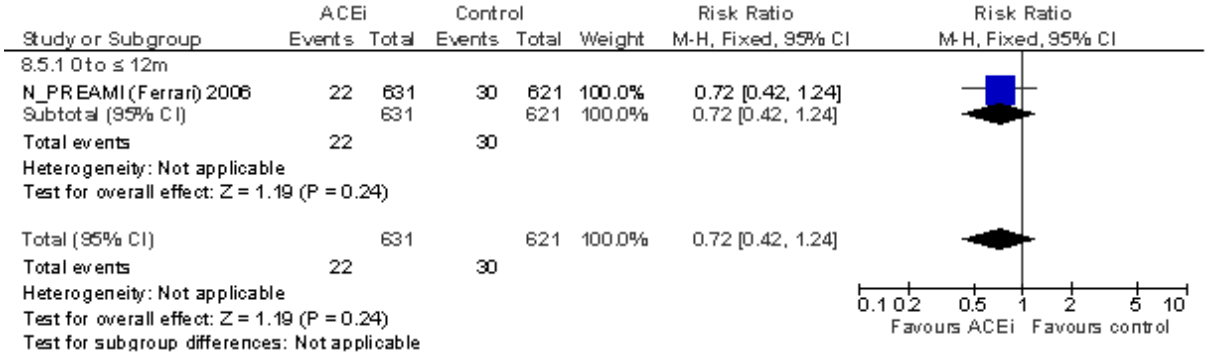


Figure 82: ACE inhibitor vs. placebo in people who have had an MI without heart failure – adverse events

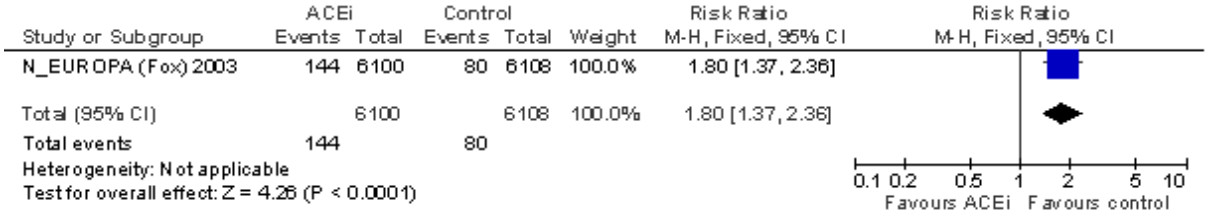


Figure 83: ACE inhibitor vs. placebo in people who have had an MI without heart failure – CV death, non-fatal MI, cardiac arrest

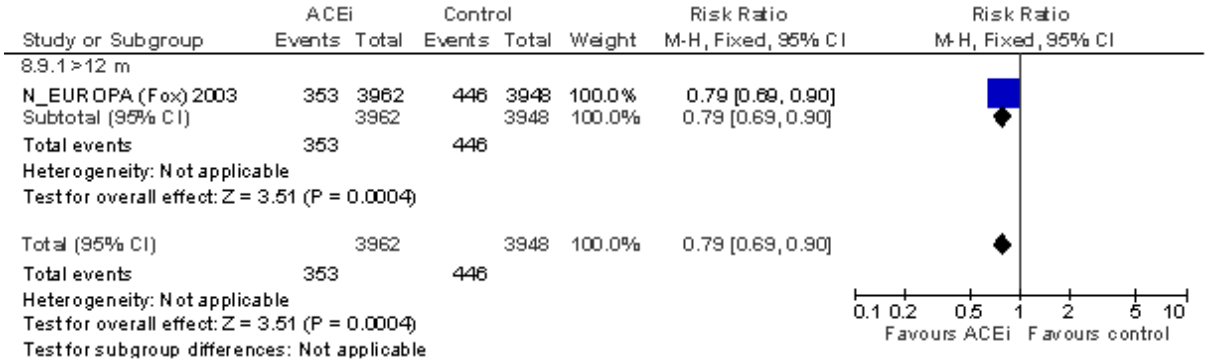


Figure 84: ACE inhibitor vs. placebo in people who have had an MI without heart failure - CV death, MI, stroke

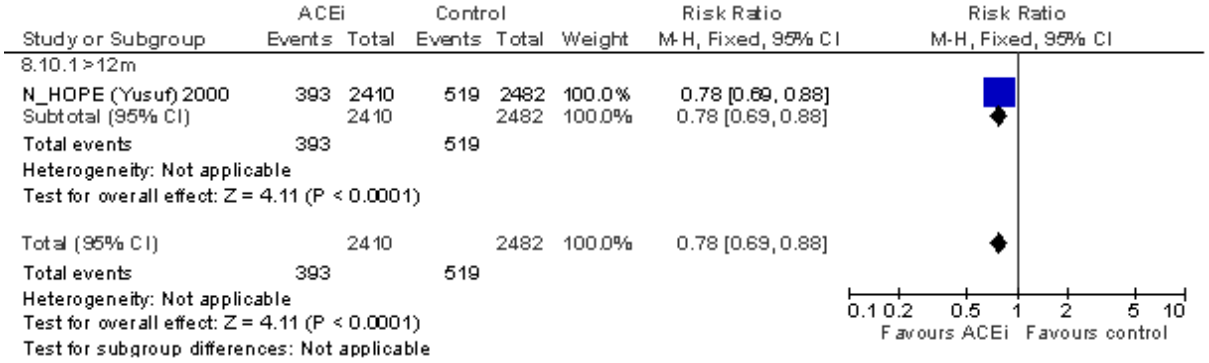


Figure 85: ACE inhibitor vs. placebo in people who have had an MI without heart failure (indirect population) – cardiac mortality

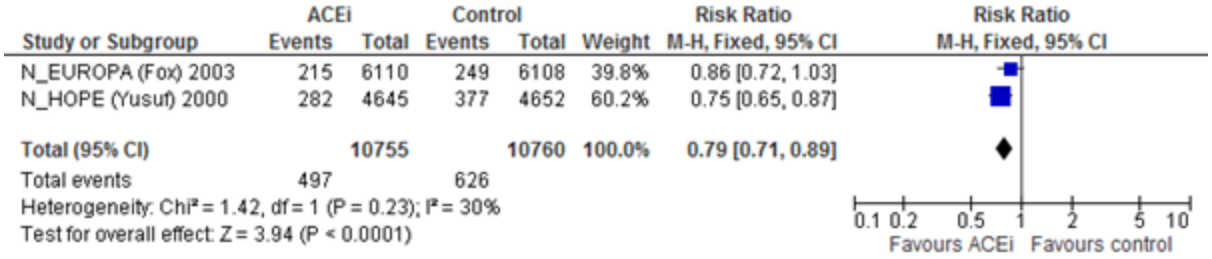


Figure 86: ACE inhibitor vs. placebo in people who have had an MI without heart failure (indirect population) - stroke

I.3.1.3 People who have had an MI with unselected LV function

Figure 87: ACE inhibitor vs. placebo in people who have had an MI with unselected LV function – all-cause mortality

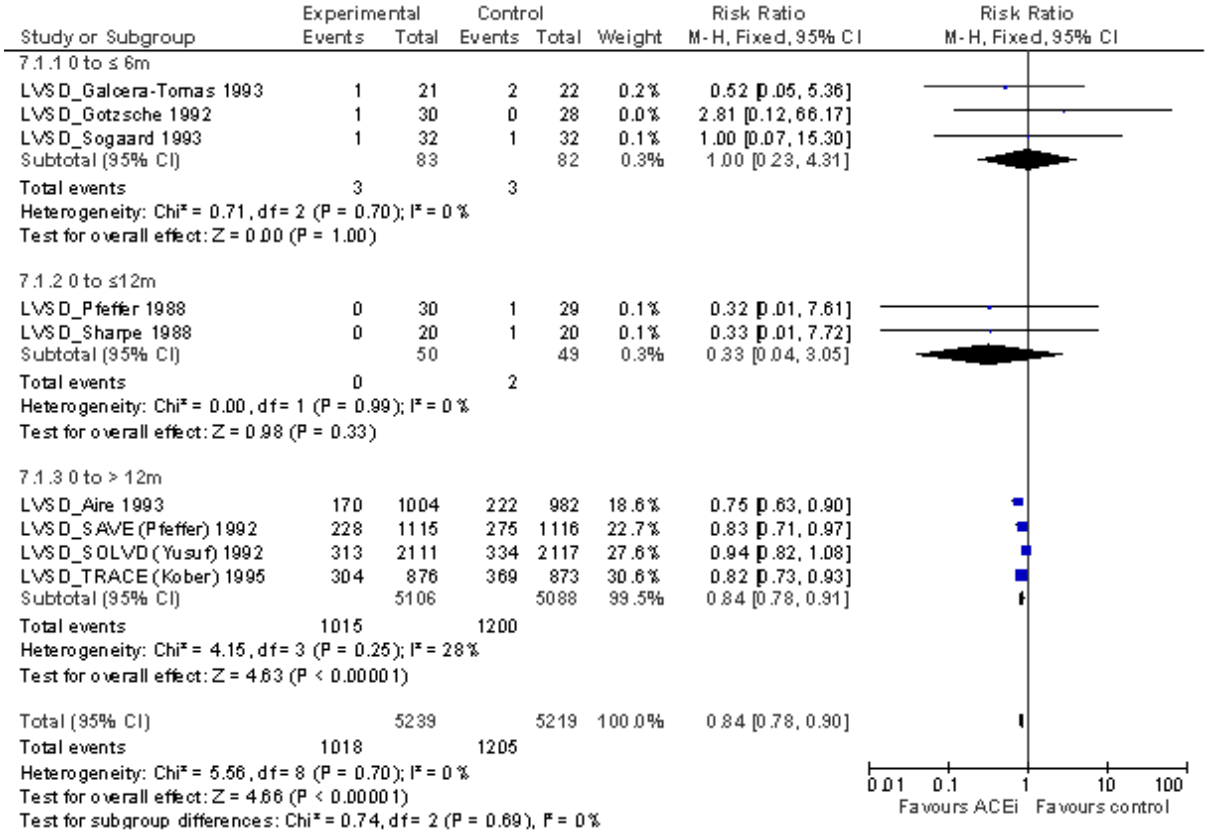


Figure 88: ACE inhibitor vs. placebo in people who have had an MI with unselected LV function – sudden death

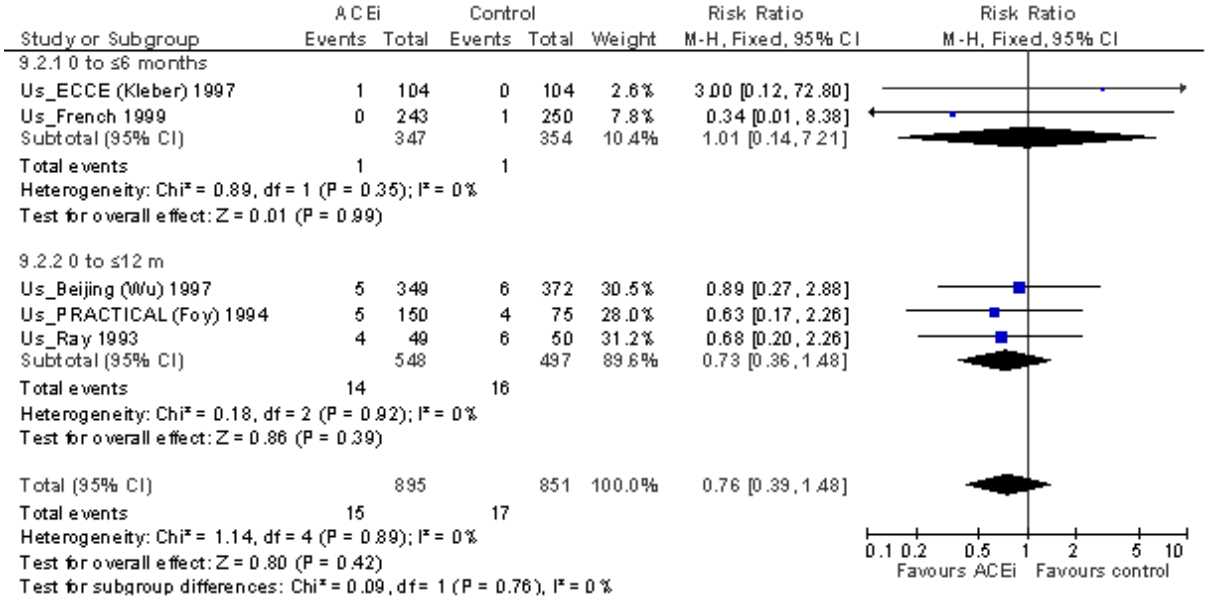


Figure 89: ACE inhibitor vs. placebo in people who have had an MI with unselected LV function – cardiac mortality

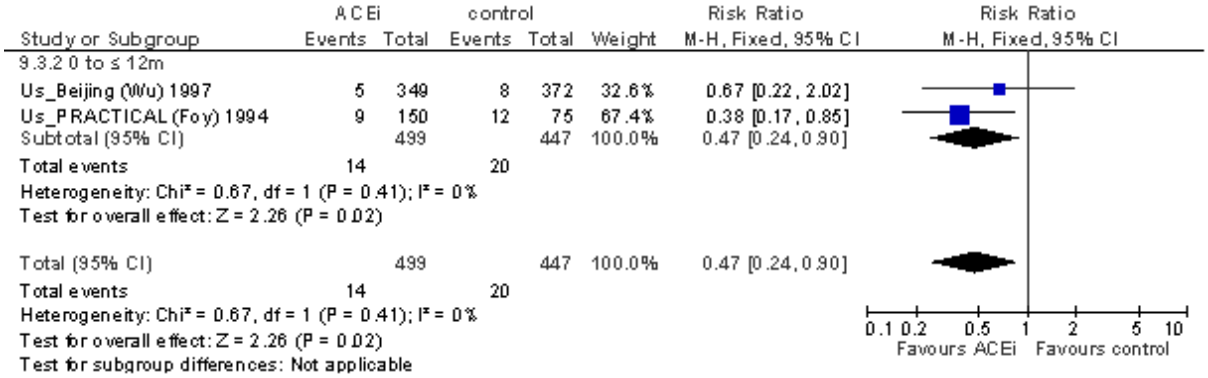


Figure 90: ACE inhibitor vs. placebo in people who have had an MI with unselected LV function - reinfarction

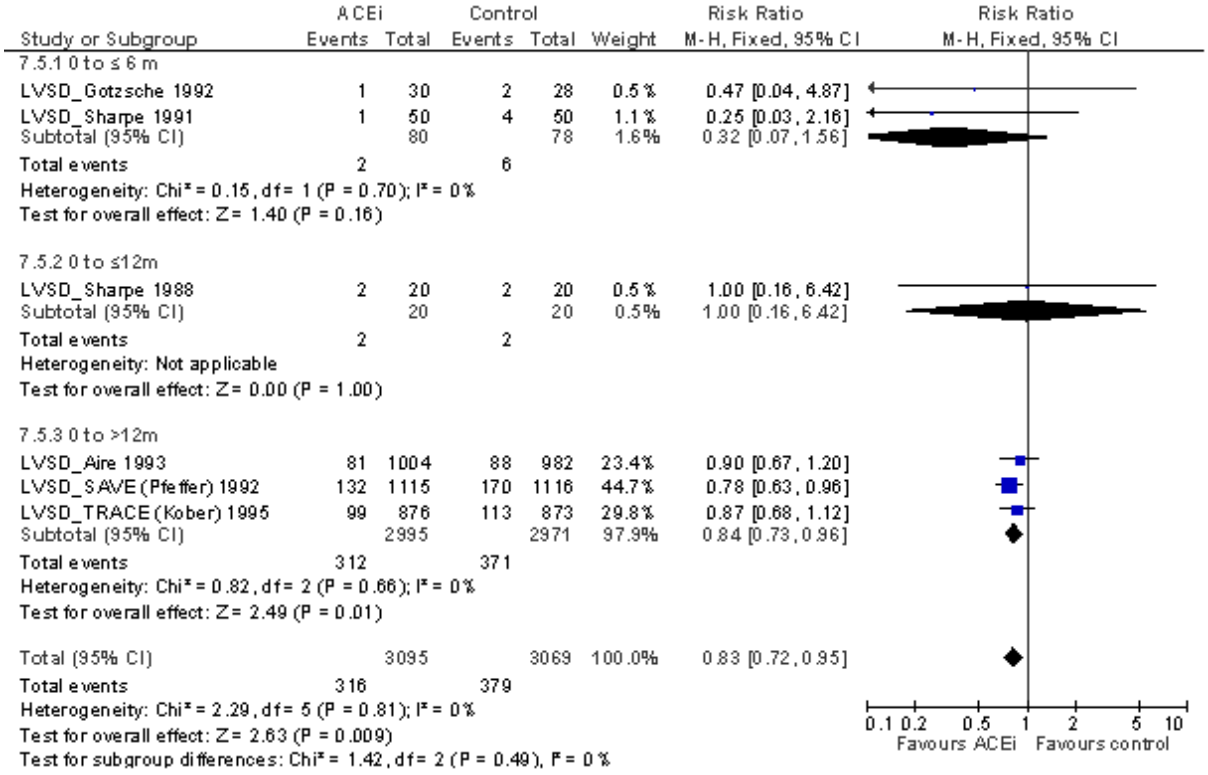


Figure 91: ACE inhibitor vs. placebo in people who have had an MI with unselected LV function - revascularisation

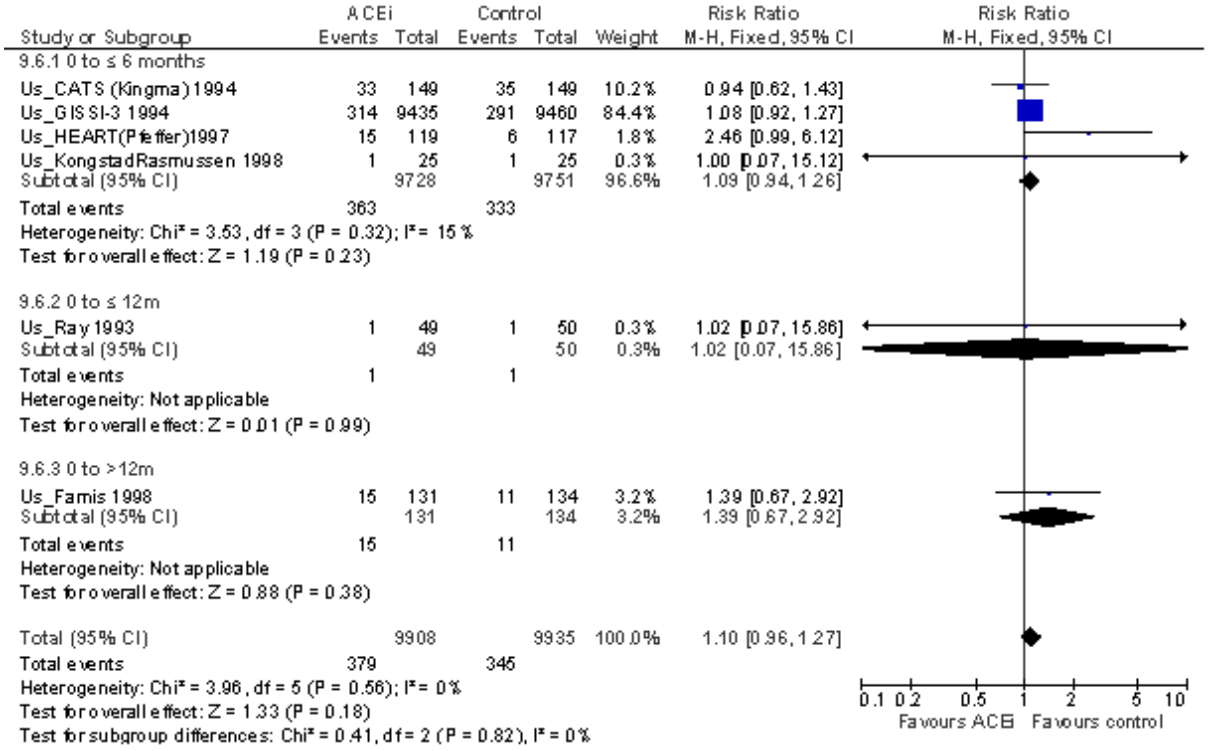


Figure 92: ACE inhibitor vs. placebo in people who have had an MI with unselected LV function - stroke

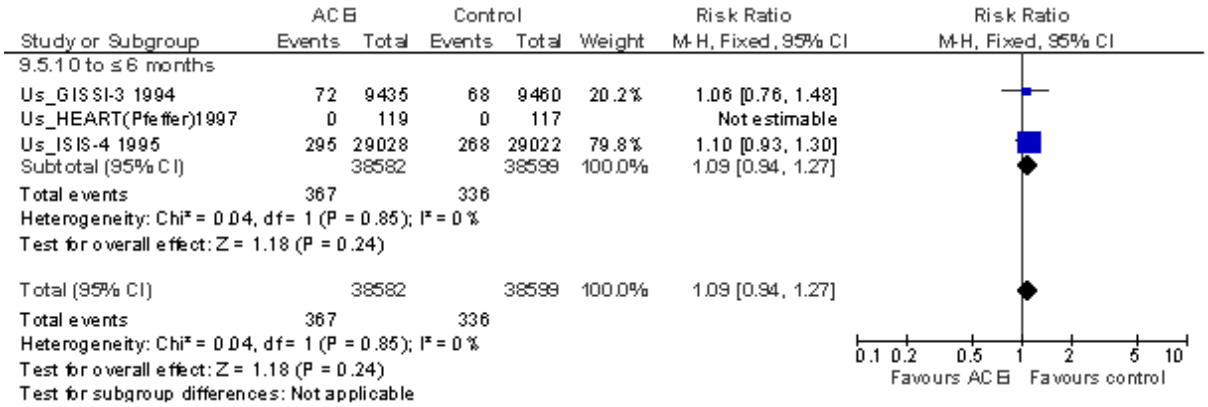


Figure 93: ACE inhibitor vs. placebo in people who have had an MI with unselected LV function – adverse events

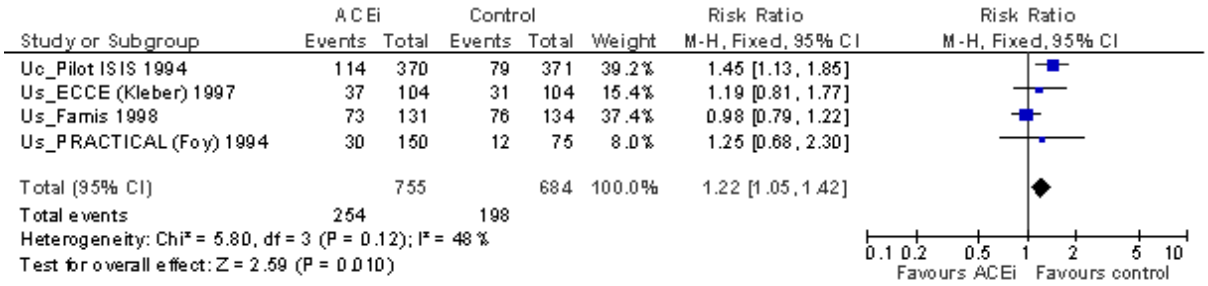


Figure 94: ACE inhibitor vs. placebo in people who have had an MI with unselected LV function - hyperkalemia

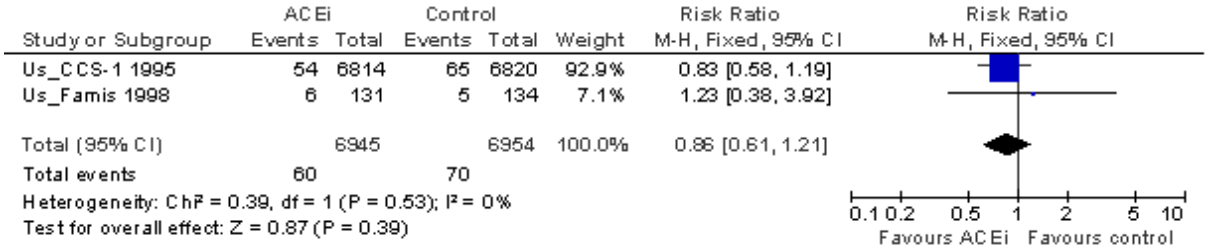


Figure 95: ACE inhibitor vs. placebo in people who have had an MI with unselected LV function – renal dysfunction

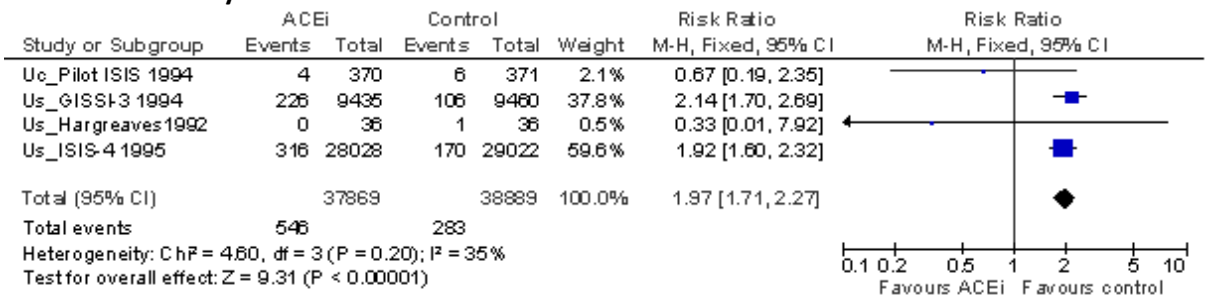
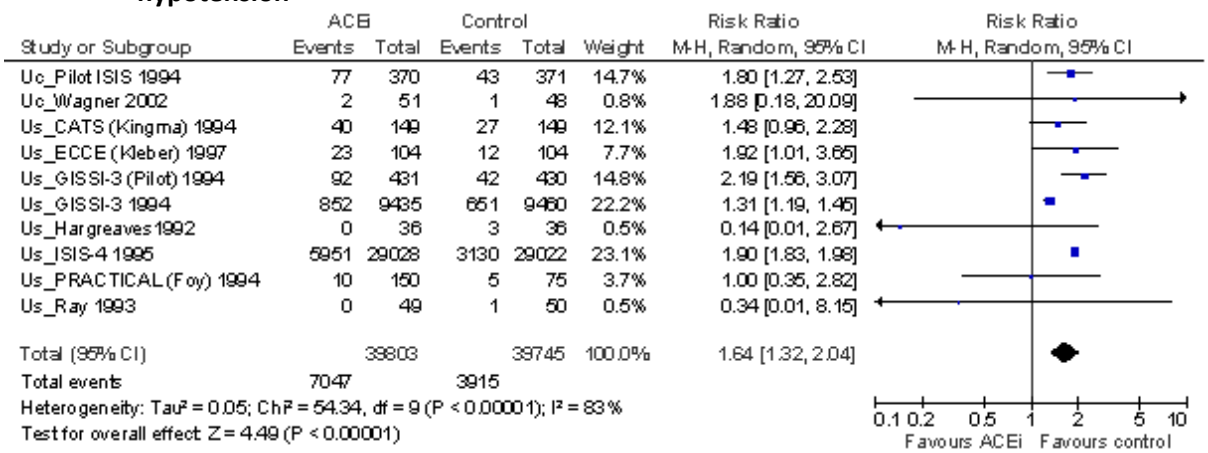


Figure 96: ACE inhibitor vs. placebo in people who have had an MI with unselected LV function - hypotension



Heterogeneity

Heterogeneity was detected at I^2 =83%, p<0.0001. Although the findings mostly show the same trend, it can be explained by the small patient numbers in these studies that result in large 95% CI. However removing these didn't remove the heterogeneity. Nor did any of the subgroups explain any of the differences. Thus to address this, the results are shown as a random effects rather than fixed effects.

Figure 97: ACE inhibitor vs. placebo in people who have had an MI with unselected LV function - dizziness

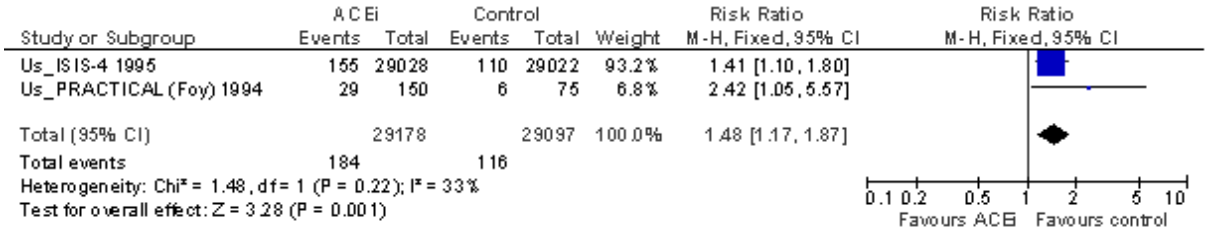


Figure 98: ACE inhibitor vs. placebo in people who have had an MI with unselected LV function – all-cause mortality (distinct time periods)

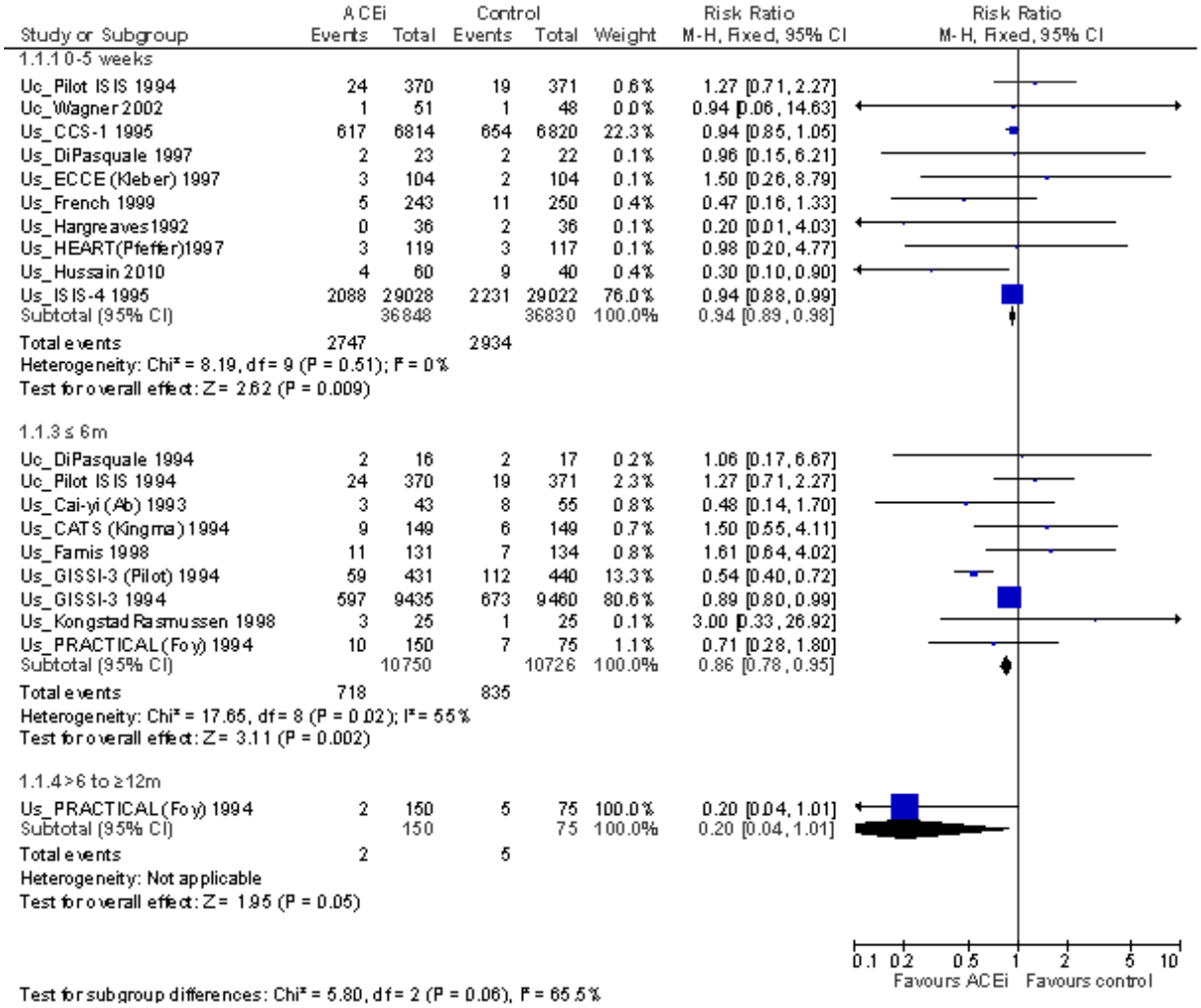


Figure 99: ACE inhibitor vs. placebo in people who have had an MI with unselected LV function – cardiac mortality (distinct time periods)

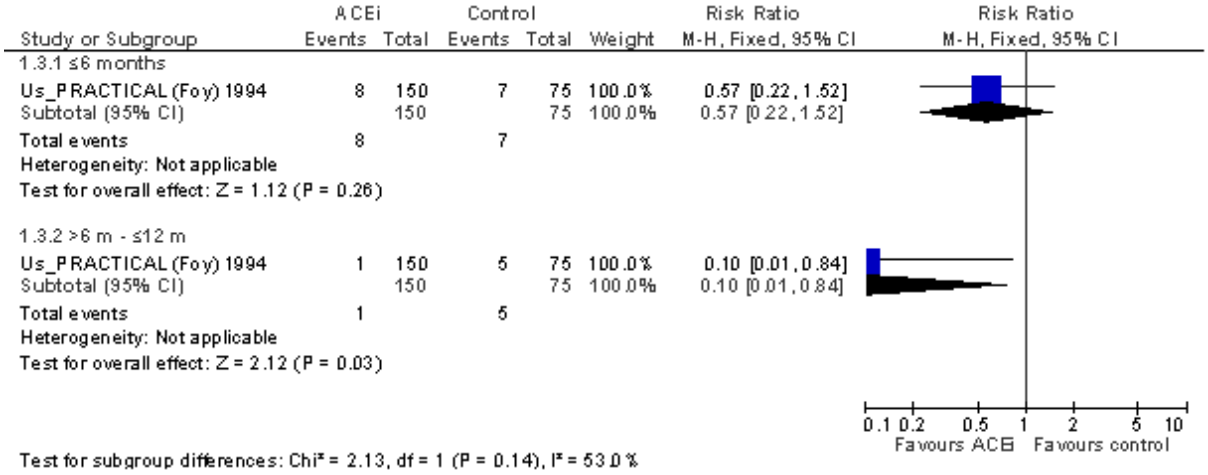


Figure 100: ACE inhibitor vs. placebo in people who have had an MI with unselected LV function – sudden death (distinct time periods)

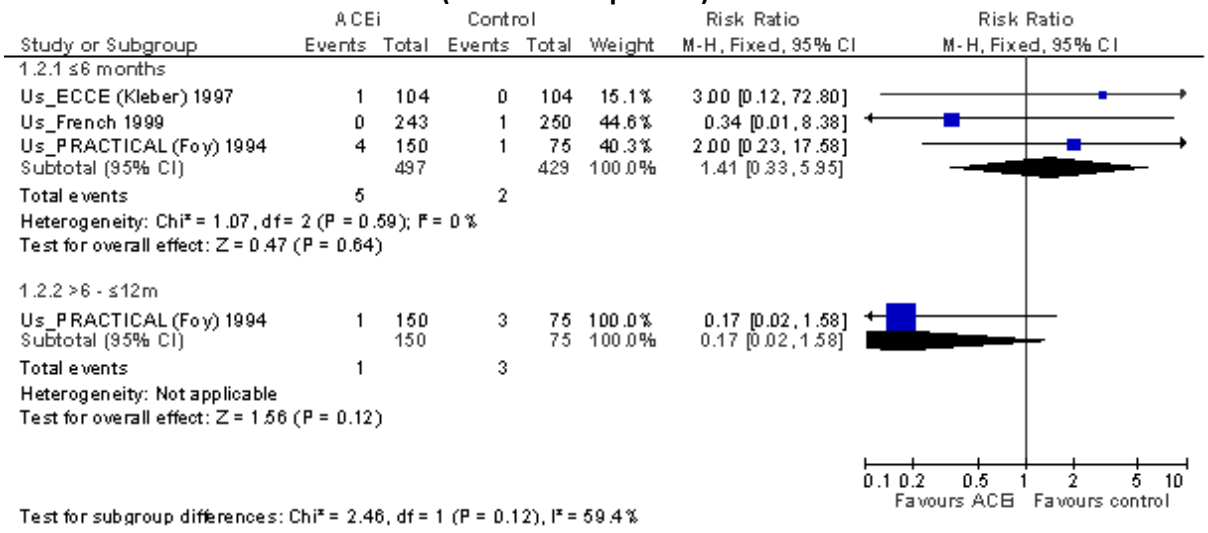
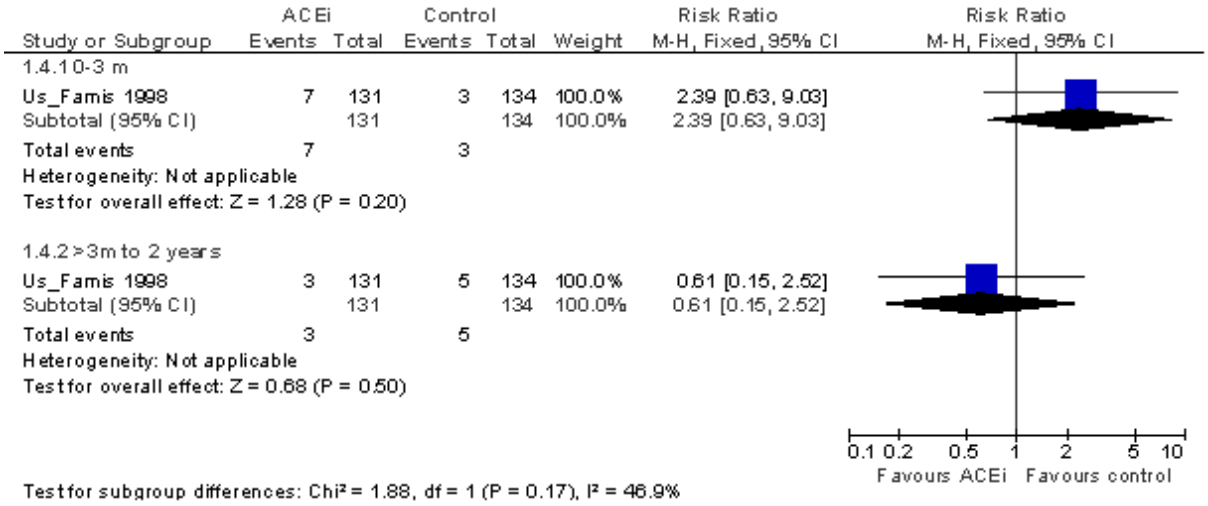
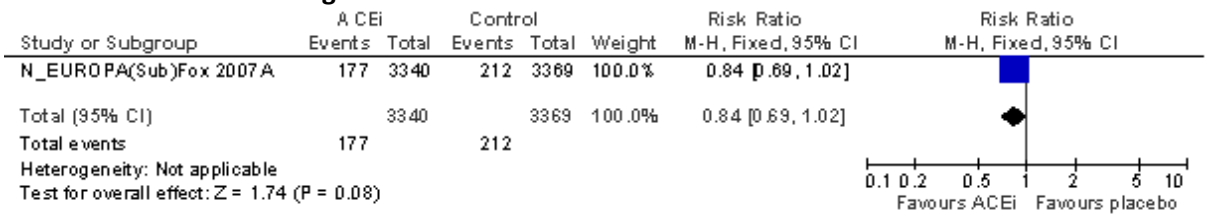


Figure 101: ACE inhibitor vs. placebo in people who have had an MI with unselected LV function – reinfarcton (distinct time periods)



I.3.1.4 Revascularisation in people who have had an MI with normal LV function

Figure 102: ACE inhibitor vs. placebo in people who have had an MI with Normal LV function who had undergone revascularisation - reinfarction



I.3.2 Initiation of ACE inhibitors

I.3.2.1 Early initiation versus late initiation of ACE inhibitors

Figure 103: ACE inhibitor (early initiation) vs. ACE inhibitor (late initiation) - all-cause mortality

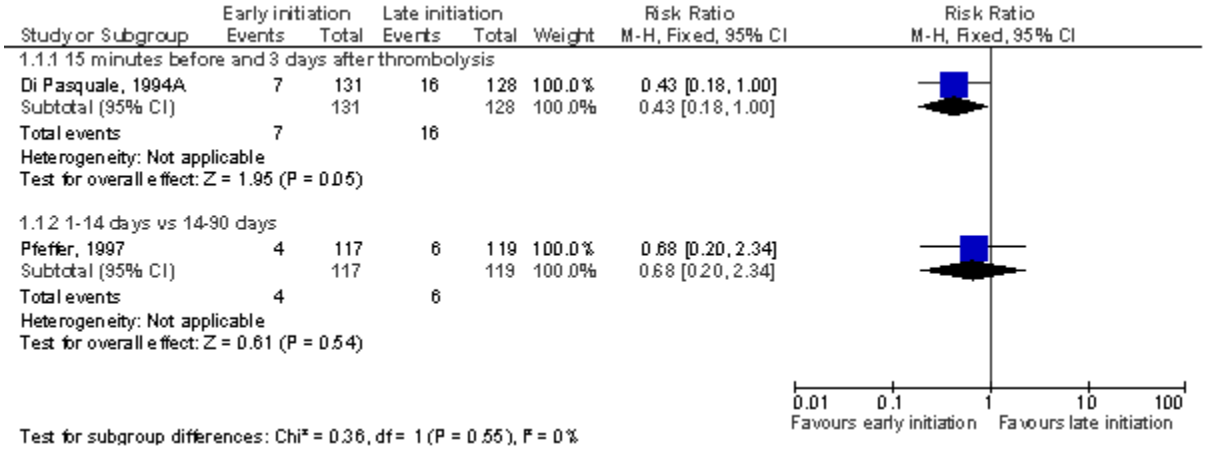


Figure 104: ACE inhibitor (early initiation) vs. ACE inhibitor (late initiation) - revascularisation

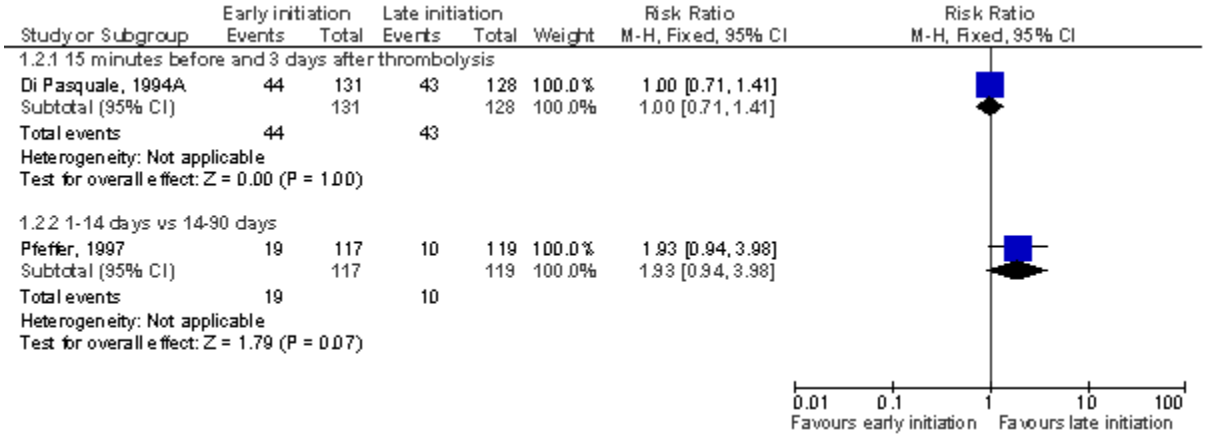


Figure 105: ACE inhibitor (early initiation) vs. ACE inhibitor (late initiation) - stroke (1-14 days vs. 14-90 days)

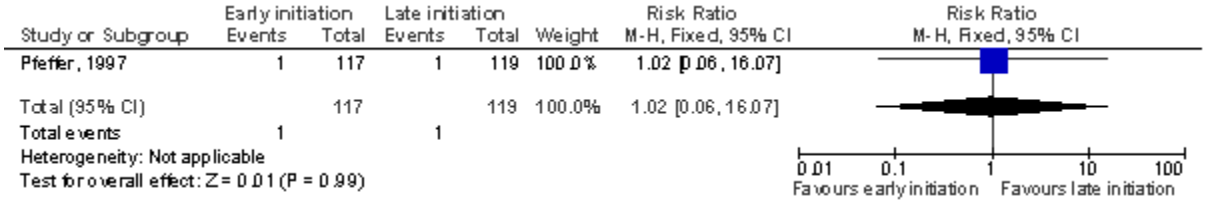


Figure 106: ACE inhibitor (early initiation) vs. ACE inhibitor (late initiation) - reinfarction (1-14 days vs. 14-90 days)

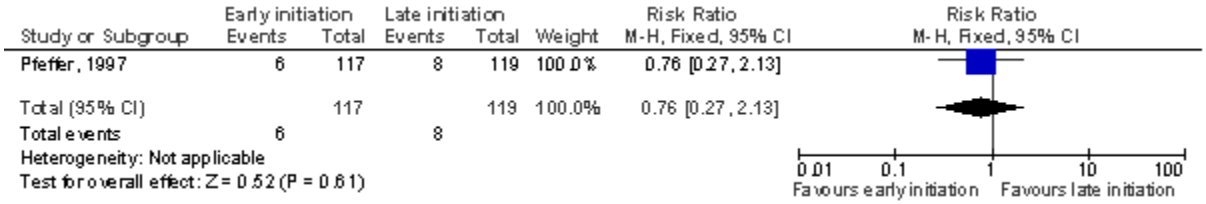
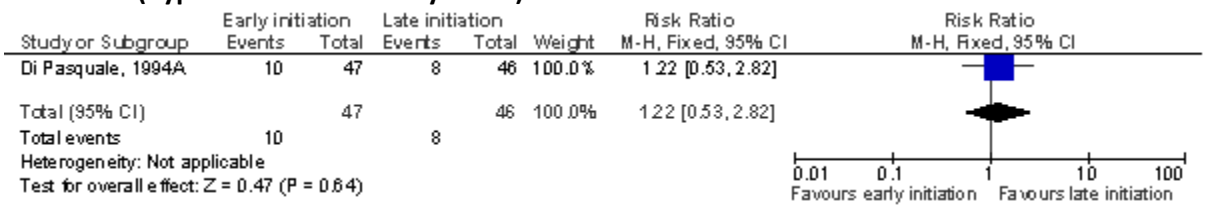


Figure 107: ACE inhibitor (early initiation) vs. ACE inhibitor (late initiation) - adverse events (hypotension and brachycardia)



I.3.3 ACE inhibitor titration methods

I.3.3.1 Ramipril (low constant dose) vs. ramipril (high dose titration)

Figure 108: Ramipril (low constant dose) vs. ramipril (high dose titration) – all-cause mortality (people who have had an MI)

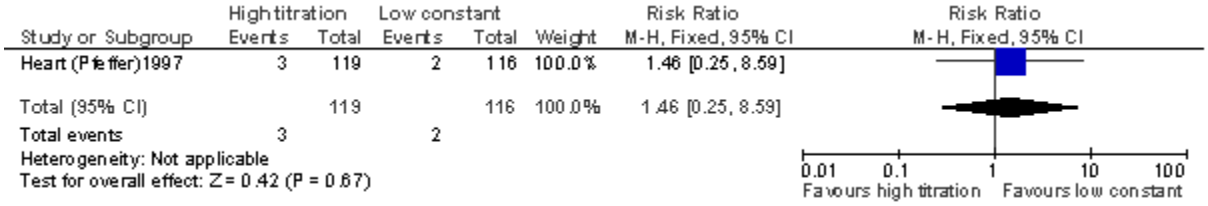


Figure 109: Ramipril (low constant dose) vs. ramipril (high dose titration) - reinfarction (people who have had an MI)

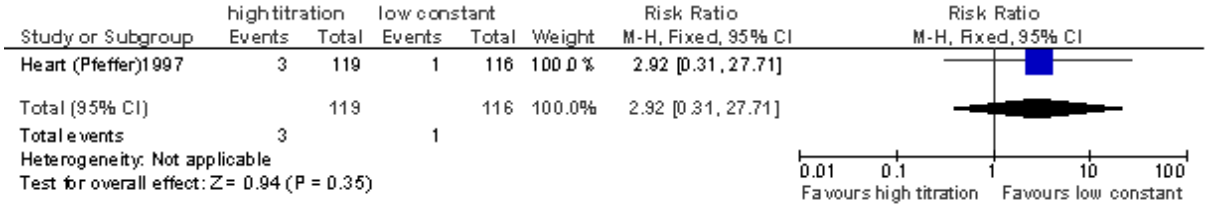


Figure 110: Ramipril (low constant dose) vs. ramipril (high dose titration) – stroke (people who have had an MI)

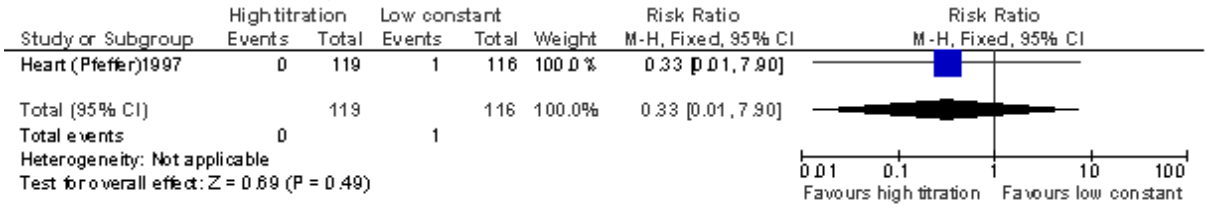


Figure 111: Ramipril (low constant dose) vs. ramipril (high dose titration) – hypotension (one SBP ≤90mm Hg reading) (people who have had an MI)

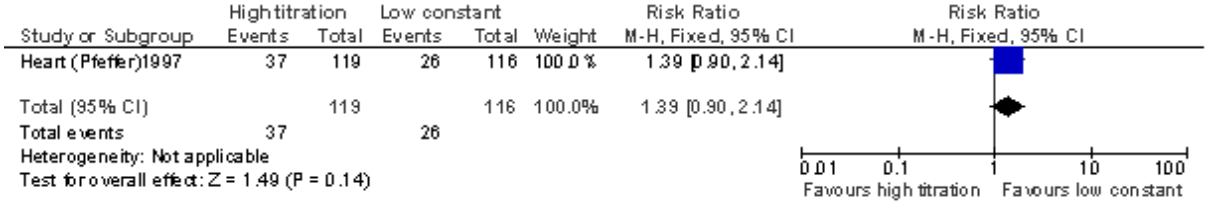


Figure 112: Ramipril (low constant dose) vs. ramipril (high dose titration) – revascularisation (people who have had an MI)

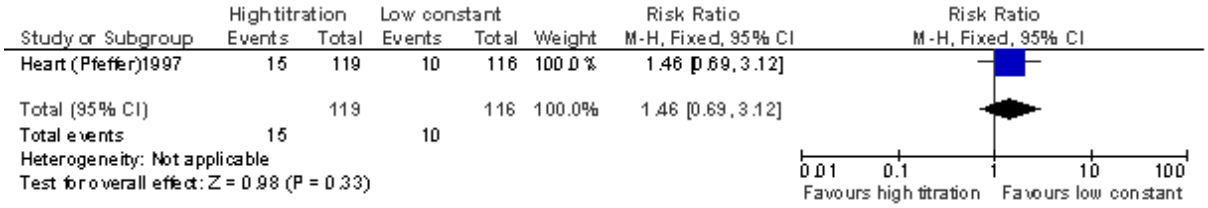
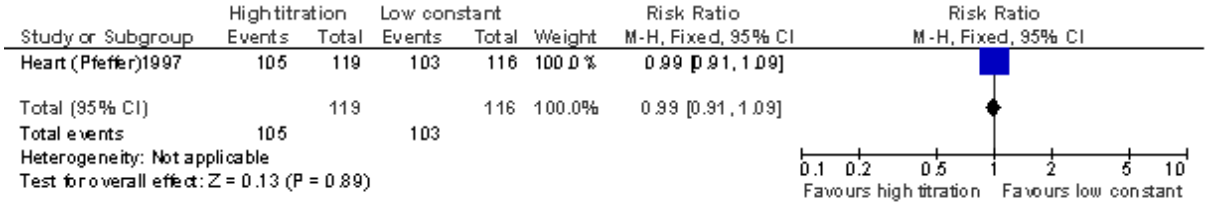


Figure 113: Ramipril (low constant dose) vs. ramipril (high dose titration) – reached final dose (people who have had an MI)



I.3.4 Captopril (low dose titration) vs. captopril (high dose titration)

Figure 114: Captopril (low dose titration) vs. captopril (high dose titration) – all-cause mortality (people who have had an MI)

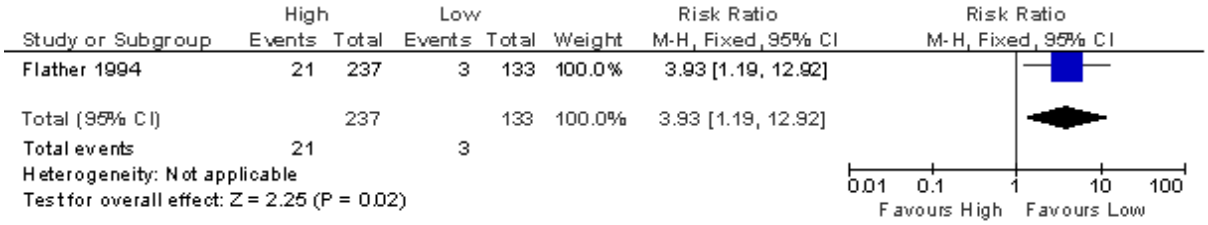


Figure 115: Captopril (low dose titration) vs. captopril (high dose titration) reinfarction (people who have had an MI)

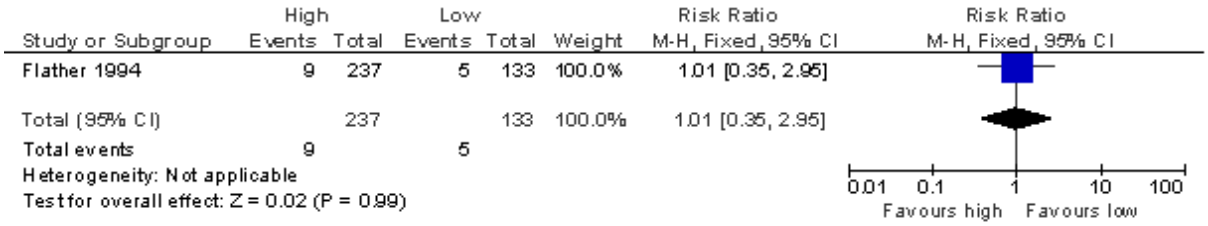


Figure 116: Captopril (low dose titration) vs. captopril (high dose titration)- hypotension people who have had an MI)

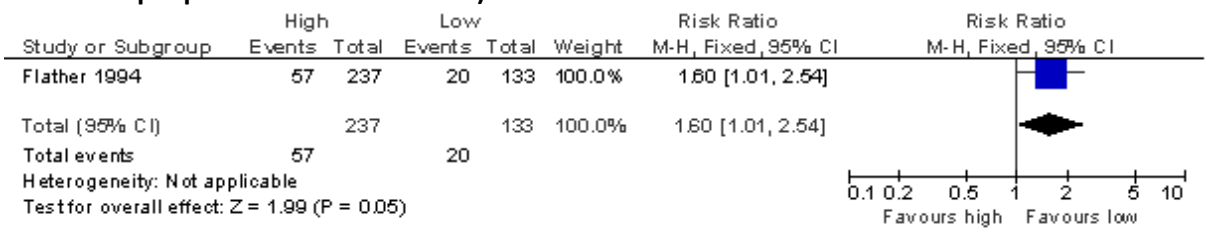


Figure 117: Captopril (low dose titration) vs. captopril (high dose titration) - renal impairment (people who have had an MI)

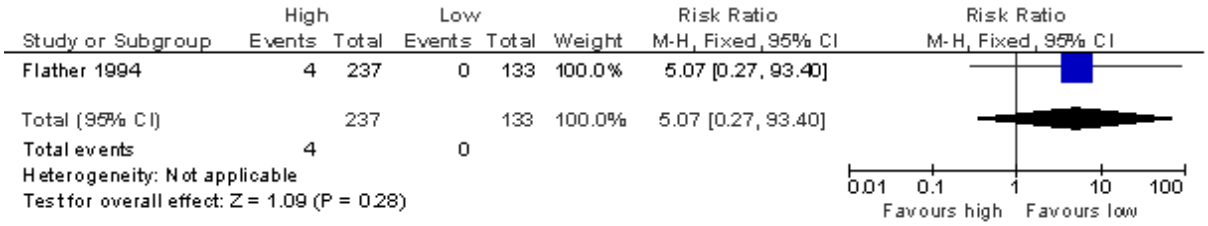


Figure 118: Captopril (low dose titration) vs. captopril (high dose titration) – adverse events (people who have had an MI)

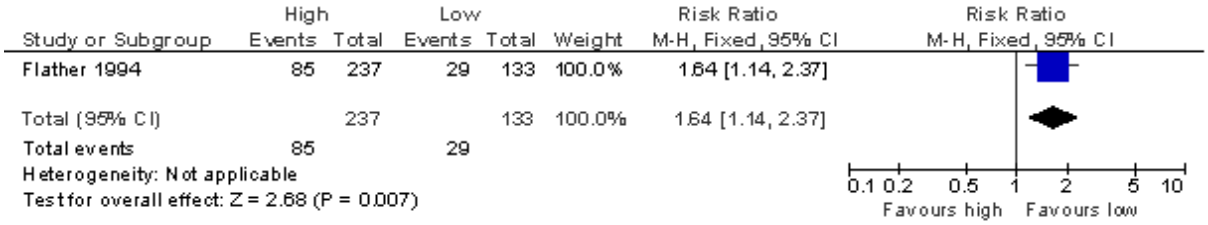


Figure 119: Captopril (low dose titration) vs. captopril (high dose titration) - systolic blood pressure on day 7 (people who have had an MI)

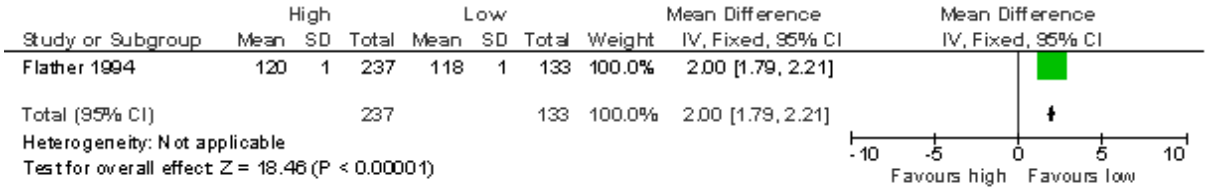
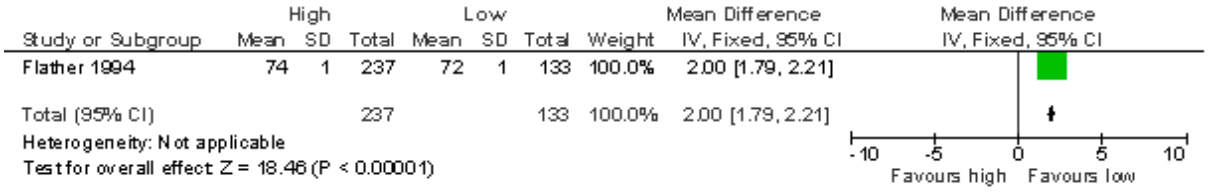


Figure 120: Captopril (low dose titration) vs. captopril (high dose titration) – diastolic blood pressure on day 7 (people who have had an MI)



I.4 ARBs

I.4.1 ARB vs. ACE inhibitors (people who have had an MI and who have been initiated with treatment within 72 hours)

Figure 121: ARB vs. ACE inhibitor (people who have had an MI and who have been initiated with treatment within 72 hours) – all-cause mortality

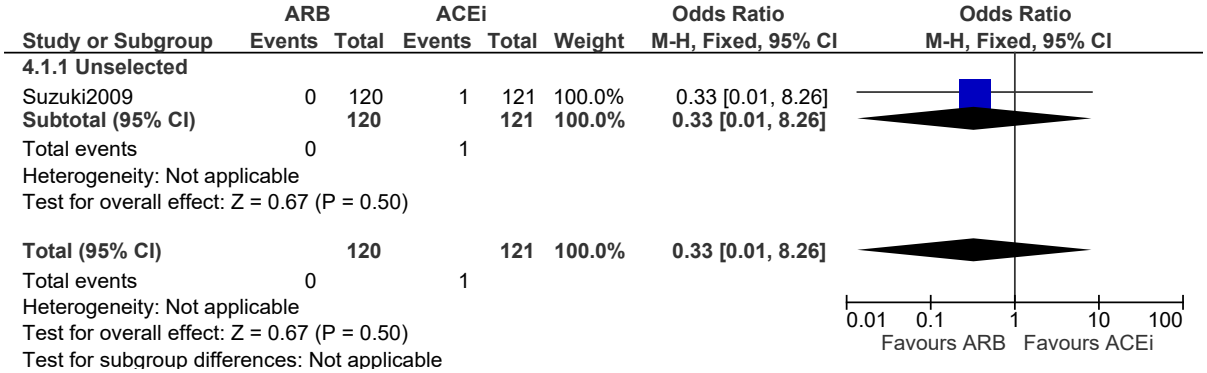


Figure 122: ARB vs. ACE inhibitor (people who have had an MI and who have been initiated with treatment within 72 hours) – cardiac mortality.

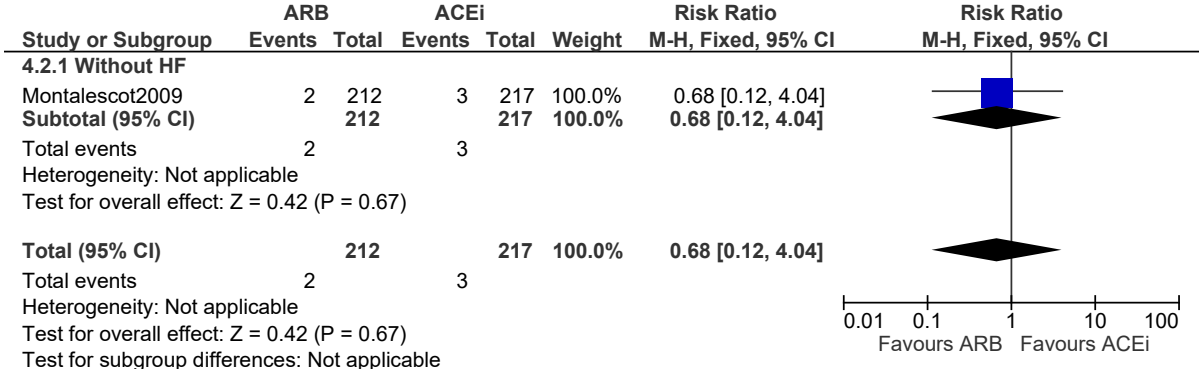


Figure 123: ARB vs. ACE inhibitor (people who have had an MI and who have been initiated with treatment within 72 hours) - reinfarction.

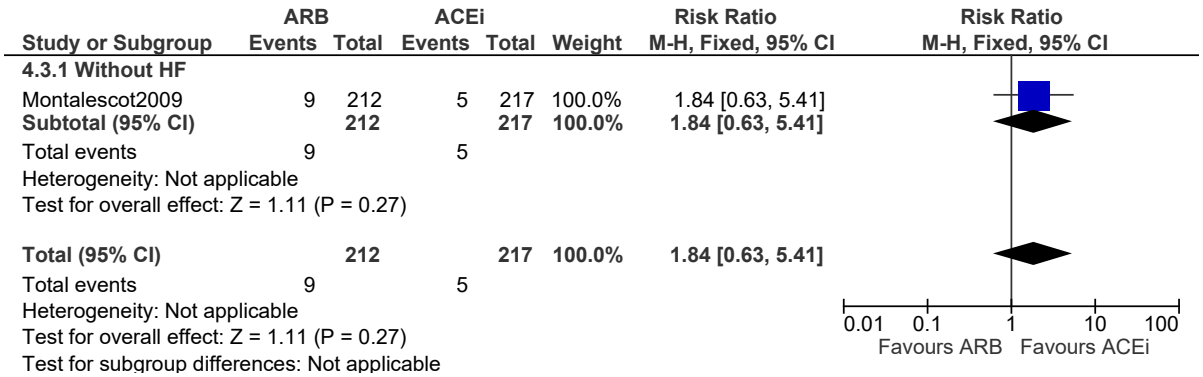


Figure 124: ARB vs. ACE inhibitor (people who have had an MI and who have been initiated with treatment within 72 hours) – stroke.

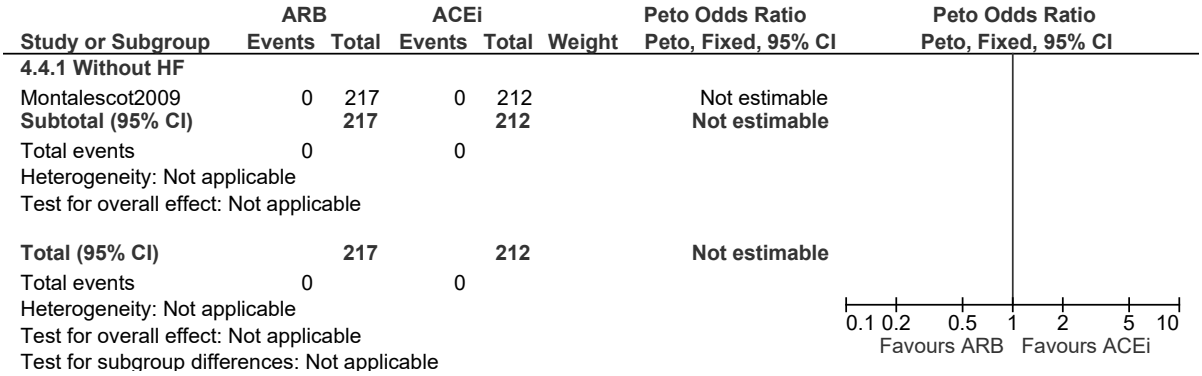


Figure 125: ARB vs. ACE inhibitor (people who have had an MI and who have been initiated with treatment within 72 hours) - revascularisation.

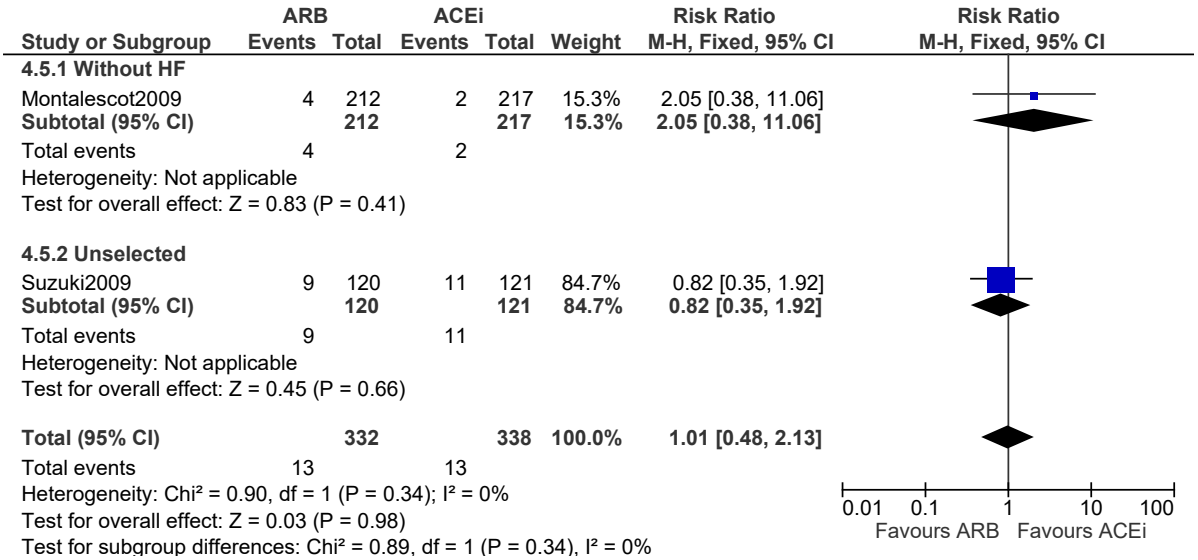


Figure 126: ARB vs. ACE inhibitor (people who have had an MI and who have been initiated with treatment within 72 hours) - rehospitalisation.

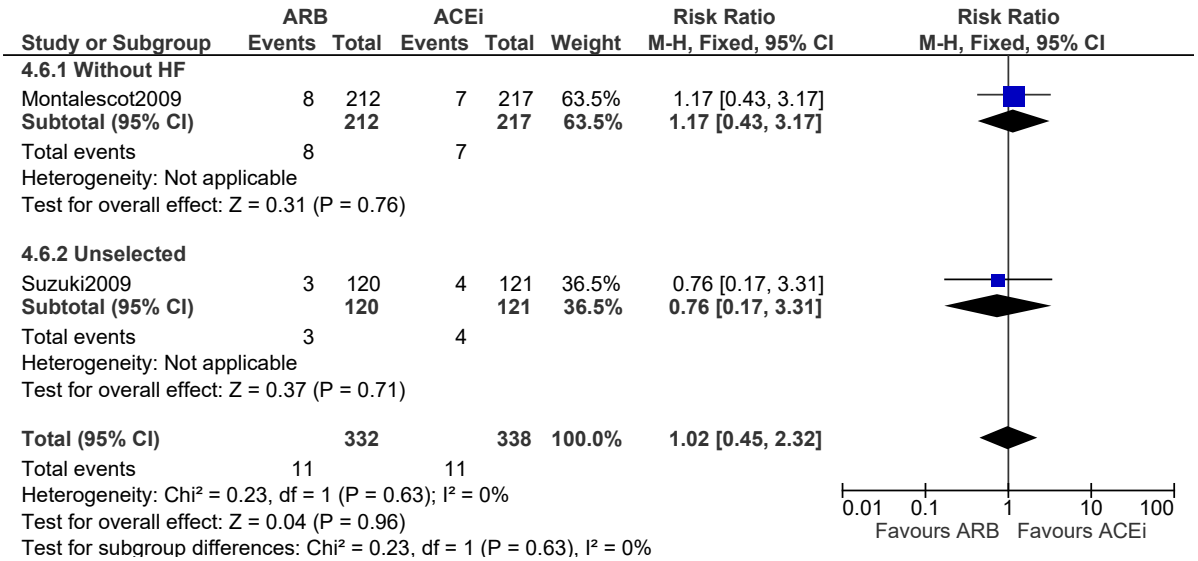


Figure 127: ARB vs. ACE inhibitor - all adverse events

Study or Subgroup	ARB Events	ARB Total	ACEi Events	ACEi Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Suzuki2009	4	120	15	121	100.0%	0.27 [0.09, 0.79]
Total (95% CI)		**120**		**121**	**100.0%**	**0.27 [0.09, 0.79]**
Total events	4		15			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.40 (P = 0.02)

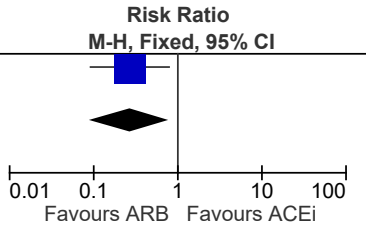


Figure 128: ARB vs. ACE inhibitor - renal dysfunction

Study or Subgroup	ARB Events	ARB Total	ACEi Events	ACEi Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Suzuki2009	0	120	1	121	100.0%	0.34 [0.01, 8.17]
Total (95% CI)		**120**		**121**	**100.0%**	**0.34 [0.01, 8.17]**
Total events	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.67 (P = 0.50)

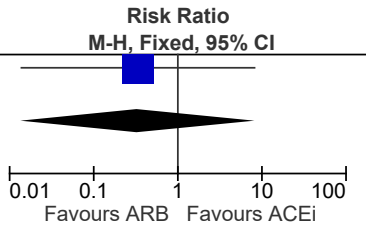
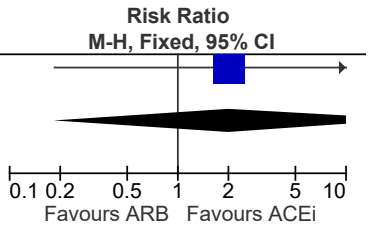


Figure 129: ARB vs. ACE inhibitor - hypotension

Study or Subgroup	ARB Events	ARB Total	ACEi Events	ACEi Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Suzuki2009	2	120	1	121	100.0%	2.02 [0.19, 21.95]
Total (95% CI)		**120**		**121**	**100.0%**	**2.02 [0.19, 21.95]**
Total events	2		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.58 (P = 0.56)



I.4.2 ARBs vs. ACE inhibitor (people who have had an MI and who have been initiated with treatment between 72 hours and 12 months)

Figure 130: ARB vs. ACE inhibitor (people who have had an MI and who have been initiated with treatment between 72 hours and 12 months) – all-cause mortality

Study or Subgroup	ARB Events	ARB Total	ACEi Events	ACEi Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 LVSD						
Pfeffer2003	979	4909	958	4909	48.6%	1.02 [0.94, 1.11]
Subtotal (95% CI)		**4909**		**4909**	**48.6%**	**1.02 [0.94, 1.11]**
Total events	979		958			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.53 (P = 0.59)

1.1.2 Without HF						
ONTARGET2008	989	8542	1014	8576	51.4%	0.98 [0.90, 1.06]
Subtotal (95% CI)		**8542**		**8576**	**51.4%**	**0.98 [0.90, 1.06]**
Total events	989		1014			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.50 (P = 0.62)

Total (95% CI)		**13451**		**13485**	**100.0%**	**1.00 [0.94, 1.06]**
Total events	1968		1972			

Heterogeneity: Chi² = 0.53, df = 1 (P = 0.47); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Chi² = 0.53, df = 1 (P = 0.47), I² = 0%

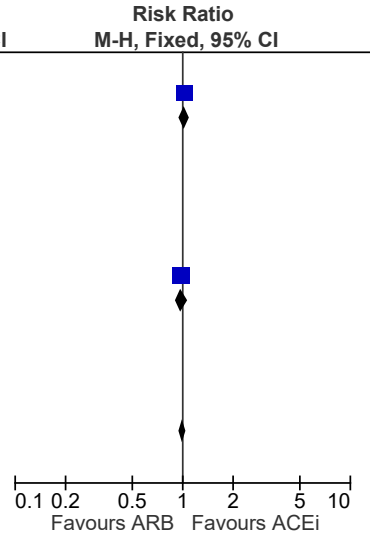


Figure 131: ARB vs. ACE inhibitor (people who have had an MI and who have been initiated with treatment between 72 hours and 12 months) – cardiac mortality

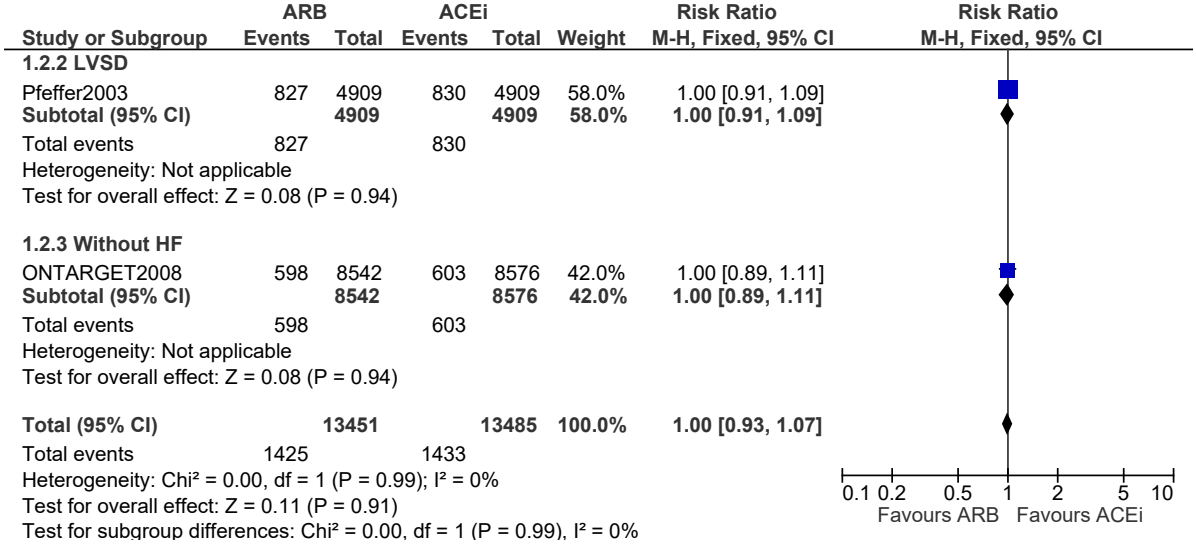


Figure 132: ARB vs. ACE inhibitor (people who have had an MI and who have been initiated with treatment between 72 hours and 12 months) – stroke (fatal + non-fatal).

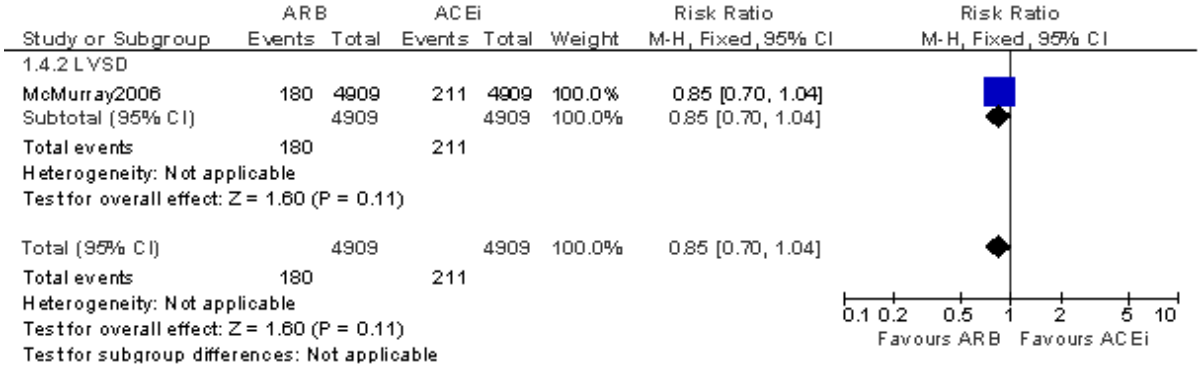


Figure 133: ARB vs. ACE inhibitor (people who have had an MI and who have been initiated with treatment between 72 hours and 12 months) - reinfarction.

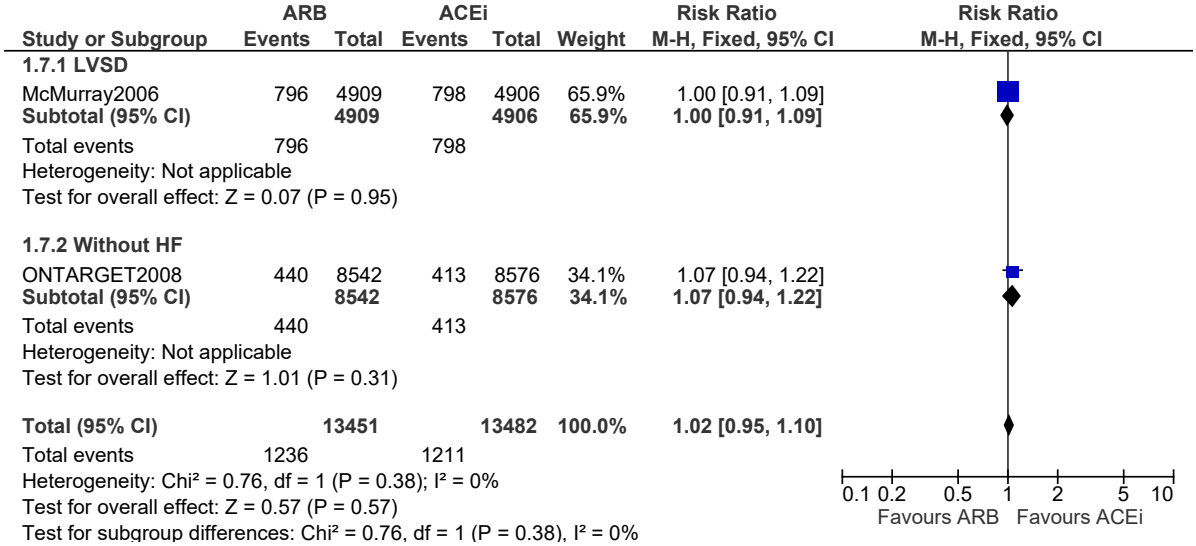


Figure 134: ARB vs. ACE inhibitor (people who have had an MI and who have been initiated with treatment between 72 hours and 12 months) - revascularisation.

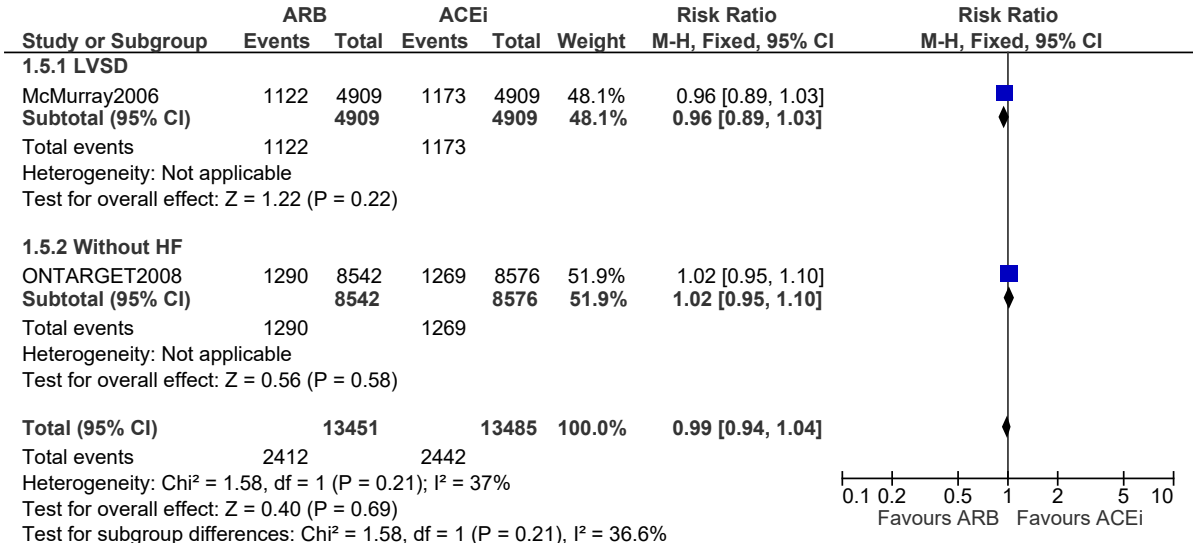


Figure 135: ARB vs. ACE inhibitor (people who have had an MI and who have been initiated with treatment between 72 hours and 12 months) - hospitalisation.

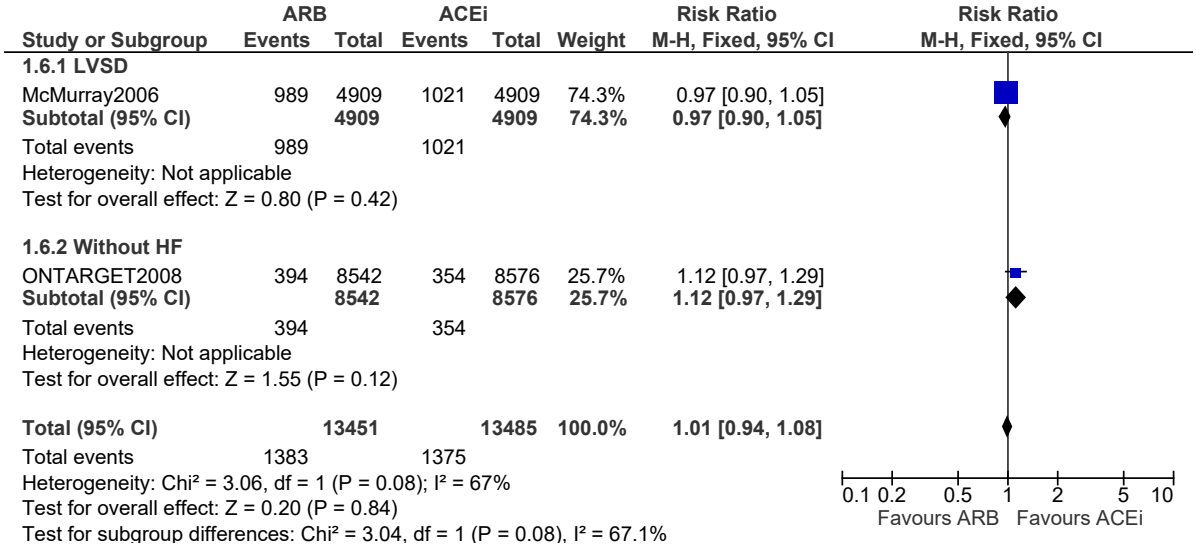


Figure 136: ARB vs. ACE inhibitor (people who have had an MI and who have been initiated with treatment between 72 hours and 12 months) – adverse events

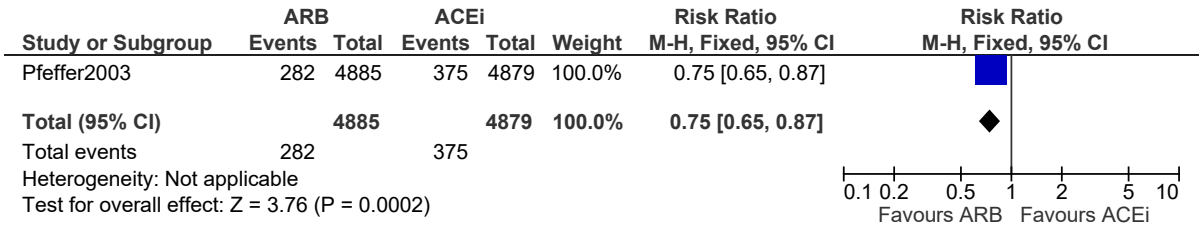


Figure 137: ARB vs. ACE inhibitor (people who have had an MI and who have been initiated with treatment between 72 hours and 12 months)– renal dysfunction.

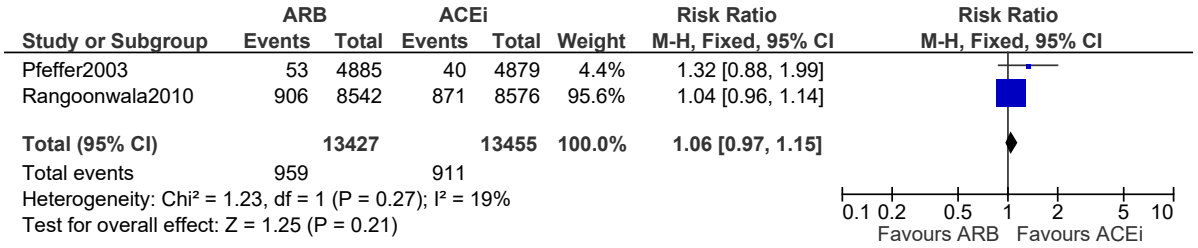
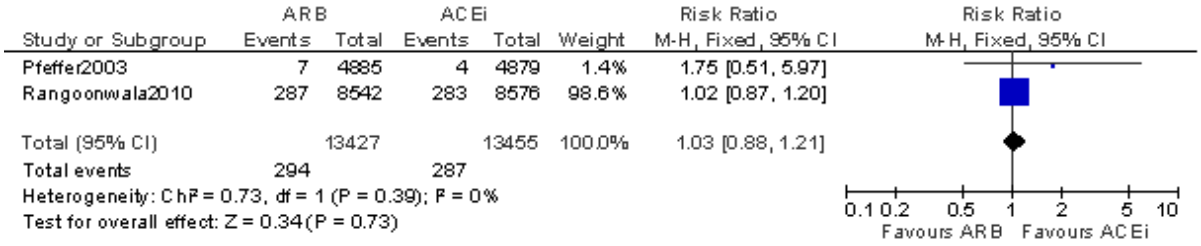
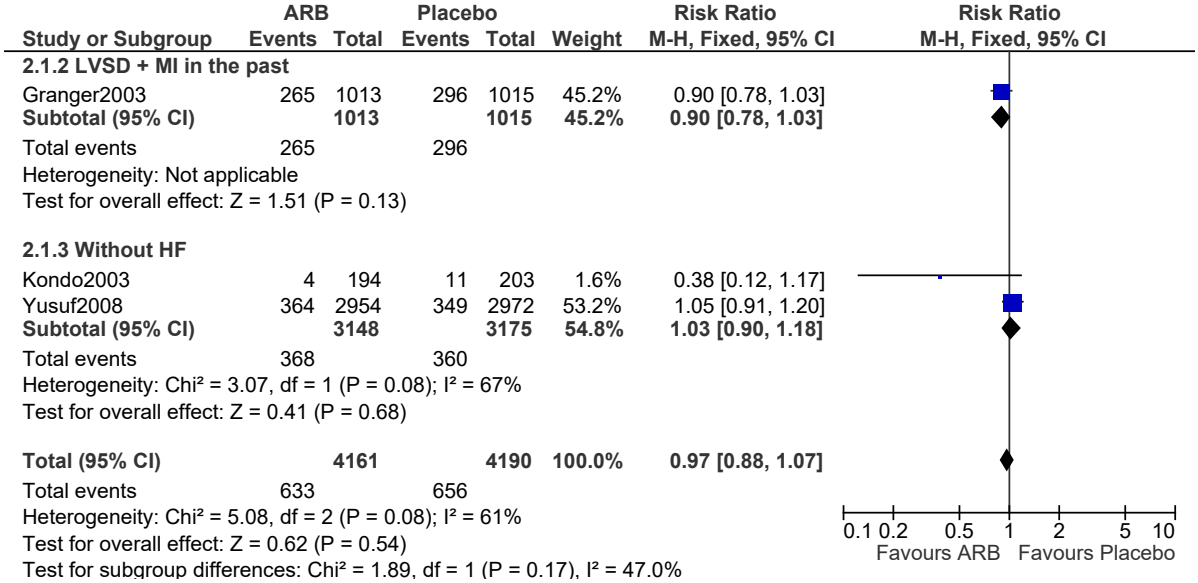


Figure 138: ARB vs. ACE inhibitor (people who have had an MI and who have been initiated with treatment between 72 hours and 12 months) - hyperkalemia.



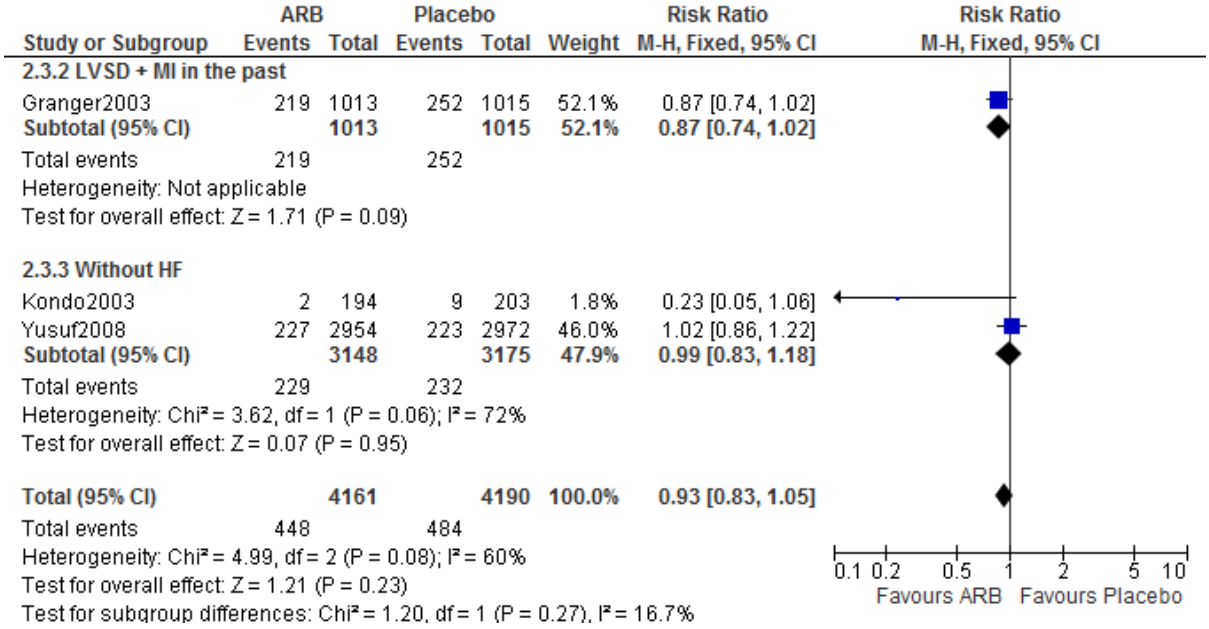
I.4.3 ARBs vs. placebo

Figure 139: ARB vs. placebo – all-cause mortality (relative risk)



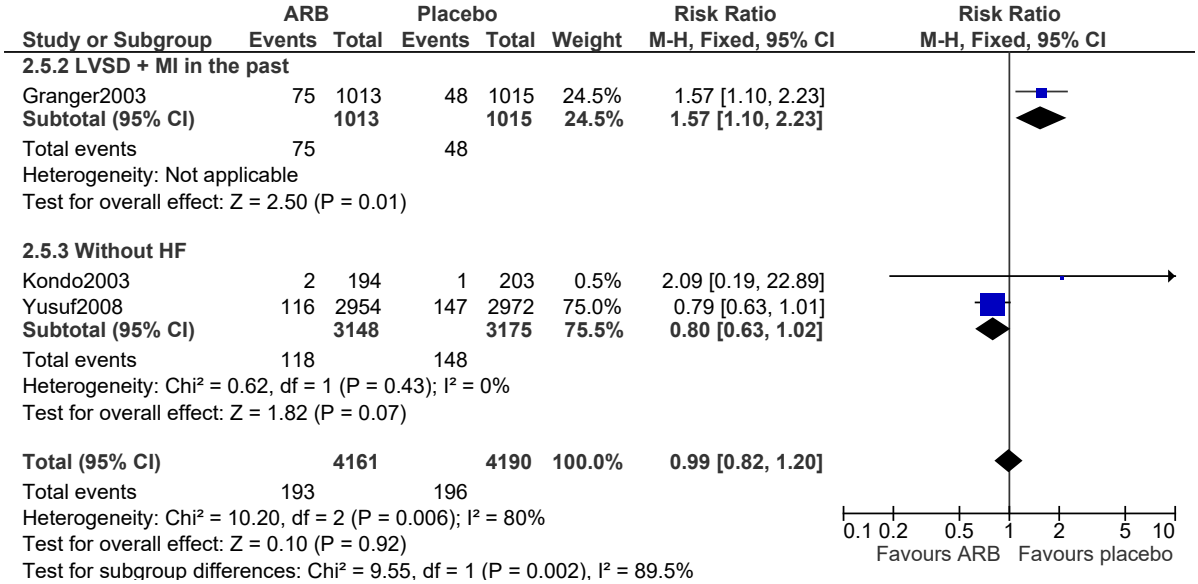
Heterogeneity was detected in the group without heart failure, with I^2=67%. This is likely to be the result of the study by Kondo that reported few events and had low patient numbers. As a result the 95% CI is very wide. It is also carries a high risk of bias since the patients nor investigators were blinded. The results are presented as random effects rather than fixed effects.

Figure 140: ARB vs. placebo – cardiac mortality (relative risk)



Heterogeneity was detected in the without heart failure group, with I^2=72%. This is likely to be the result of the study by Kondo that reported few events and had low patient numbers. As a result the 95% CI is very wide. It is also carries a high risk of bias since the patients nor investigators were blinded. The results are presented as random effects rather than fixed effects.

Figure 141: ARB vs. placebo – reinfarction (relative risk)



Heterogeneity was detected in the total meta-analysis, I^2=89.5%, which can be explained by the differences detected between the subgroups.

Figure 142: ARB vs. placebo – stroke (fatal + non-fatal)

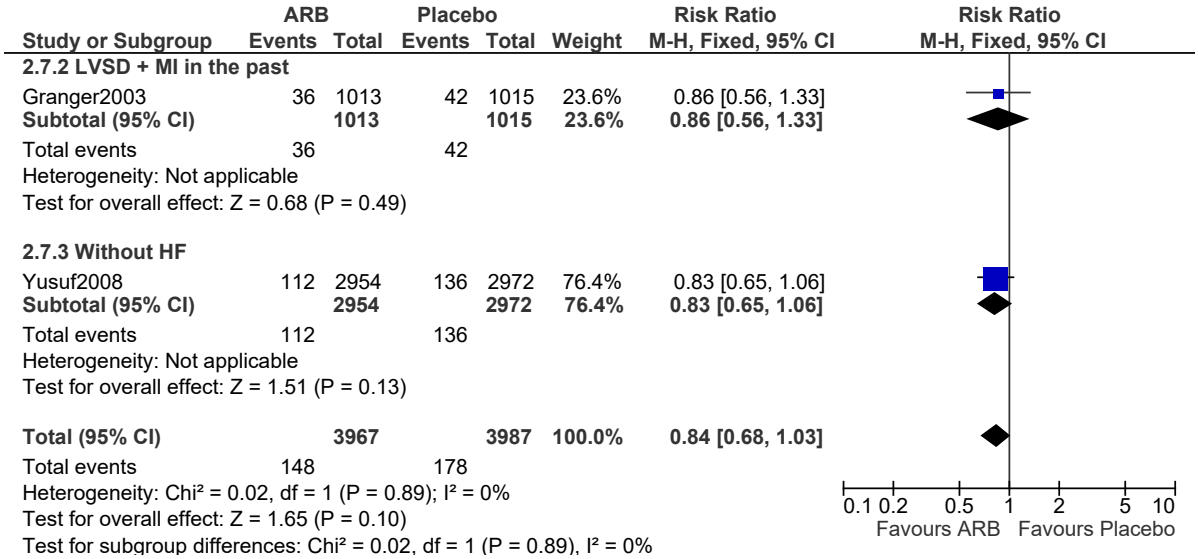


Figure 143: ARB vs. placebo – revascularisation

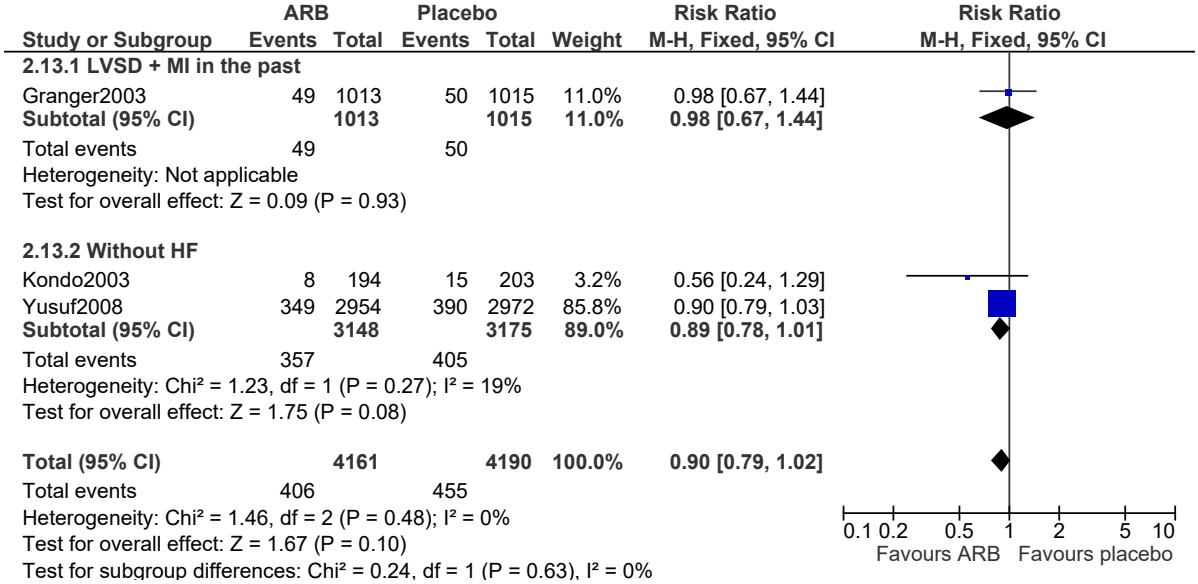


Figure 144: ARB vs. placebo – hospitalisation

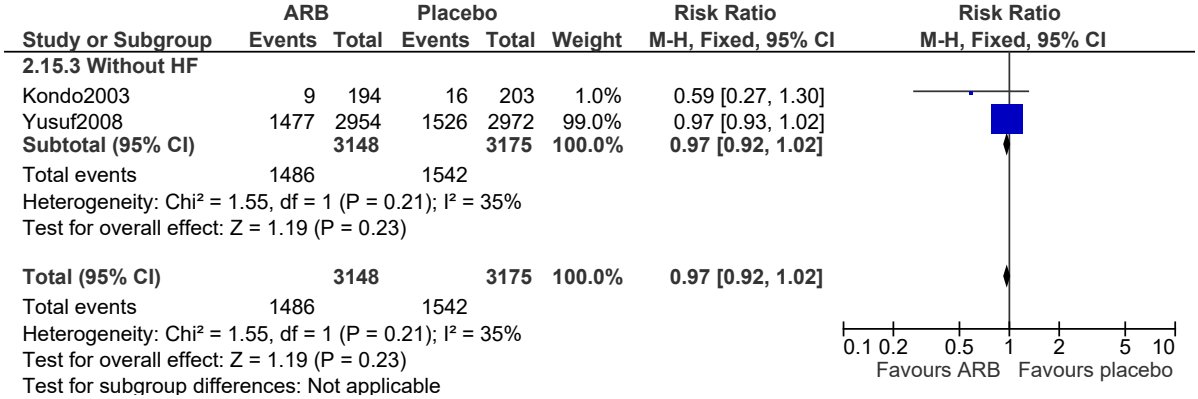


Figure 145: ARB vs. placebo - adverse events

Heterogeneity was detected at I^2=76%. This appears to be the result of Yusuf that reported more adverse events in the placebo arm then in the ARB group. The difference with Yusuf is that it uses patients with normal LV function, while the other paper uses patients with LVSD. The other factors to investigate if heterogeneity was detected cannot be pursued since the patients are an indirect population, so we cannot separate according to whether they are STEMI or NSTEMI patients, nor their treatment type (PCI, medical or CABG), and their age range is similar. As such the results are presented as random effects, instead of fixed effects.

Figure 146: ARB vs. placebo - renal dysfunction

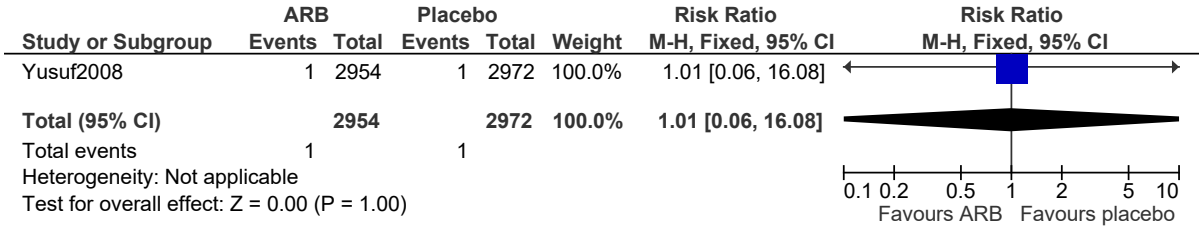
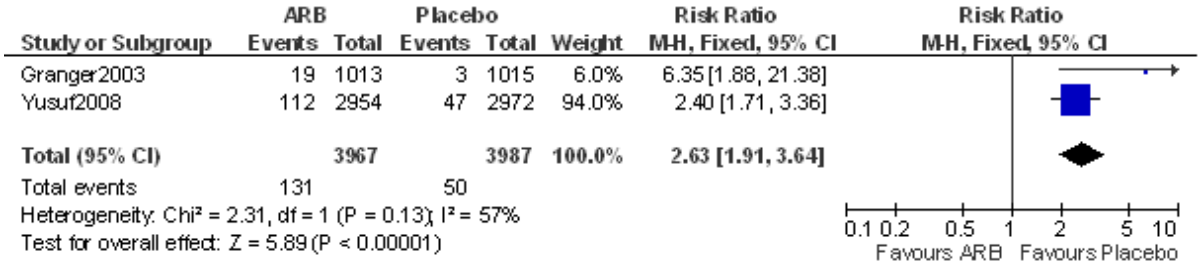
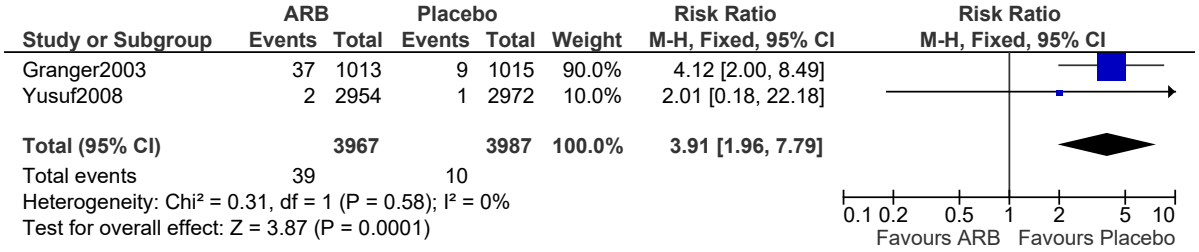


Figure 147: ARB vs. placebo - hyperkalemia



Heterogeneity was detected, I^2=57%. This is likely to be the result of few events being reported in the two studies resulting in a large 95% CIs.

Figure 148: ARB vs. placebo - hypotension



I.5 ACE inhibitor + ARB vs. ACE inhibitor

Figure 149: ACE inhibitor + ARB vs. ACE inhibitor - all-cause mortality

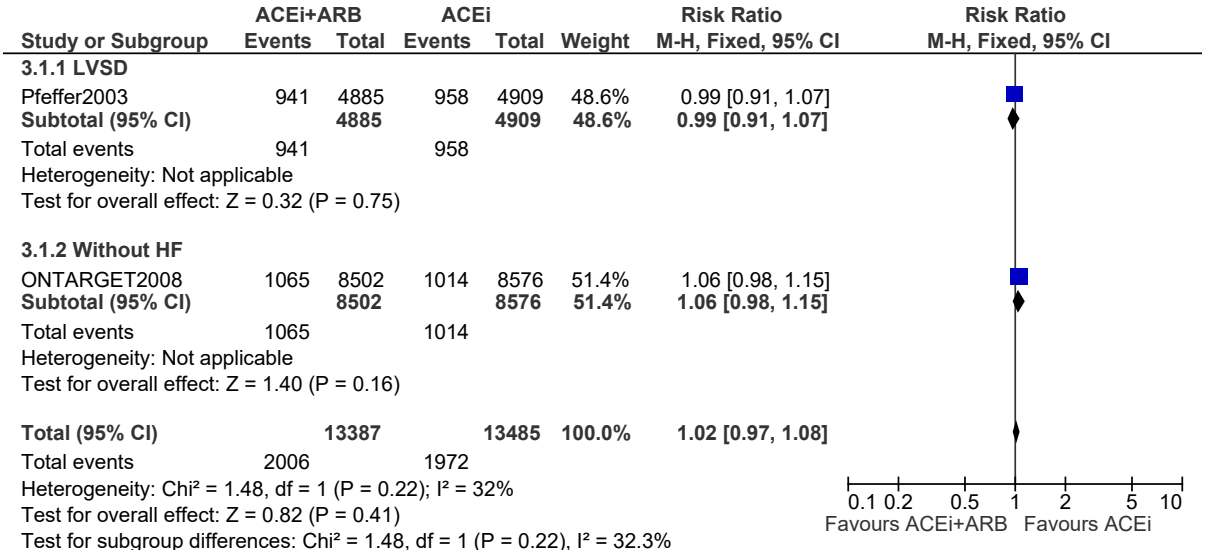


Figure 150: ACE inhibitor + ARB vs. ACE inhibitor – cardiac mortality

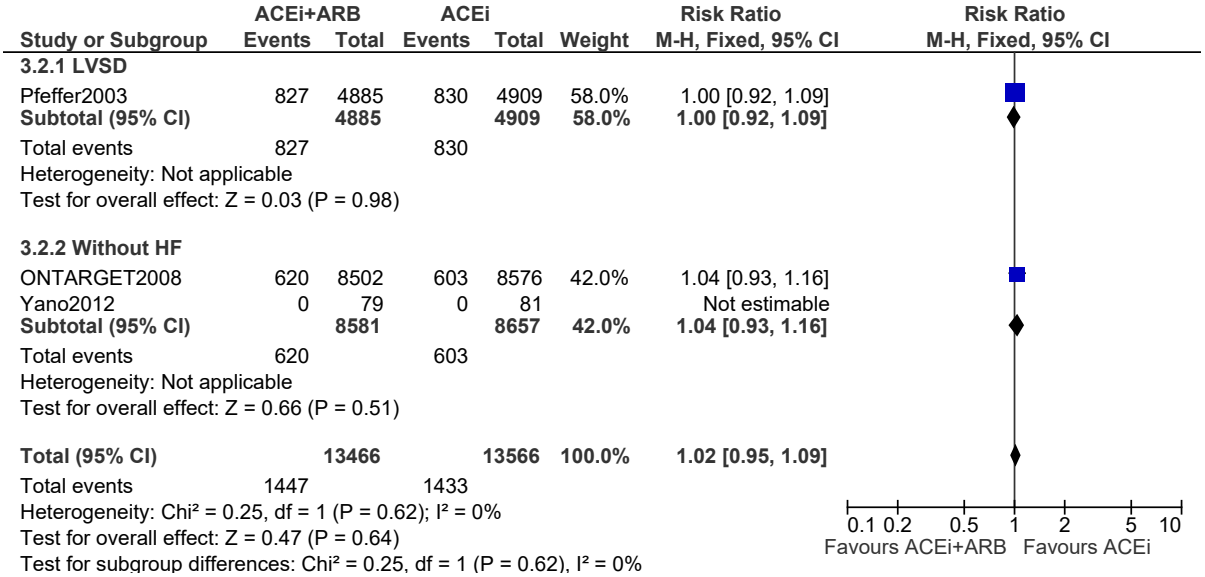


Figure 151: ACE inhibitor +ARB vs. ACE inhibitor - reinfarction

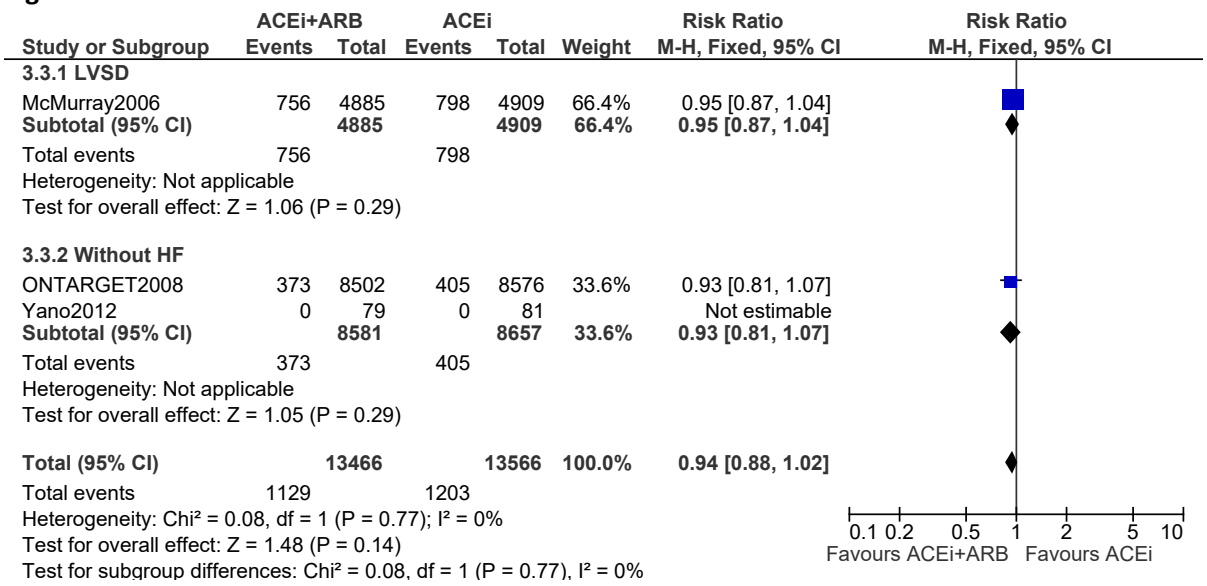


Figure 152: ACE inhibitor +ARB vs. ACE inhibitor - stroke

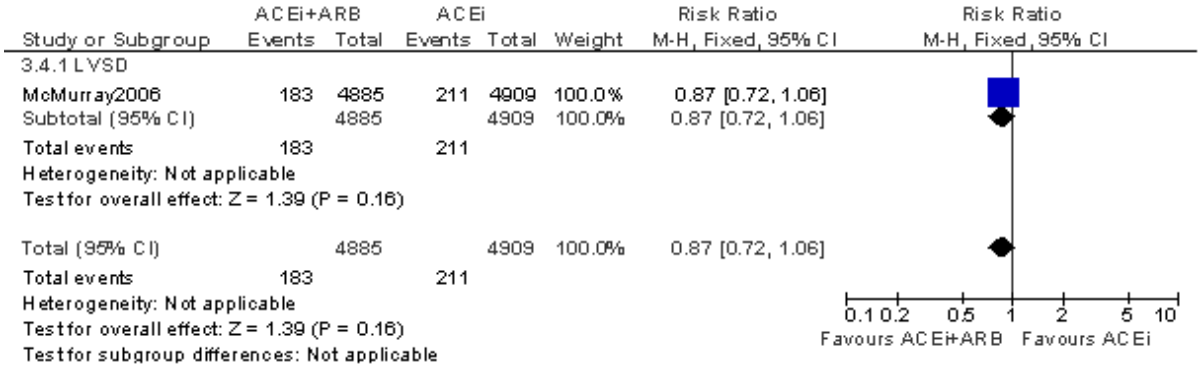


Figure 153: ACE inhibitor +ARB vs. ACE inhibitor - revascularisation

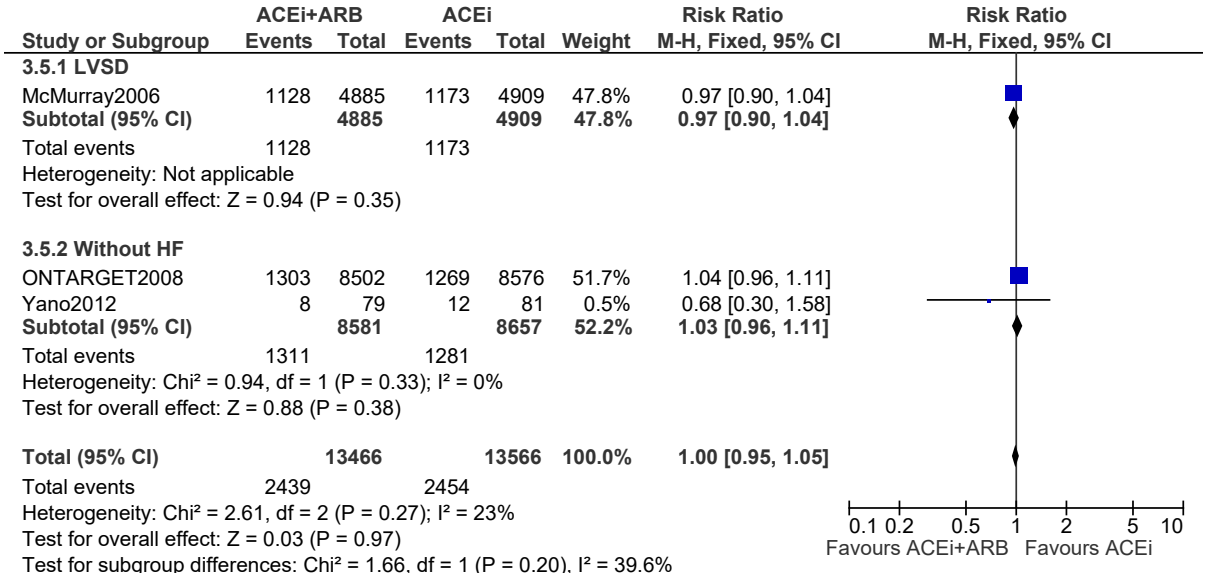


Figure 154: ACE inhibitor +ARB vs. ACE inhibitor - hospitalisation

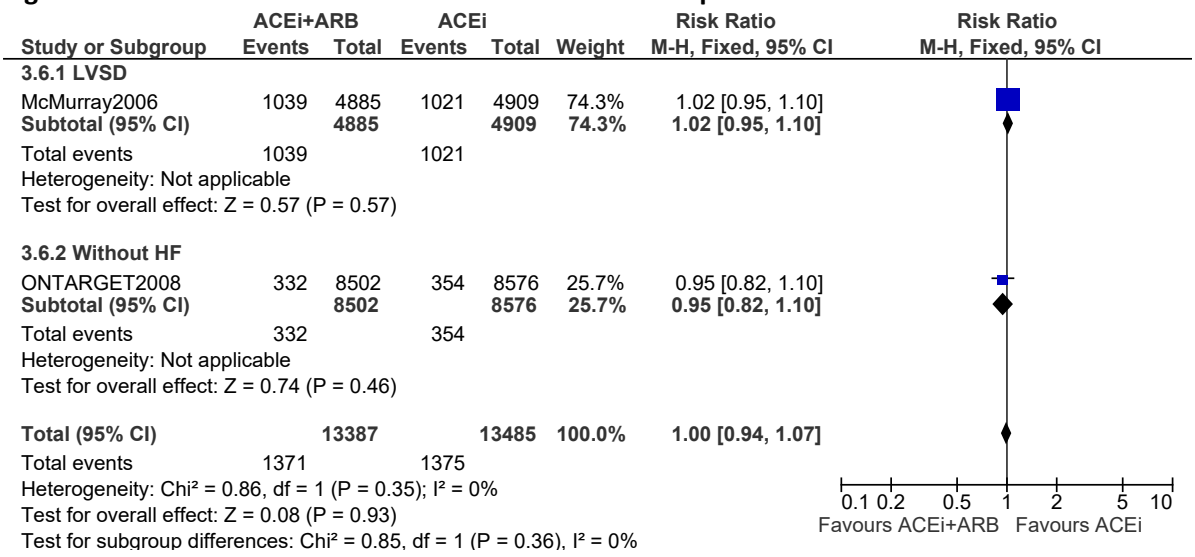


Figure 155: ACE inhibitor + ARB vs. ACE inhibitor – all adverse events

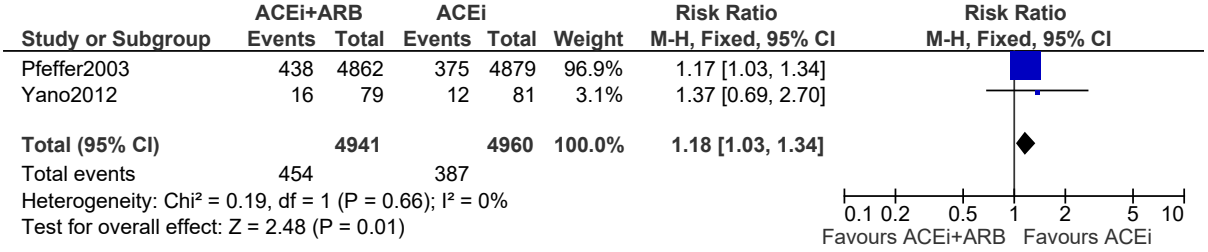


Figure 156: ACE inhibitor + ARB vs. ACE inhibitor – renal dysfunction

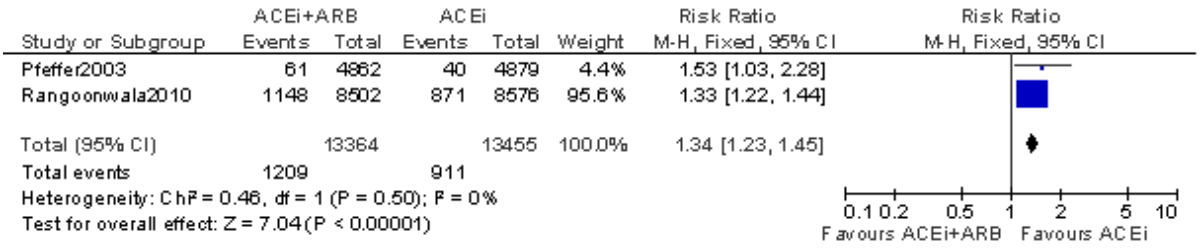


Figure 157: ACE inhibitor + ARB vs. ACE inhibitor - hyperkalemia

I.6 Antiplatelet therapy

I.6.1 Duration of clopidogrel + aspirin vs. aspirin

Data from indirect studies are not included in the meta-analysis unless they were the only source of data available for that outcome or subgroup. For incidence of major and minor bleeding data from indirect populations are included since bleeding risk is unlikely to be influenced by the type of cardiovascular disease.

The results from the total meta-analysis were not displayed if results from the same study are presented in different subgroups to avoid double counting.

I.6.1.1 Long versus short treatment

Figure 158: Clopidogrel long vs. short-term – all-cause mortality

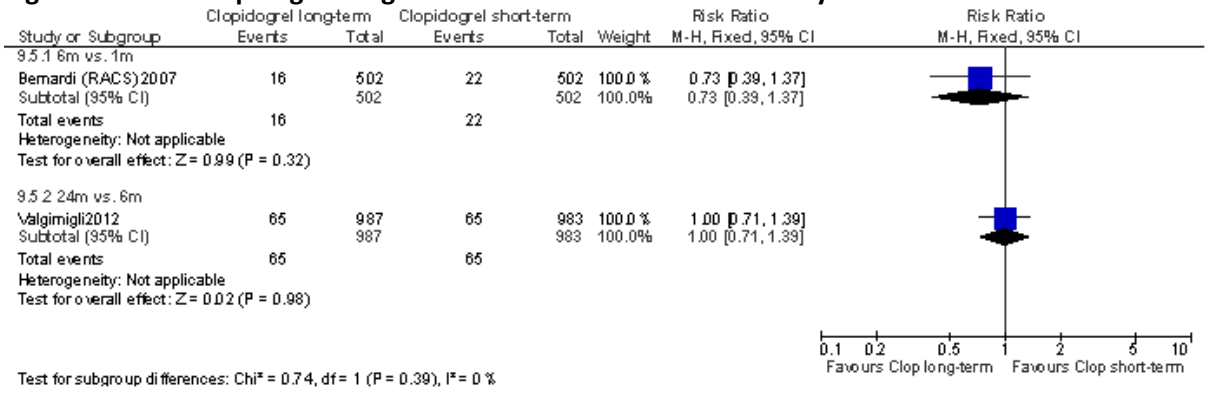


Figure 159: Clopidogrel long vs. short-term – cardiac mortality

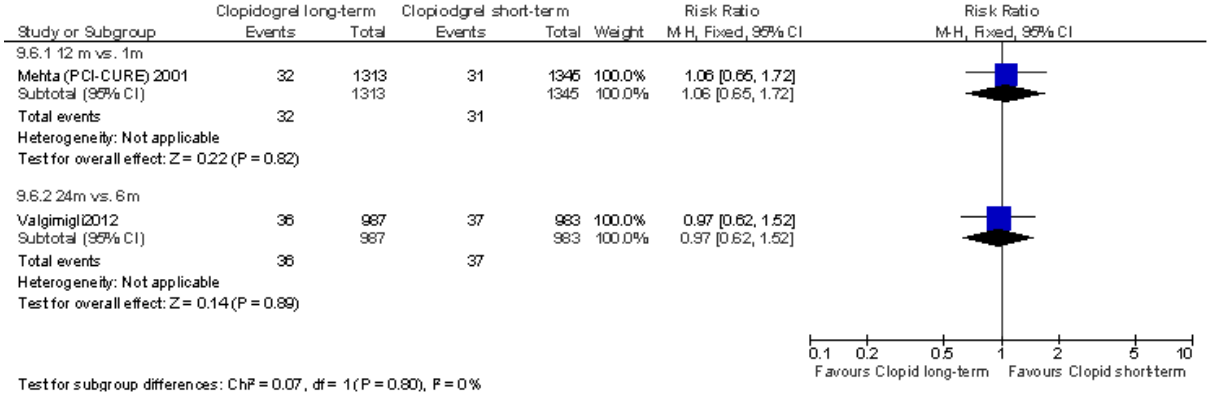


Figure 160: Clopidogrel long vs. short-term - reinfarction

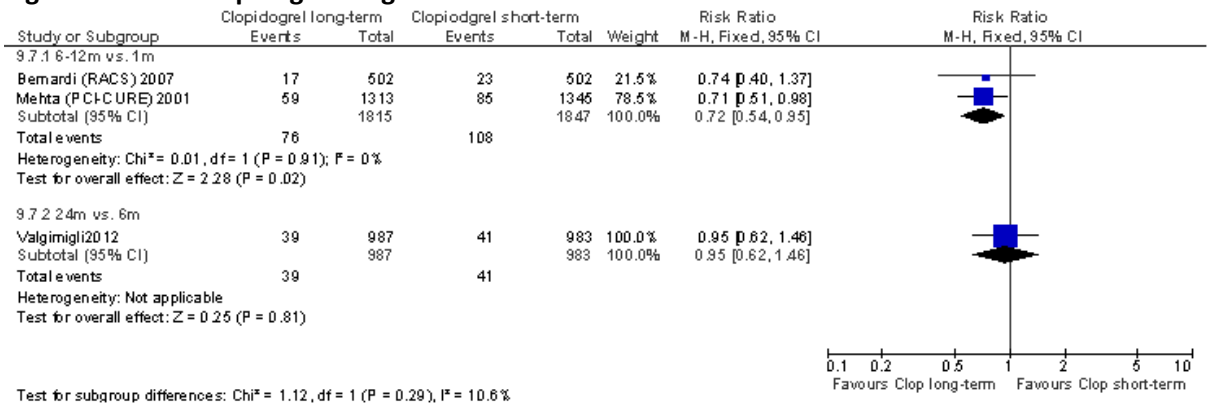


Figure 161: Clopidogrel long vs. short-term - stroke

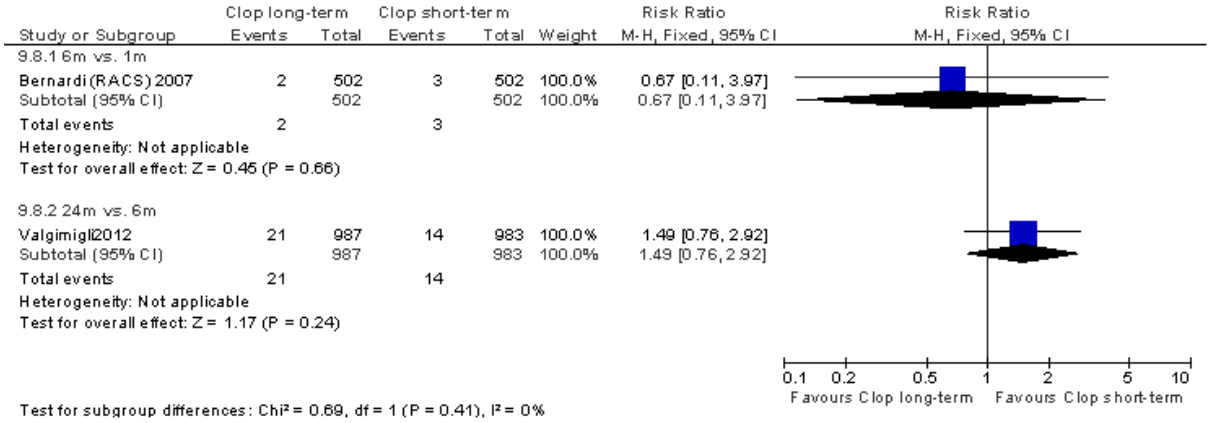


Figure 162: Clopidogrel long vs. short-term. - revascularisation

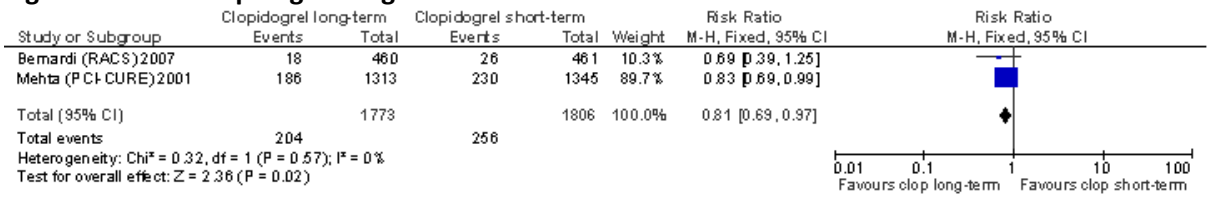


Figure 163: Clopidogrel long vs. short-term. – minor bleeding

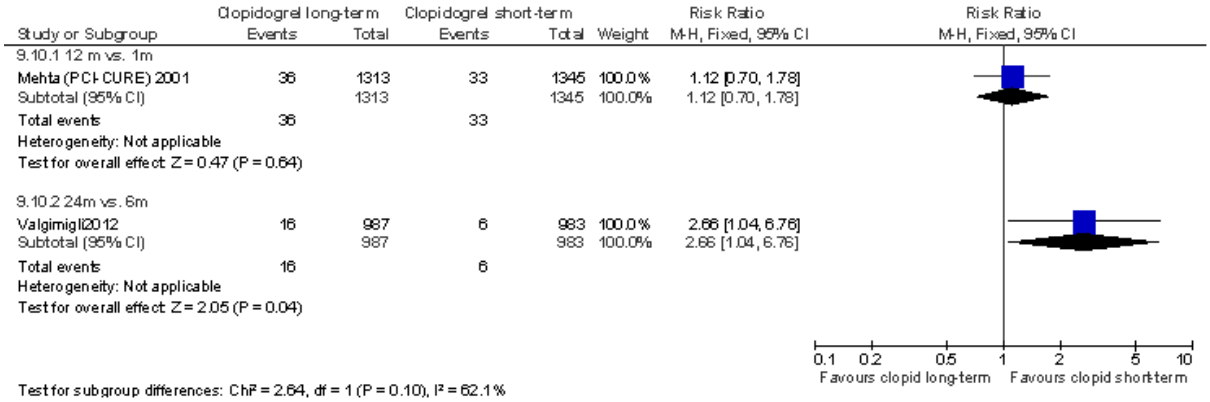
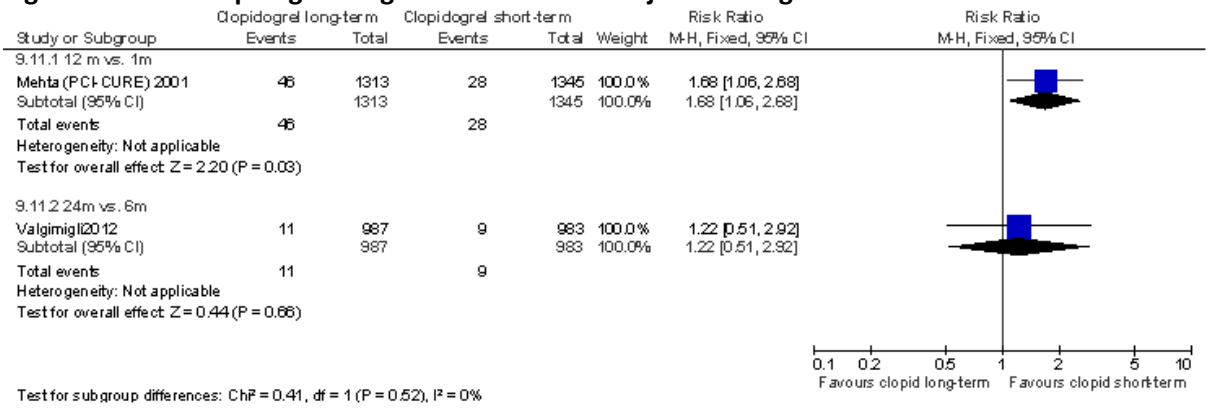


Figure 164: Clopidogrel long vs. short-term. – major bleeding



I.6.1.2 Clopidogrel + aspirin vs. aspirin different follow-up time points

Figure 165: Clopidogrel+aspirin vs. aspirin (STEMI population) – all-cause mortality

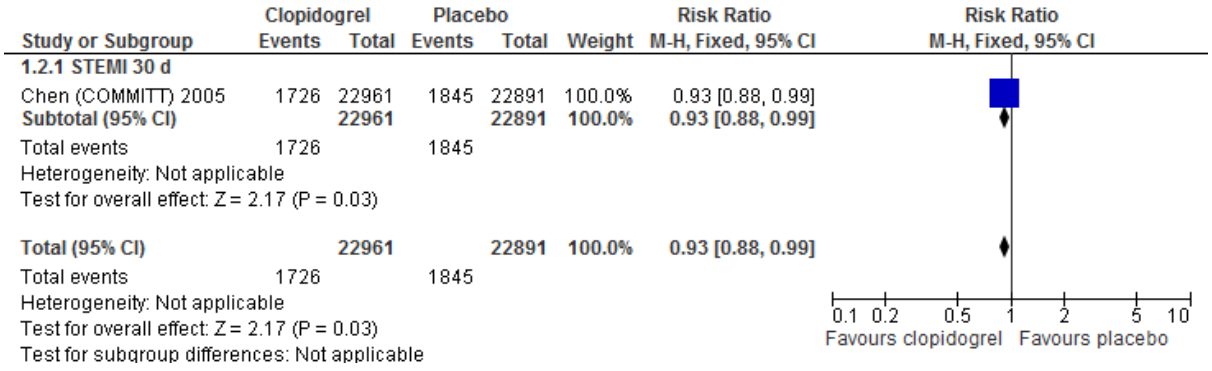


Figure 166: -Clopidogrel + aspirin vs. aspirin (NSTEMI)- all-cause mortality

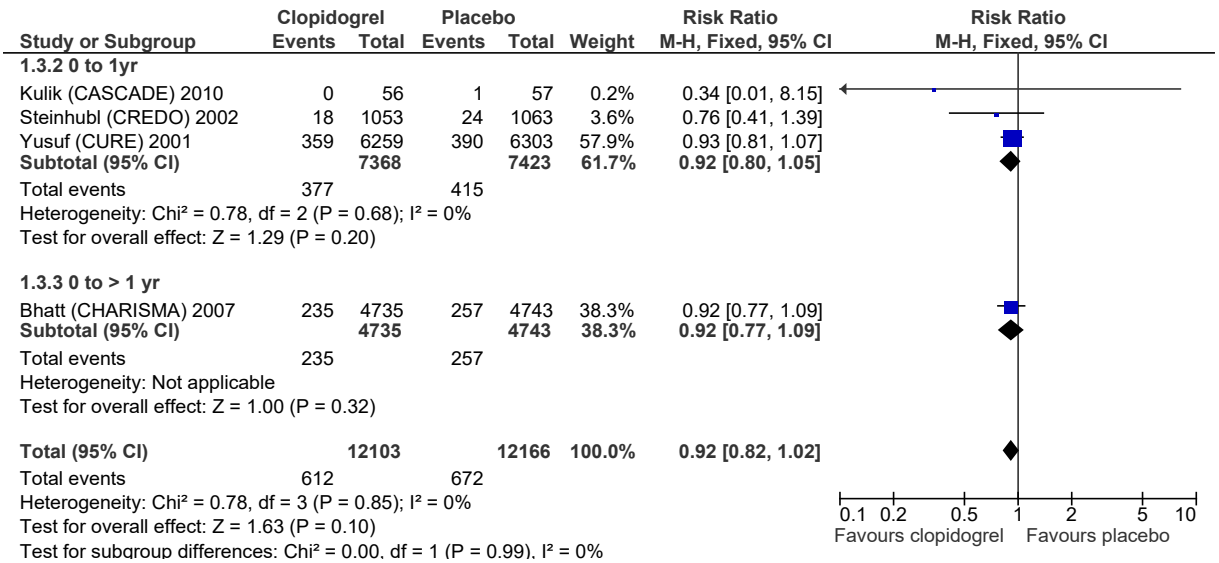


Figure 167: Clopidogrel + aspirin vs. aspirin (type of treatment) – all-cause mortality

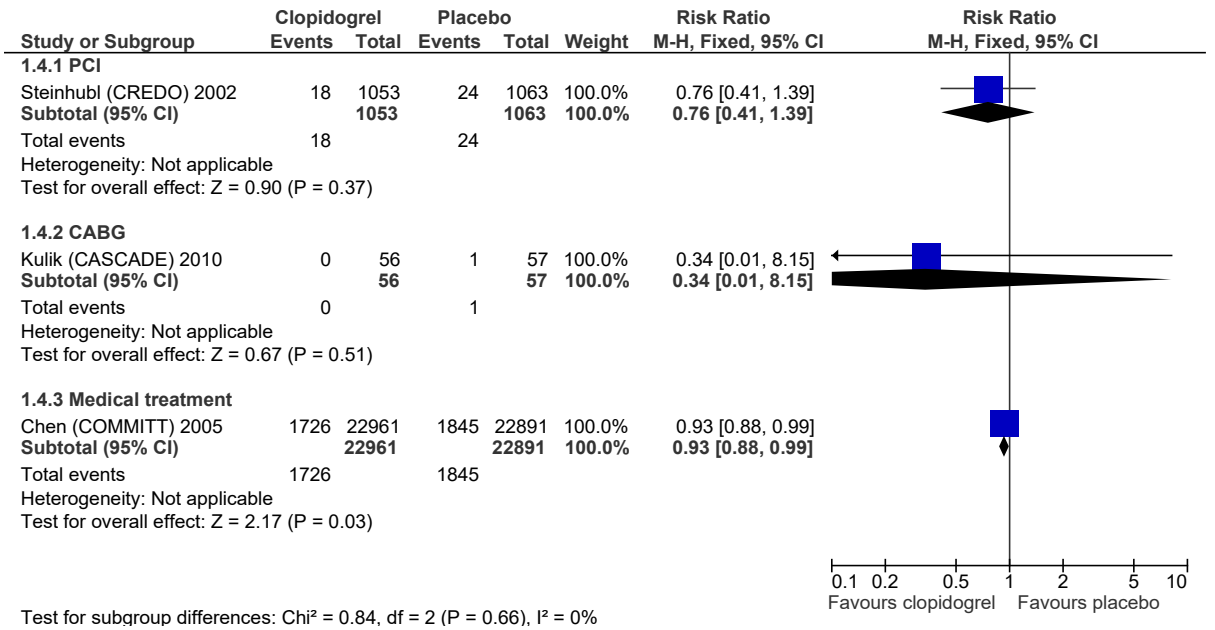


Figure 168: Clopidogrel + aspirin vs. aspirin (duration of treatment)– cardiac mortality

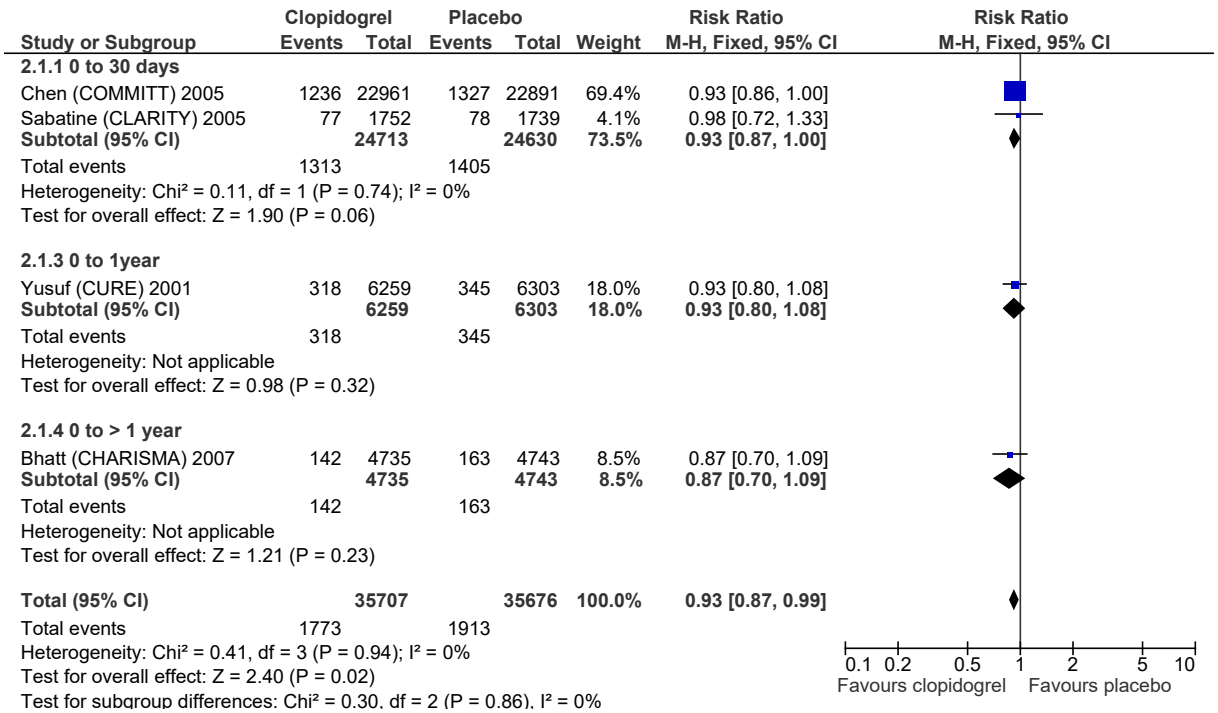


Figure 169: Clopidogrel+aspirin vs. aspirin (STEMI) – cardiac mortality

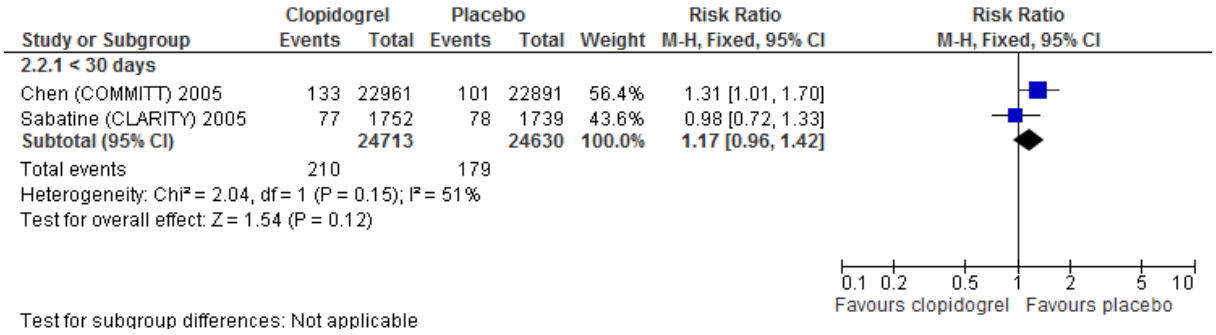


Figure 170: Clopidogrel+aspirin vs. aspirin (NSTEMI) – cardiac mortality

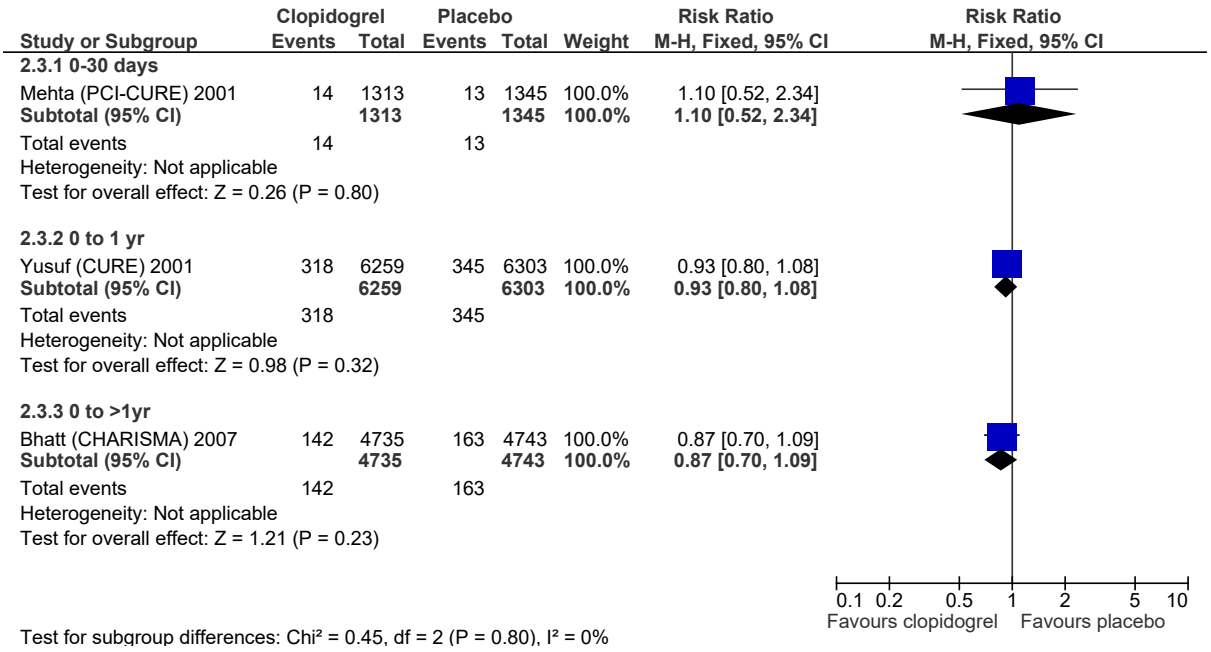


Figure 171: -Clopidogrel+ aspirin vs. aspirin (type of treatment) -cardiac mortality

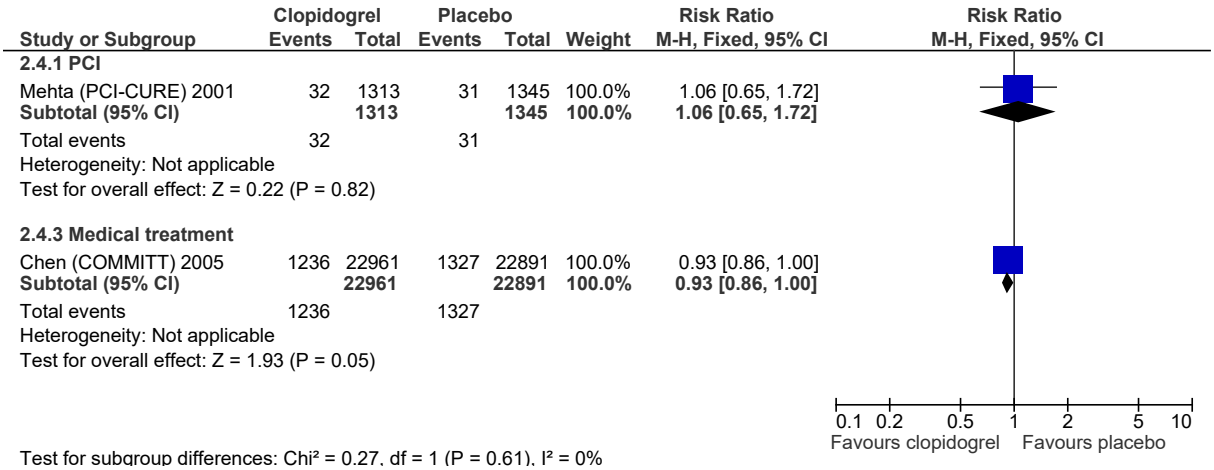
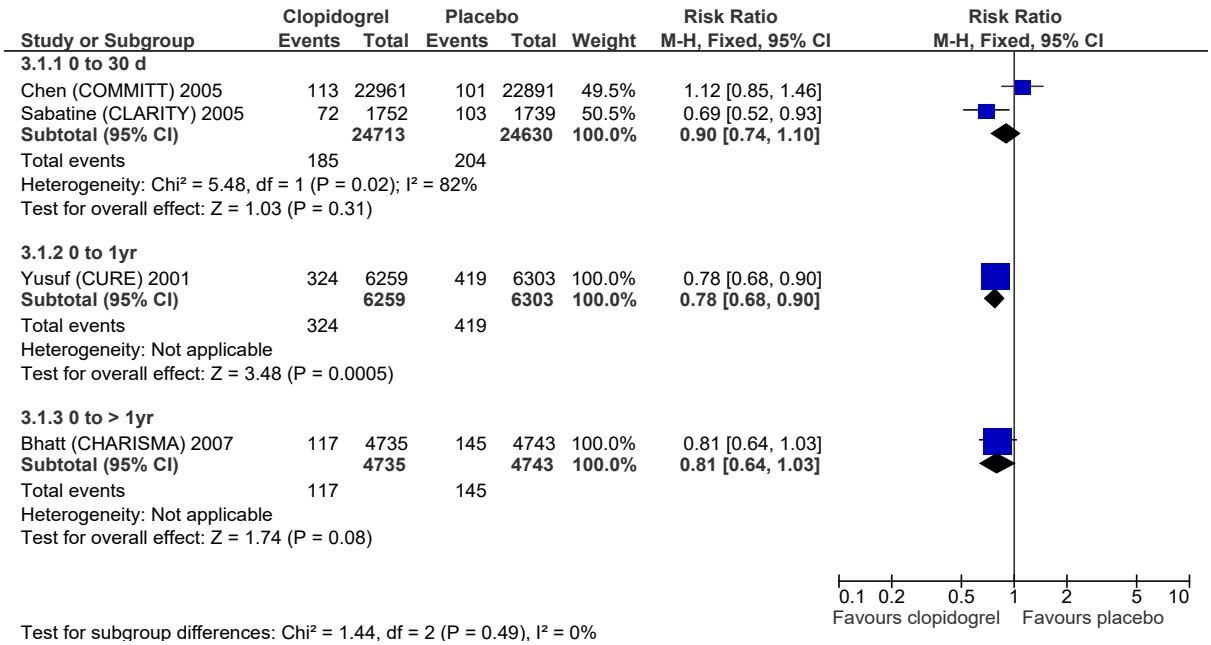


Figure 172: -Clopidogrel+aspirin vs. aspirin (duration of treatment) - reinfarction



Heterogeneity

Heterogeneity was detected in the subgroup analysis on the risk of reinfarction in the clopidogrel and aspirin versus aspirin groups, after 30 days of treatment. To investigate this, we first looked to see if we could eliminate papers that had a high risk of bias. Since this was not the case, we then investigated whether the types of stents used, bare metal vs. drug eluting stents, explained the heterogeneity. None of the papers reported the type of stents used for PCI, so this could not be used to explain the heterogeneity. Consequently RR results were presented as random effects rather than fixed effects (see below).

Figure 173:Clopidogrel+aspirin vs. aspirin (duration of treatment) – myocardial infarction (random effects)

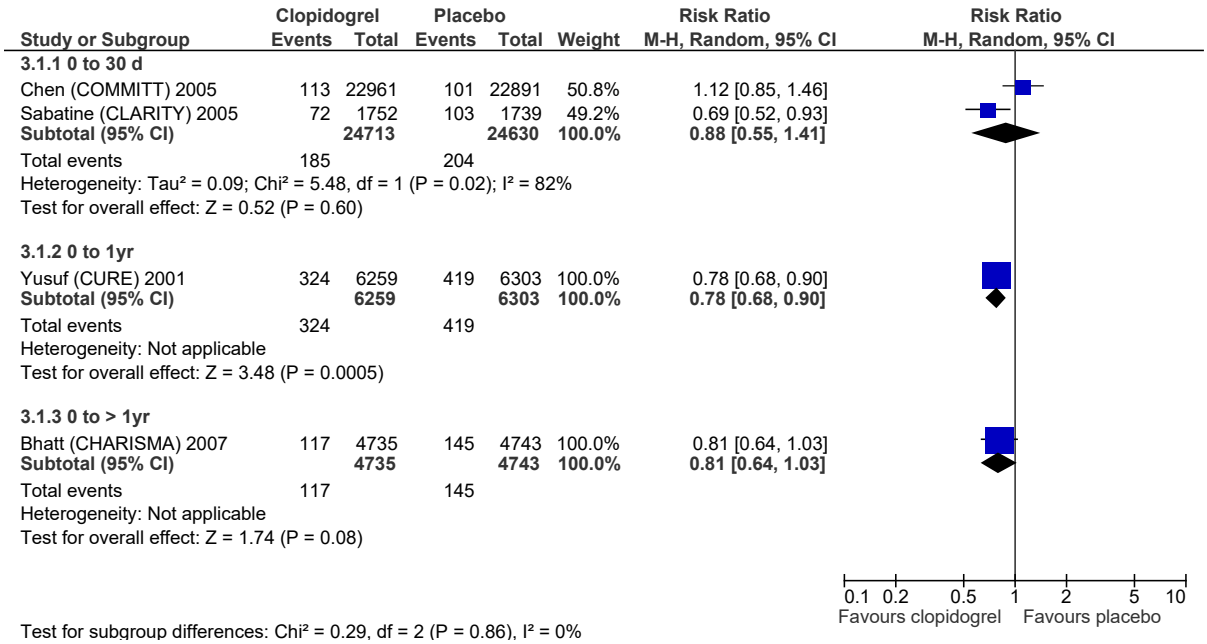
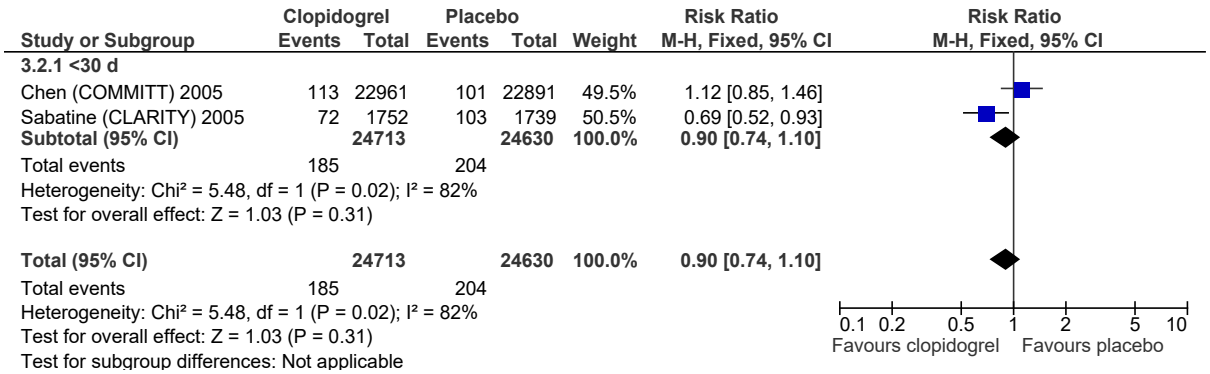


Figure 174: Clopidogrel+aspirin vs. aspirin(STEMI) - reinfarction



Heterogeneity

Heterogeneity was detected in the subgroup analysis on the risk of reinfarction in the clopidogrel and aspirin versus aspirin groups in a STEMI population. To investigate this, we first looked to see if we could eliminate papers that had a high risk of bias. Since this was not the case, we then investigated whether the types of stents used, bare metal vs. drug eluting stents, explained the heterogeneity. None of the papers reported which types of stents were used for PCI, so this could not be used to explain the heterogeneity. Consequently RR results were presented as random effects rather than fixed effects (see below).

Figure 175: Clopidogrel+aspirin vs. aspirin(STEMI) – reinfarction (random effects)

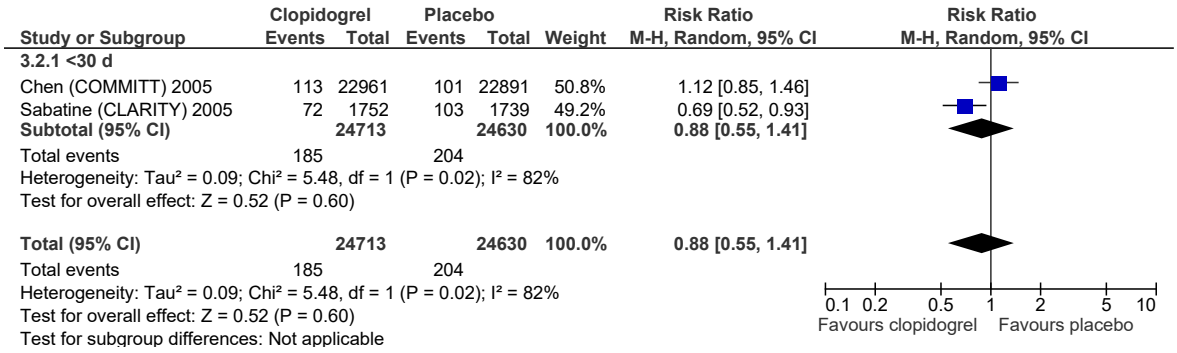


Figure 176: Clopidogrel+aspirin vs. aspirin(NSTEMI) - reinfarction

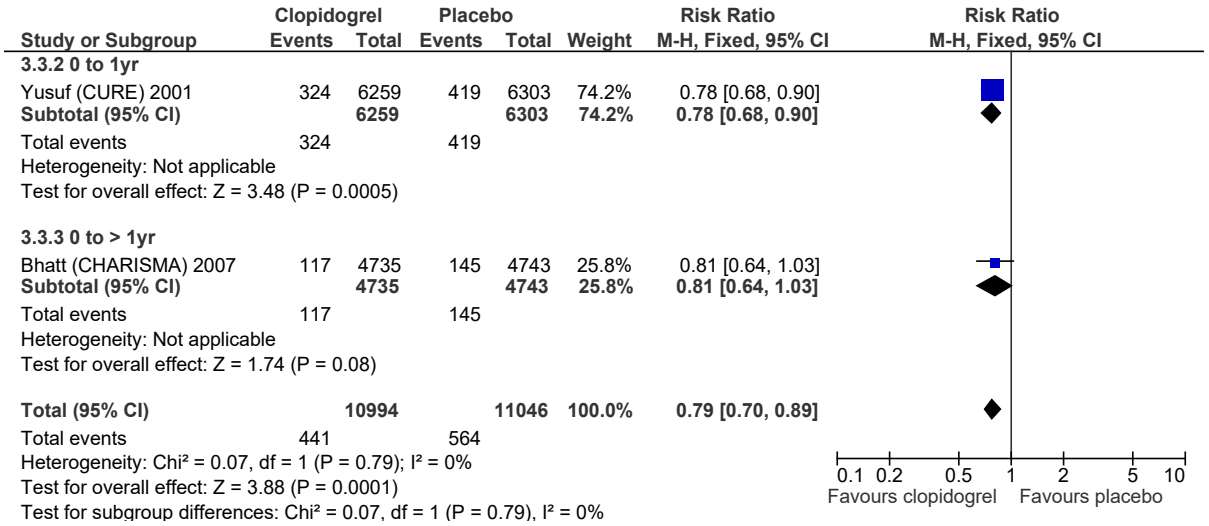


Figure 177: Clopidogrel+aspirin vs. aspirin(type of treatment) - reinfarction

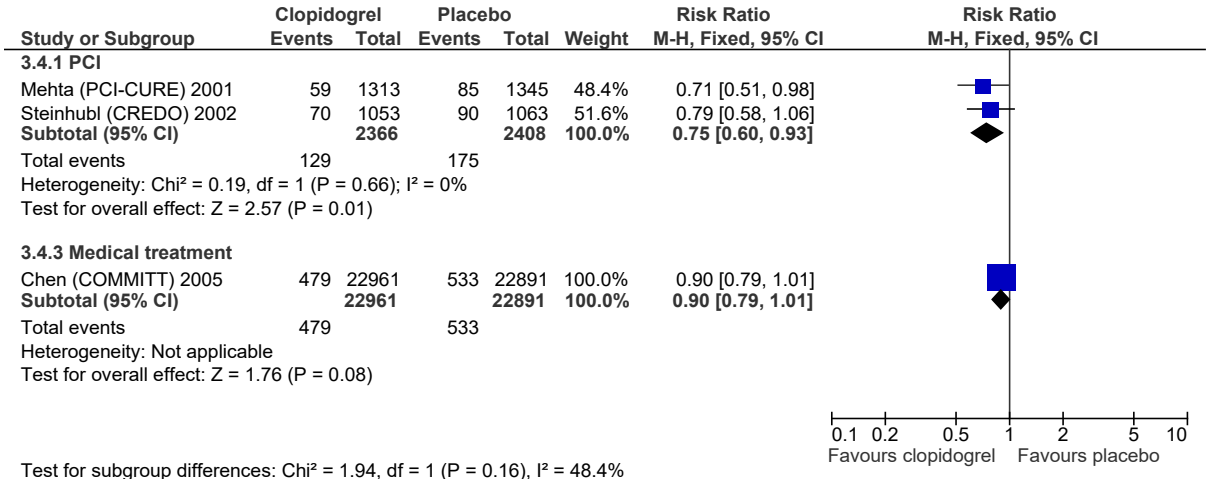
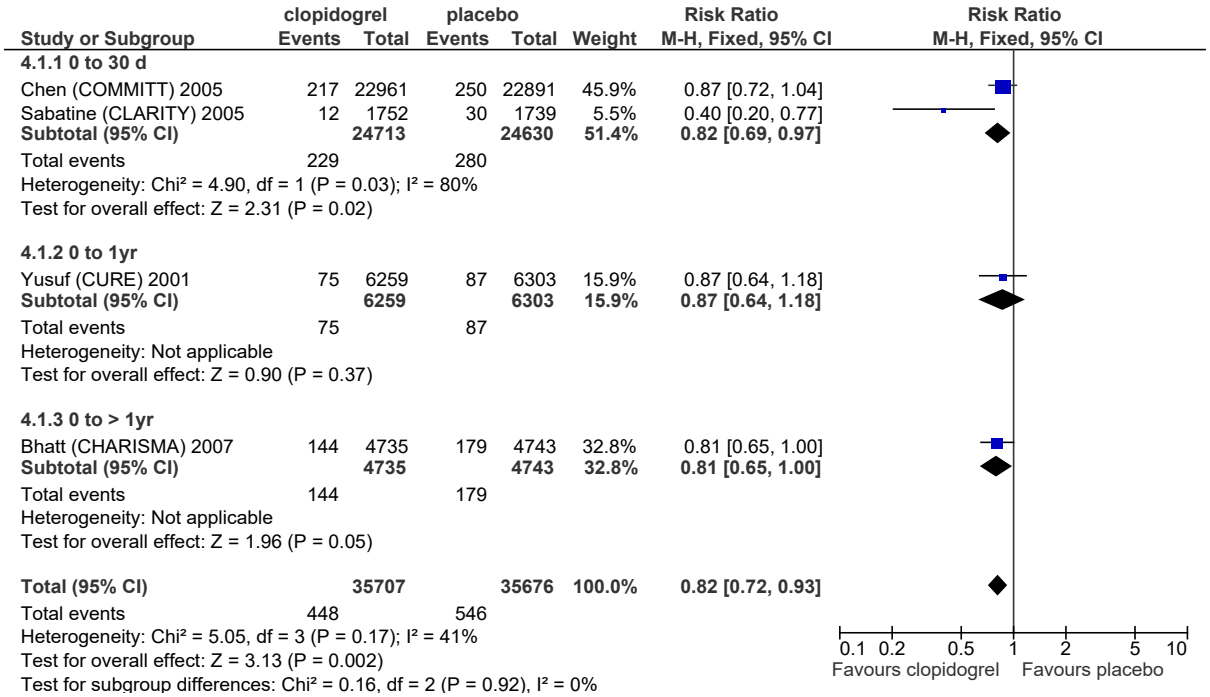


Figure 178: Clopidogrel+aspirin vs. aspirin(duration of treatment) - stroke



Heterogeneity

Heterogeneity was detected in the subgroup analysis on the risk of stroke in the clopidogrel and aspirin versus aspirin groups after 30 days of treatment. To investigate this, we first looked to see if we could eliminate papers that had a high risk of bias. Since this was not the case, we then investigated whether the types of stents used, bare metal vs. drug eluting stents, explained the heterogeneity. None of the papers reported which types of stents were used for PCI, so this could not be used to explain the heterogeneity. The RR results are therefore, presented as random effects RR rather than fixed effects. See below for the random effects RR result for the 0-30 d subgroup and for Total result.

Figure 179: - Clopidogrel + aspirin vs. aspirin (relative risk) (0-30 day results for random effects– stroke (random effects))

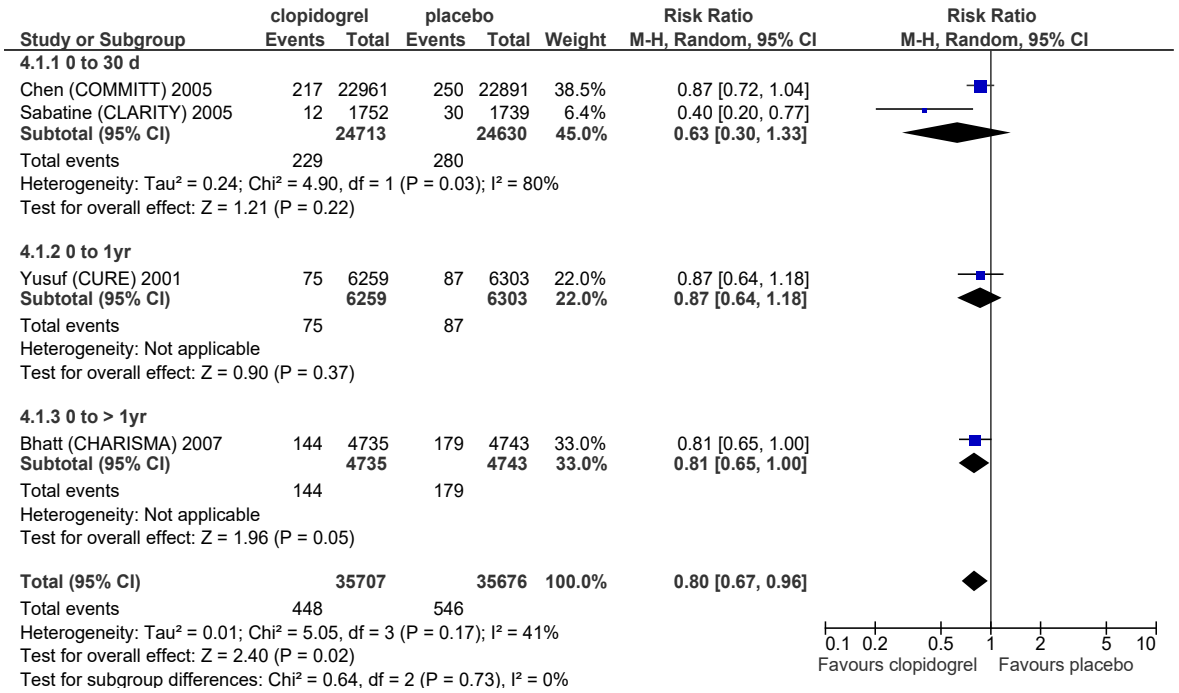
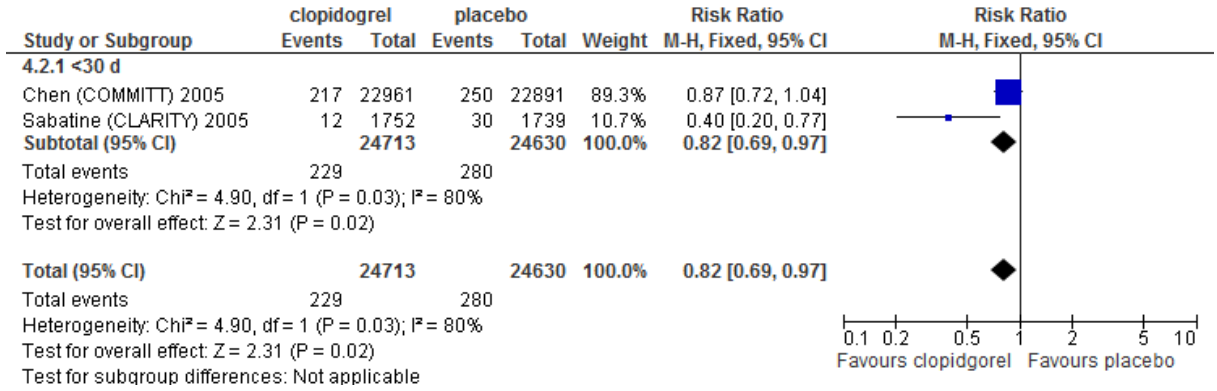


Figure 180: Clopidogrel+aspirin vs. aspirin(STEMI) - stroke



Heterogeneity

Heterogeneity was detected in the subgroup analysis on the risk of stroke in the clopidogrel and aspirin versus aspirin groups in a STEMI population. To investigate this, we first looked to see if we could eliminate papers that had a high risk of bias. Since this was not the case, we then investigated whether the types of stents used, bare metal vs. drug eluting stents, explained the heterogeneity. None of the papers reported which types of stents were used for PCI, so this could not be used to explain the heterogeneity. The RR results are therefore presented as random effects RR rather than fixed effects. See below.

Figure 181: Clopidogrel + aspirin vs. aspirin (STEMI) - stroke (random effects)

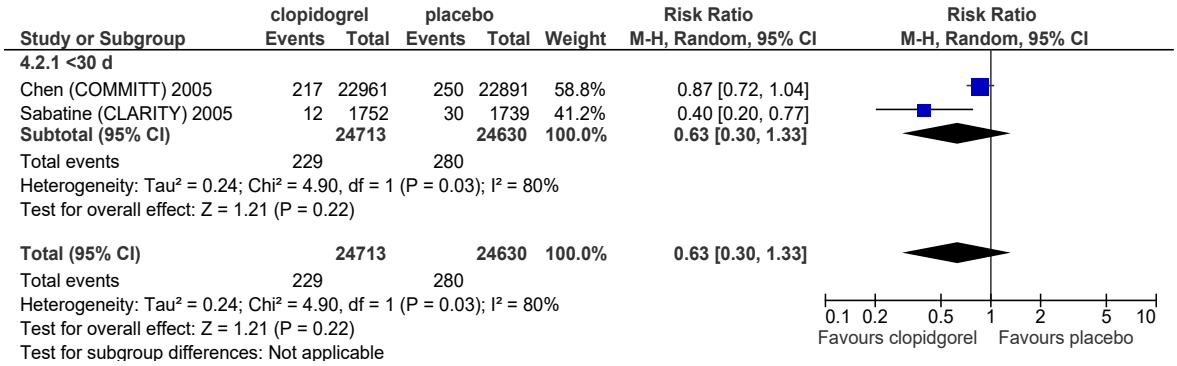


Figure 182: Clopidogrel+aspirin vs. aspirin(NSTEMI) - stroke

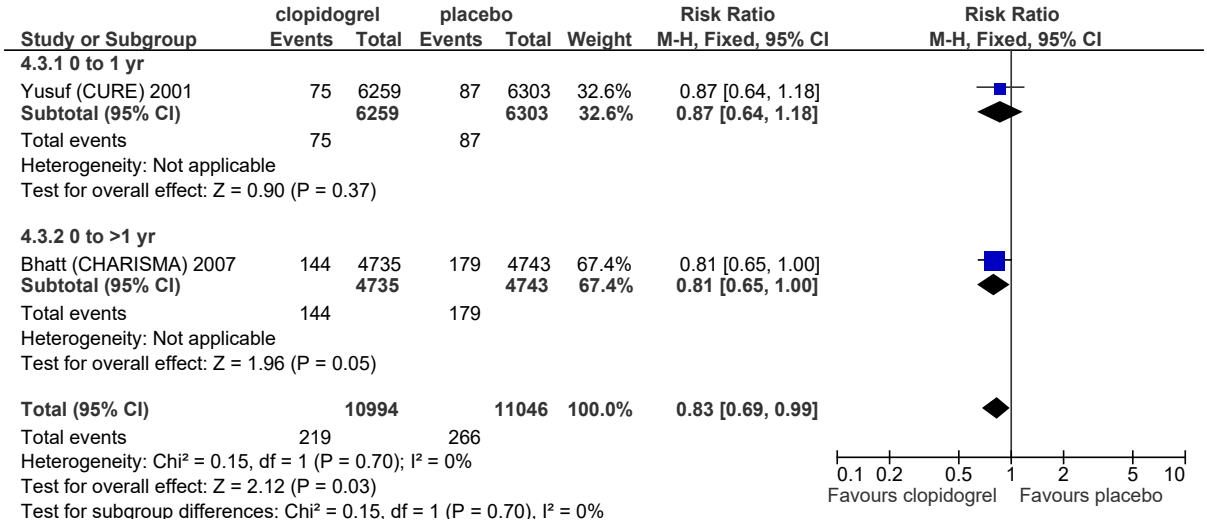


Figure 183: Clopidogrel+aspirin vs. aspirin(type of treatment) - stroke

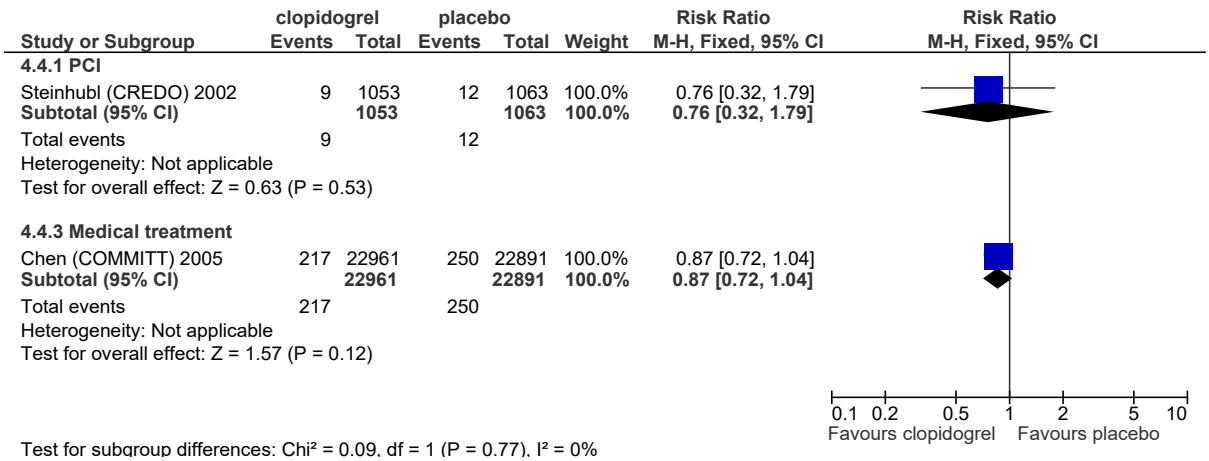


Table 168: Clopidogrel+aspirin vs. aspirin (duration of treatment) - revascularisation

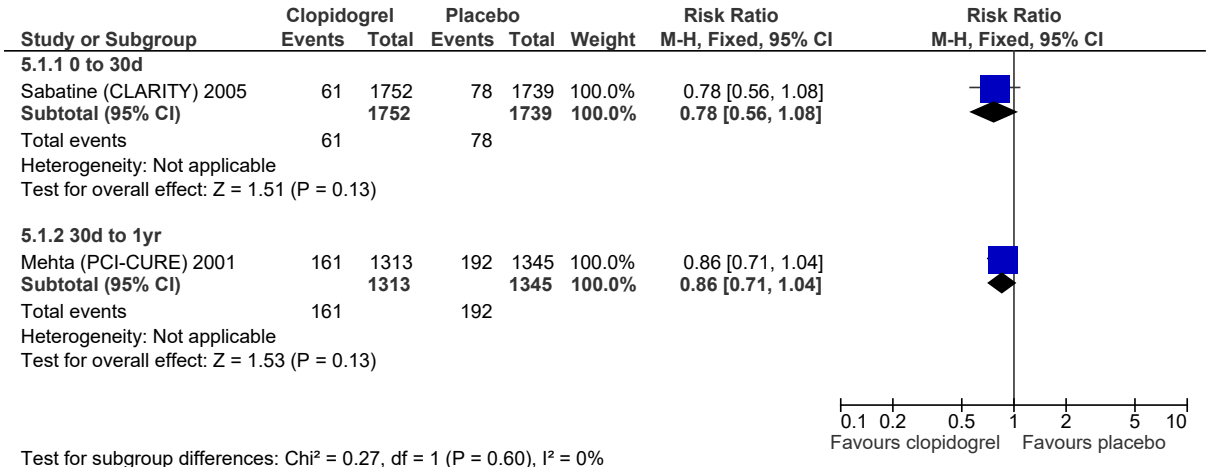


Figure 184: Clopidogrel+aspirin vs. aspirin(STEMI) - revascularisation

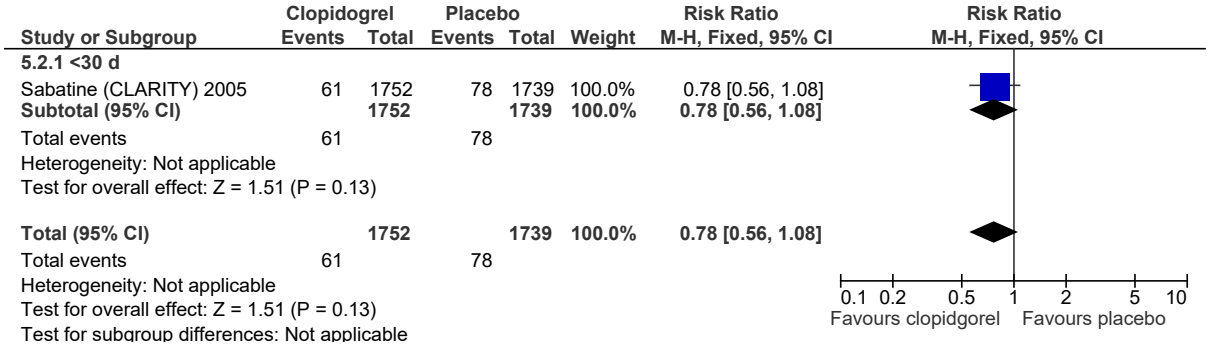


Figure 185: Clopidogrel+aspirin vs. aspirin(NSTEMI) - revascularisation

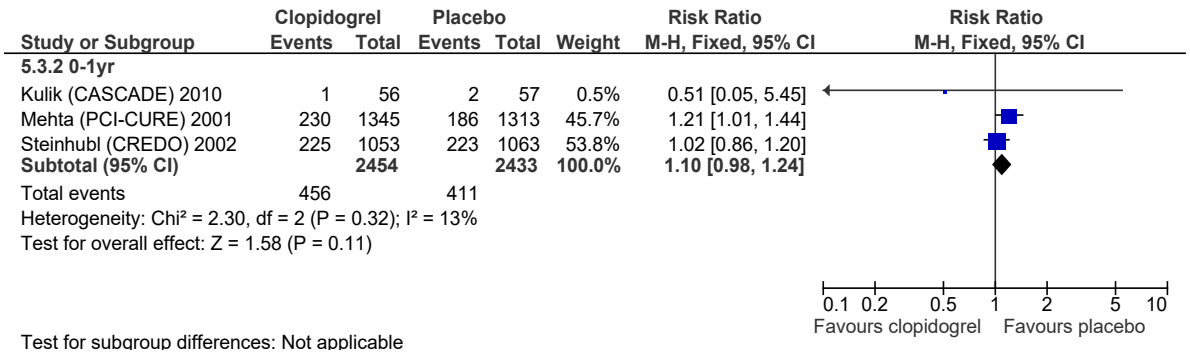


Figure 186: Clopidogrel+aspirin vs. aspirin(type of treatment) - revascularisation

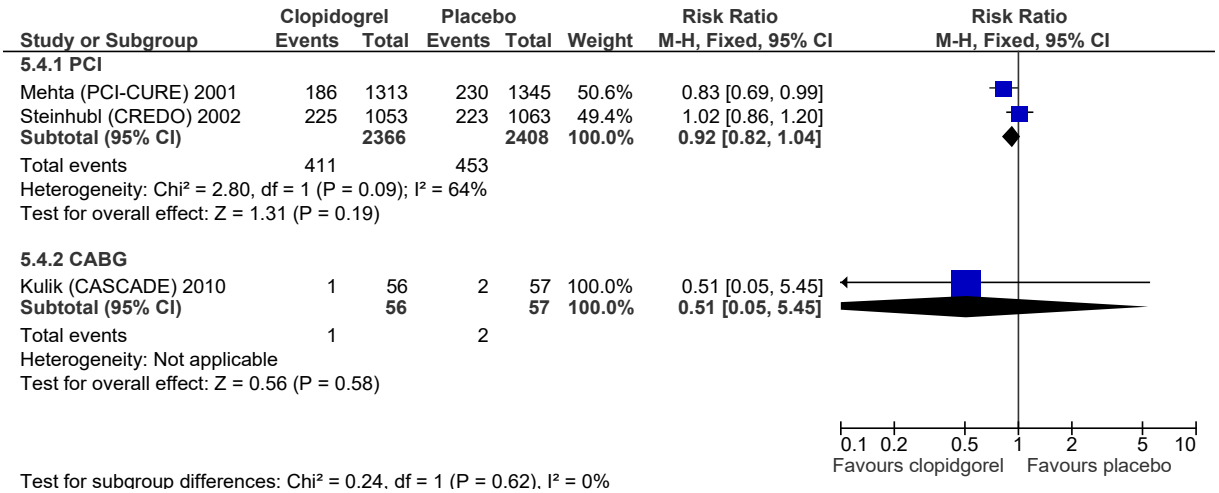


Figure 187: Clopidogrel + aspirin vs. aspirin (NSTEMI + CABG patients) – cardiovascular mortality/stroke/MI

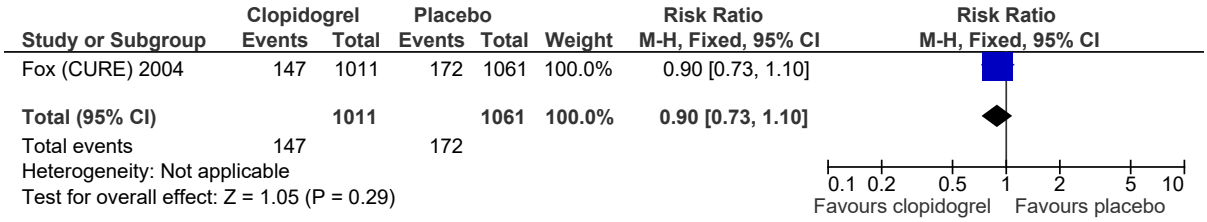


Figure 188: Clopidogrel + aspirin vs. aspirin (NSTEMI + medically treated patients) – cardiovascular mortality/stroke/MI

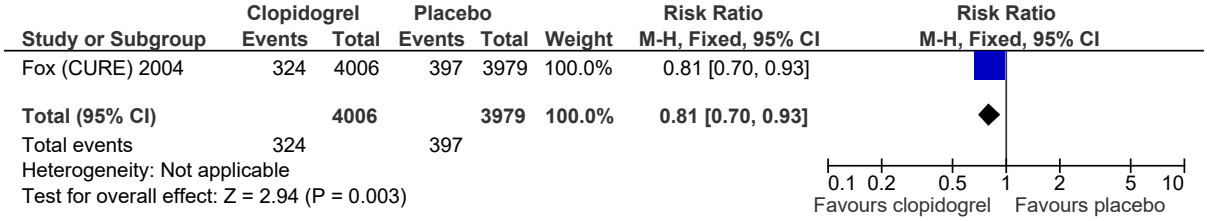


Figure 189: Clopidogrel + aspirin vs. aspirin (NSTEMI + medically treated patients) - cardiovascular mortality/stroke/MI

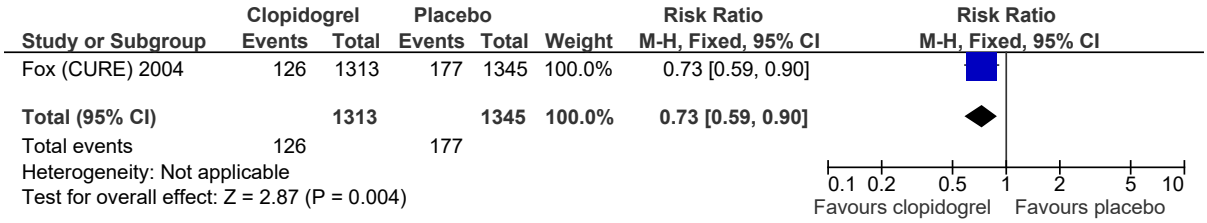


Figure 190: Clopidogrel+aspirin vs. aspirin(duration of treatment) – major bleeding

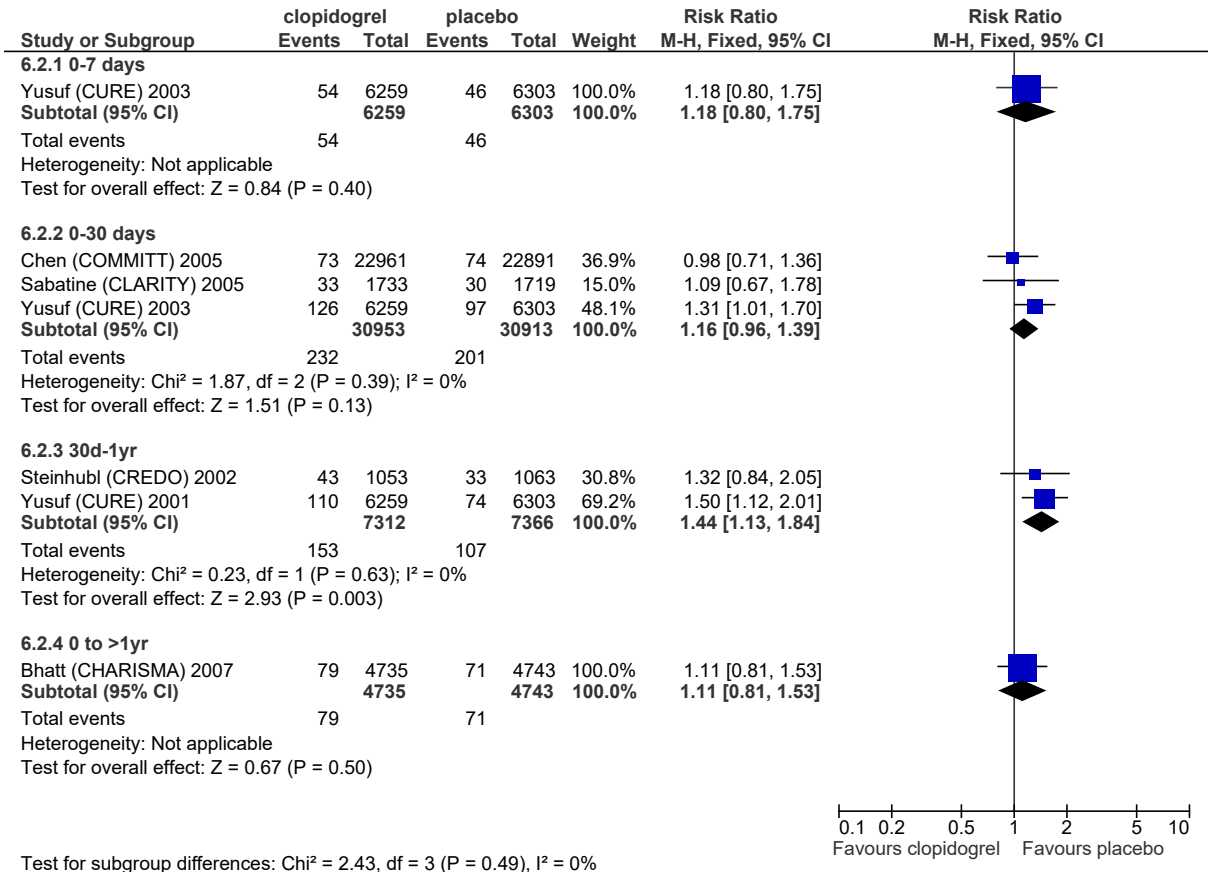


Figure 191: Clopidogrel+aspirin vs. aspirin(type of treatment) – major bleeding

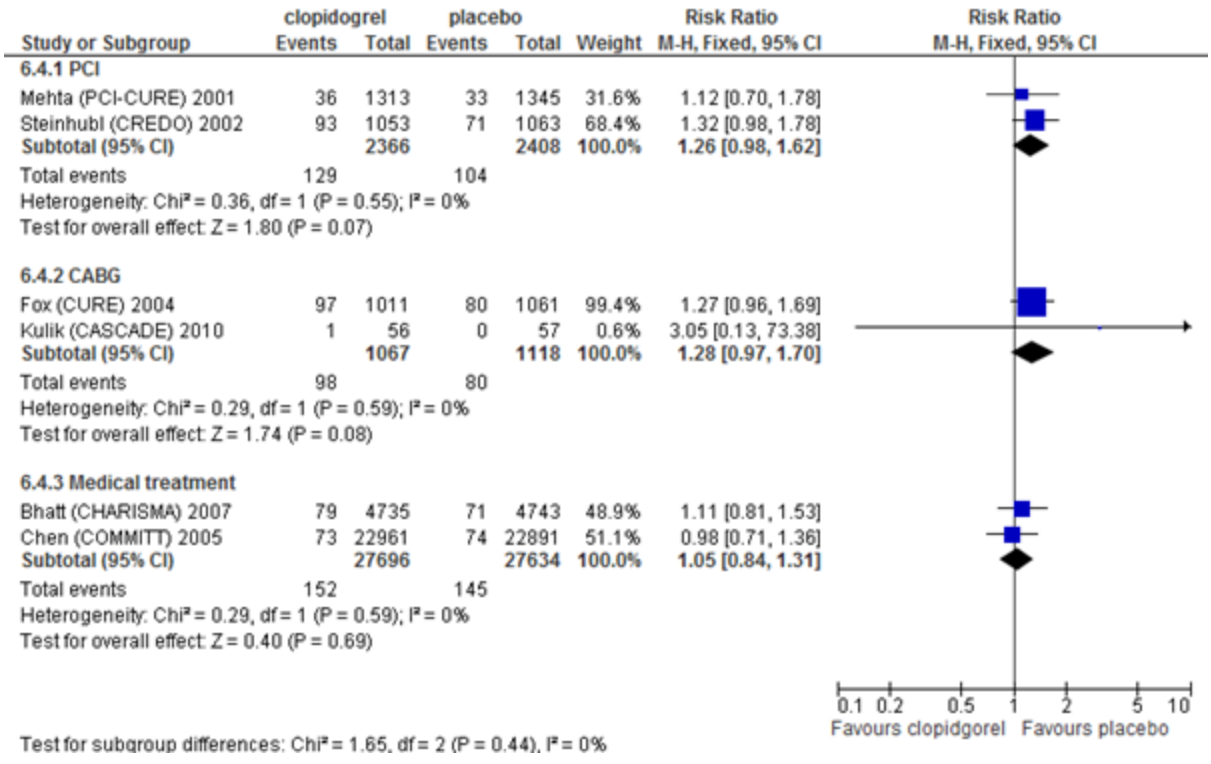
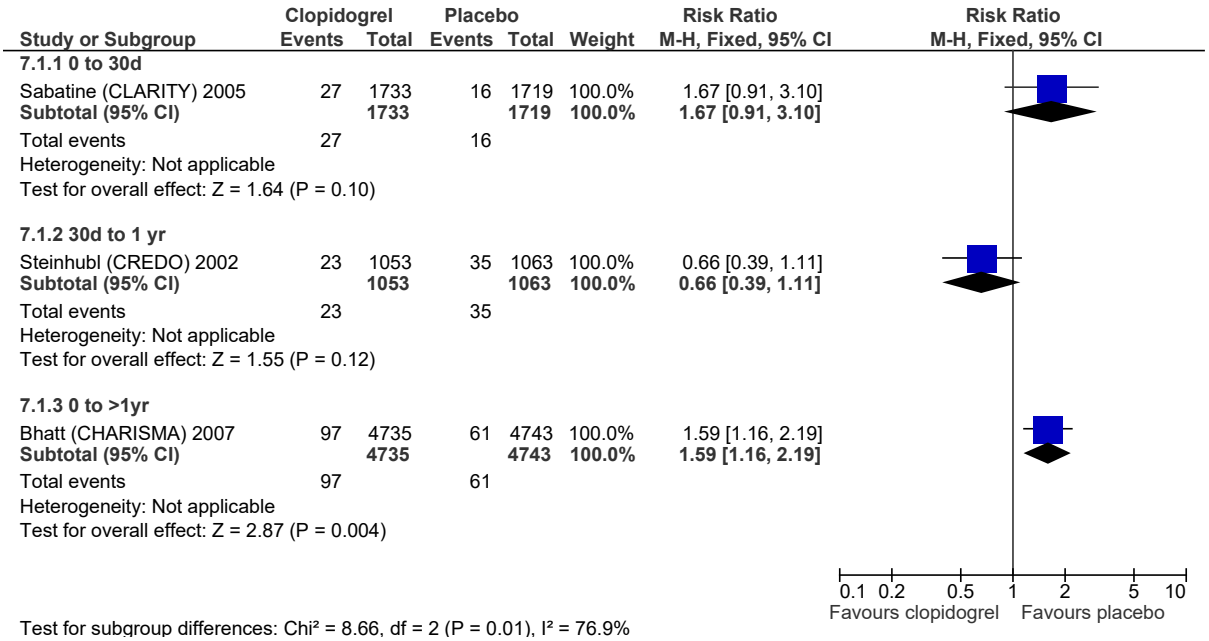


Figure 192: Clopidogrel+aspirin vs. aspirin(duration of treatment) – minor bleeding



Test for subgroup differences: Chi² = 8.66, df = 2 (P = 0.01), I² = 76.9%

Figure 193: Clopidogrel+aspirin vs. aspirin(type of treatment) – minor bleeding

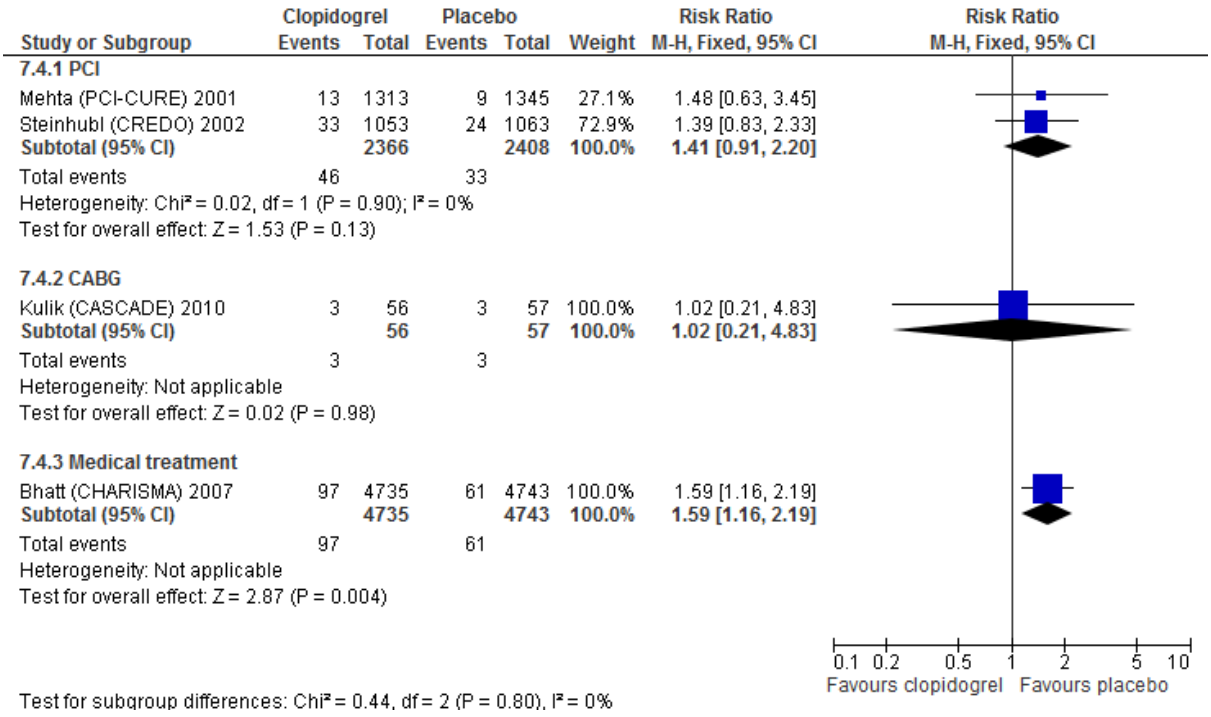
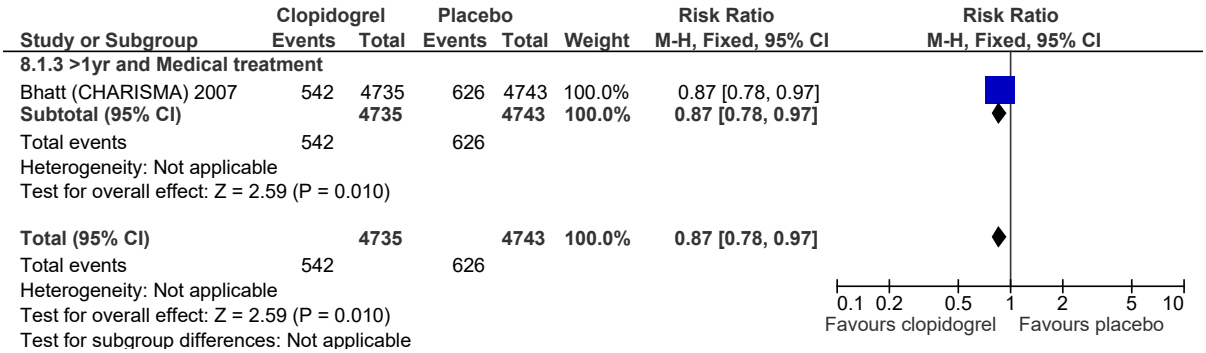


Figure 194: Clopidogrel+aspirin vs.aspirin(duration/type of treatment) - rehospitalisation



I.6.2 Late initiation of antiplatelet therapy

I.6.2.1 Clopidogrel + aspirin vs. aspirin in those not treated acutely

Figure 195: Clopidogrel + aspirin vs. aspirin alone – all-cause mortality

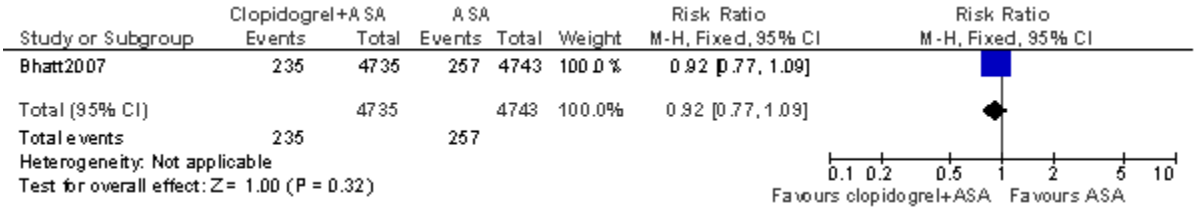


Figure 196: Clopidogrel+aspirin vs. aspirin alone - reinfarction

Study or Subgroup	Clopidogrel+ASA Events	Total	ASA Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bhatt2007	117	4735	145	4743	100.0%	0.81 [0.64, 1.03]
Total (95% CI)		**4735**		**4743**	**100.0%**	**0.81 [0.64, 1.03]**
Total events	117		145			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.74 (P = 0.08)

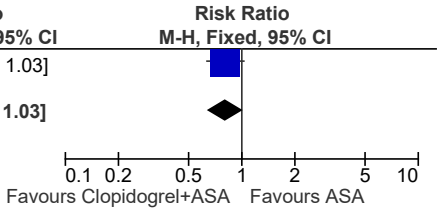


Figure 197: Clopidogrel+aspirin vs. aspirin alone - stroke

Study or Subgroup	Clopidogrel+ASA Events	Total	ASA Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bhatt2007	144	4735	179	4743	100.0%	0.81 [0.65, 1.00]
Total (95% CI)		**4735**		**4743**	**100.0%**	**0.81 [0.65, 1.00]**
Total events	144		179			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.96 (P = 0.05)

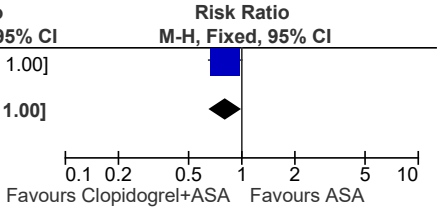


Figure 198: Clopidogrel+aspirin vs. aspirin alone - hospitalisation

Study or Subgroup	Clopidogrel+ASA Events	Total	ASA Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bhatt2007	542	4735	626	4743	100.0%	0.87 [0.78, 0.97]
Total (95% CI)		**4735**		**4743**	**100.0%**	**0.87 [0.78, 0.97]**
Total events	542		626			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.59 (P = 0.010)

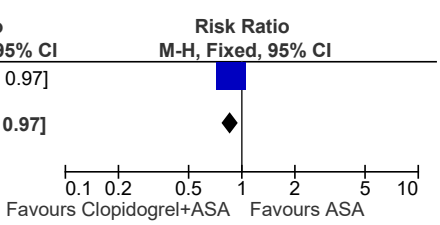


Figure 199: Clopidogrel+aspirin vs. aspirin alone - major bleeding

Study or Subgroup	Clopidogrel+ASA Events	Total	ASA Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bhatt2007	79	4735	71	4743	100.0%	1.11 [0.81, 1.53]
Total (95% CI)		**4735**		**4743**	**100.0%**	**1.11 [0.81, 1.53]**
Total events	79		71			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.67 (P = 0.50)

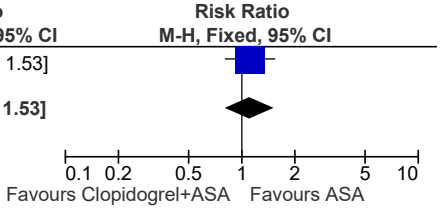


Figure 200: Clopidogrel+aspirin vs. aspirin alone - moderate bleeding

Study or Subgroup	Clopidogrel+ASA Events	Total	ASA Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bhatt2007	97	4735	61	4743	100.0%	1.59 [1.16, 2.19]
Total (95% CI)		**4735**		**4743**	**100.0%**	**1.59 [1.16, 2.19]**
Total events	97		61			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.87 (P = 0.004)

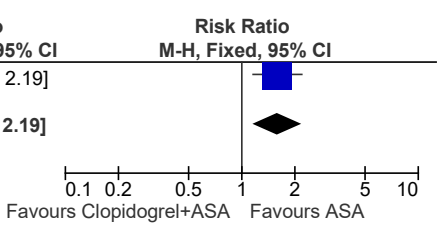
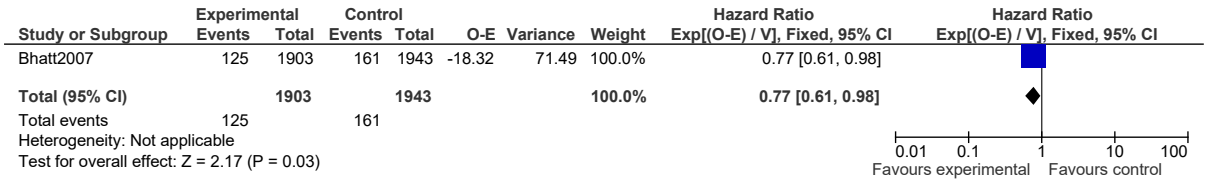


Figure 201: Clopidogrel+aspirin vs. aspirin alone - cardiovascular death/MI/Stroke – prior MI patients only (hazard ratio)



I.6.3 Antiplatelet therapy in those with an additional indication for anticoagulation

This section was updated and replaced in 2020. See www.nice.org.uk/guidance/ng185 for the 2020 evidence review.

I.6.3.1 Warfarin + dual antiplatelet vs. warfarin + clopidogrel (indirect population I)

Figure 202: Warfarin + dual vs. warfarin + clopidogrel - all-cause mortality.

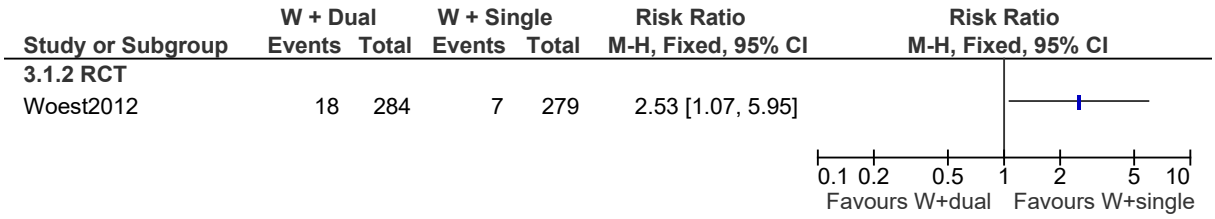


Figure 203: Warfarin + dual vs. warfarin + clopidogrel – all-cause mortality (hazard ratio)

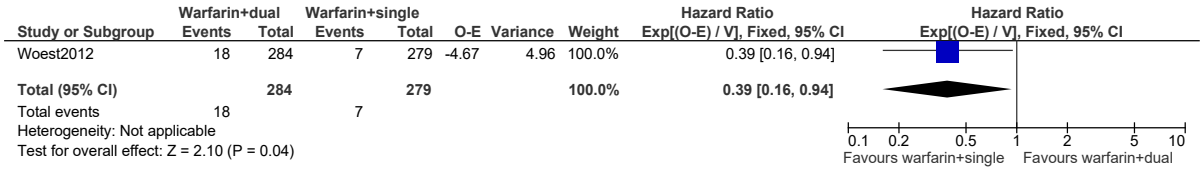


Figure 204: Warfarin + dual vs. warfarin + clopidogrel - reinfarction

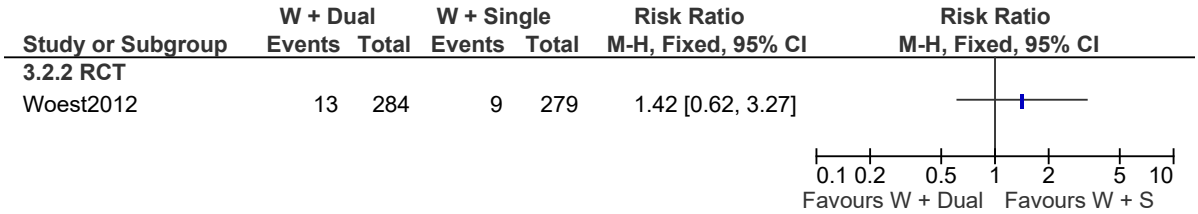


Figure 205: Warfarin + dual vs. warfarin + clopidogrel - stroke

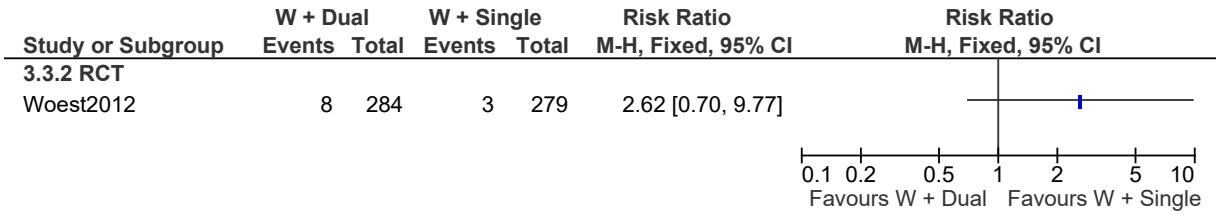


Figure 206: Warfarin + dual vs. warfarin + clopidogrel - revascularisation

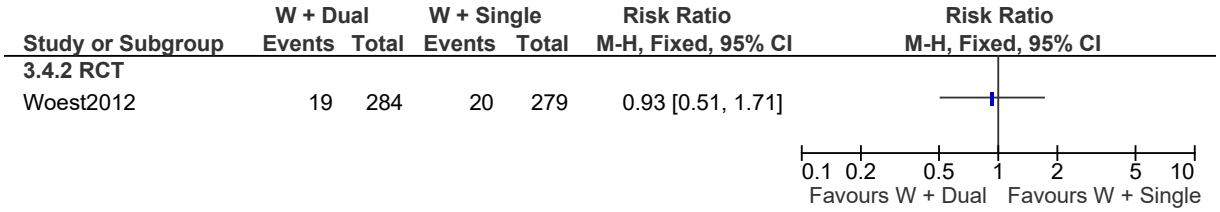


Figure 207: Warfarin + dual vs. warfarin + clopidogrel – major bleeding

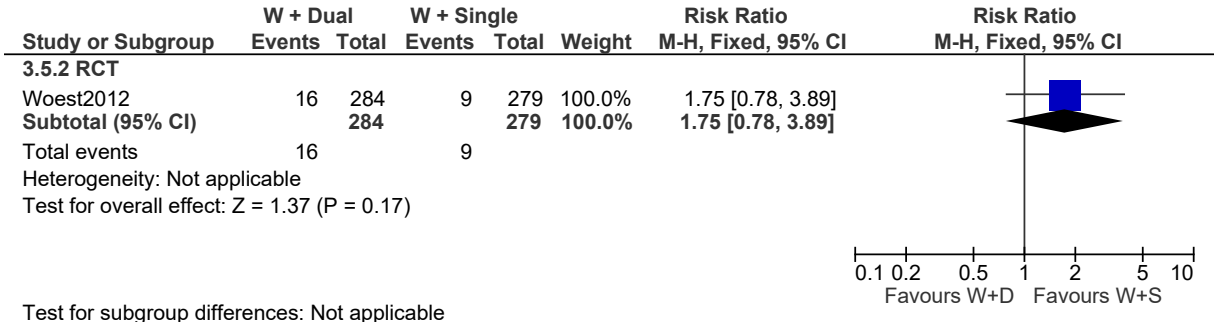


Figure 208: Warfarin + dual vs. warfarin + clopidogrel – minor bleeding

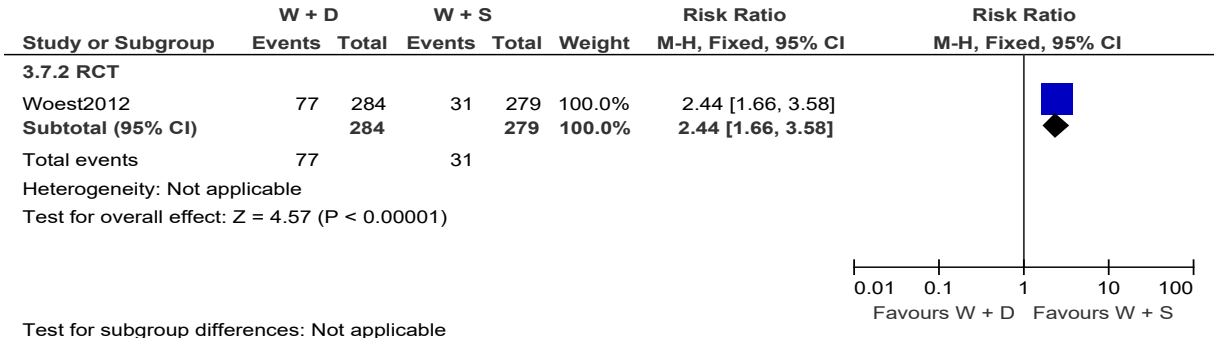
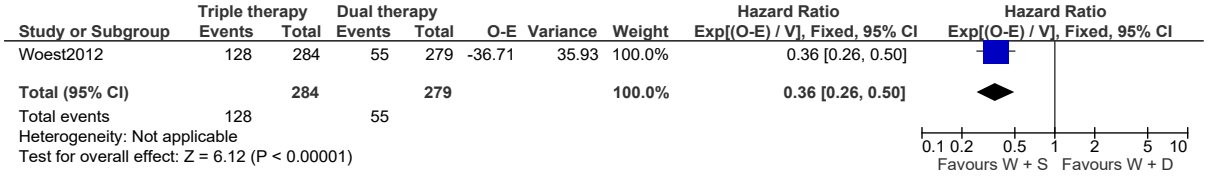
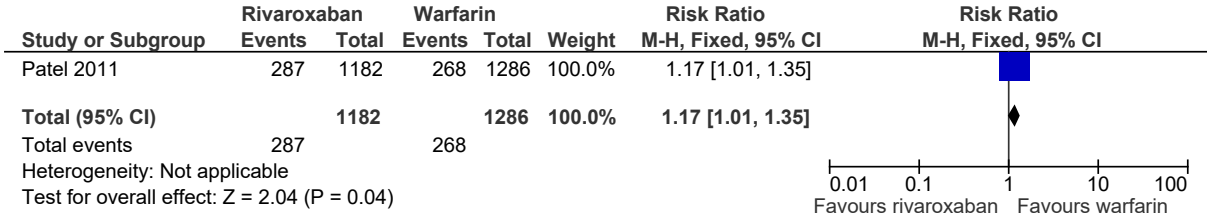


Figure 209: Warfarin + dual vs. warfarin + clopidogrel – any bleeding event



I.6.3.2 Rivaroxaban vs. warfarin (direct population)

Figure 210: Rivaroxaban vs. warfarin - major and non-major clinically relevant bleeding (direct population)



I.6.3.3 Warfarin + dual antiplatelet vs. warfarin + aspirin

Figure 211: Warfarin + dual antiplatelet vs. warfarin + aspirin - all-cause mortality

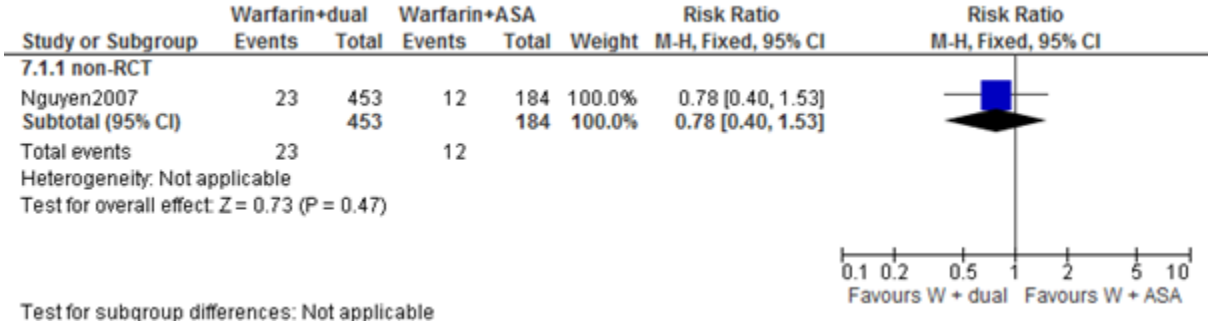


Figure 212: Warfarin + dual vs. warfarin + clopidogrel – stent thrombosis

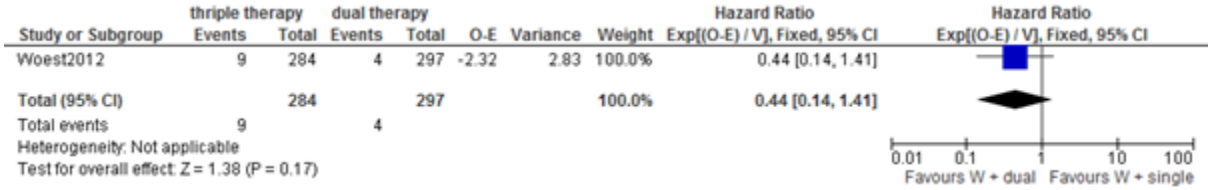


Figure 213: Warfarin + dual antiplatelet therapy vs. warfarin + aspirin – cardiac mortality

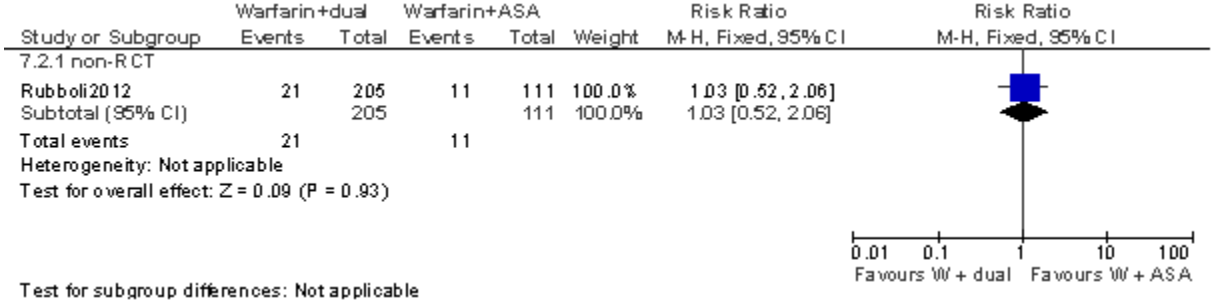


Figure 214: Warfarin + dual vs. warfarin + aspirin - reinfarction

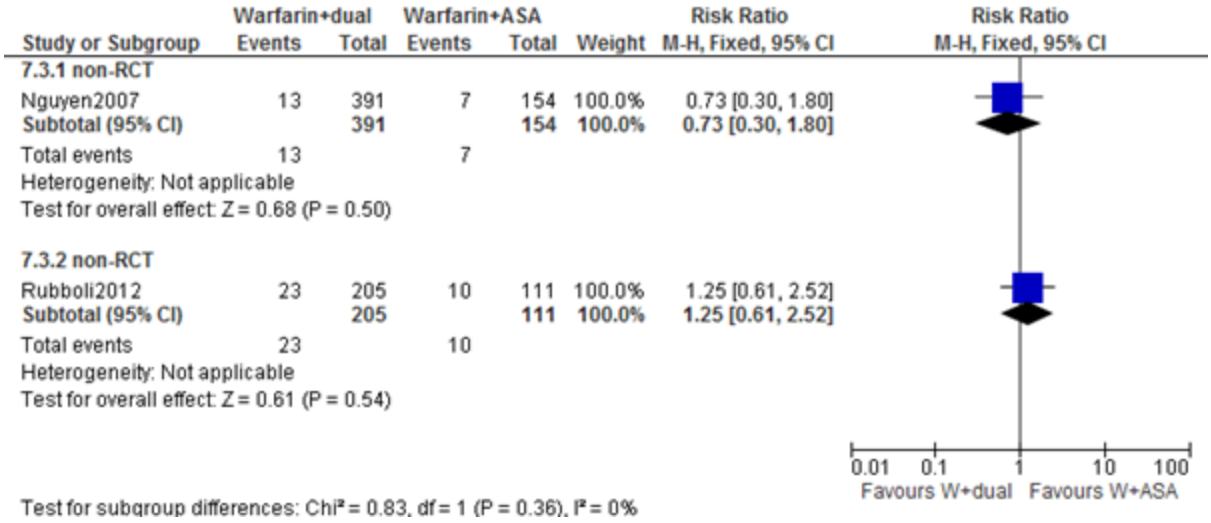


Figure 215: Warfarin + dual vs. warfarin + aspirin - stroke

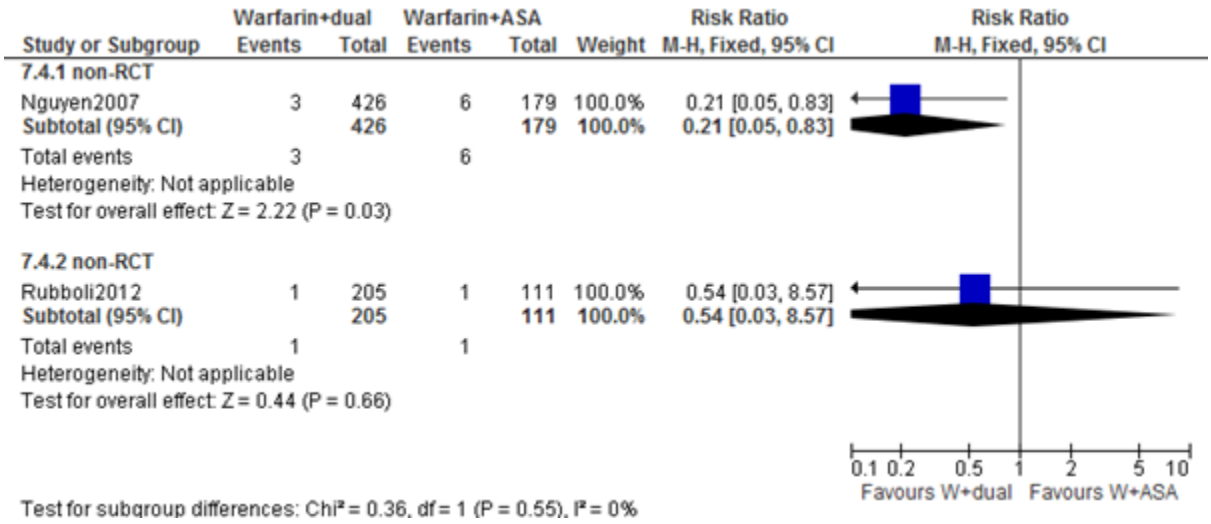
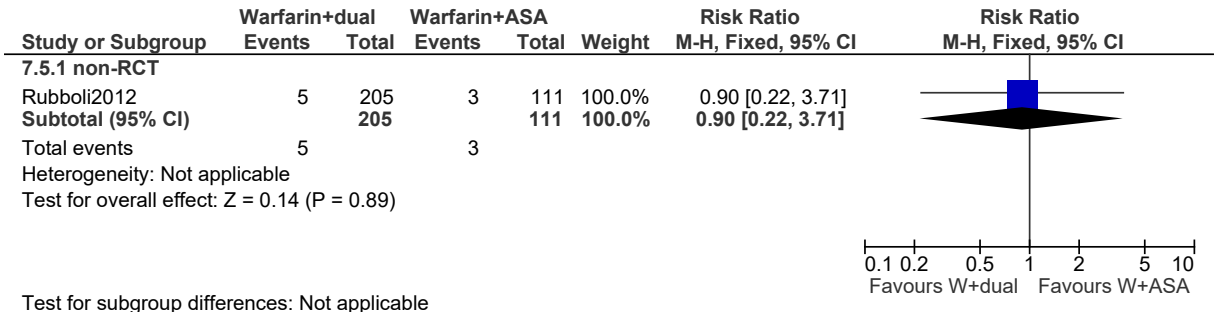


Figure 216: Warfarin + dual vs. warfarin + aspirin – major bleeding



I.6.3.4 Triple therapy vs. dual therapy (indirect therapy I & II)

Figure 217: Triple therapy (oral anticoagulation and dual antiplatelet therapy) vs. dual antiplatelet therapy– all-cause mortality

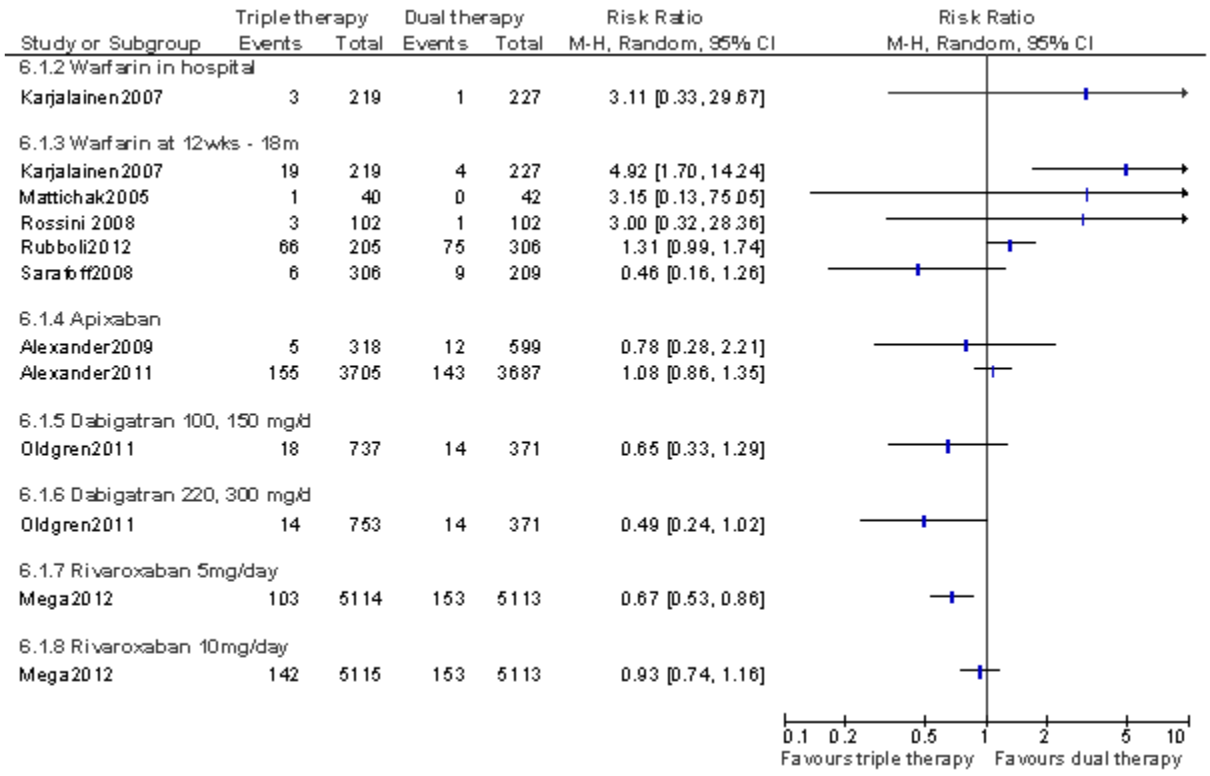


Figure 218: Triple therapy (oral anticoagulation and dual antiplatelet therapy) vs. dual antiplatelet therapy (Indirect population I) – cardiac mortality

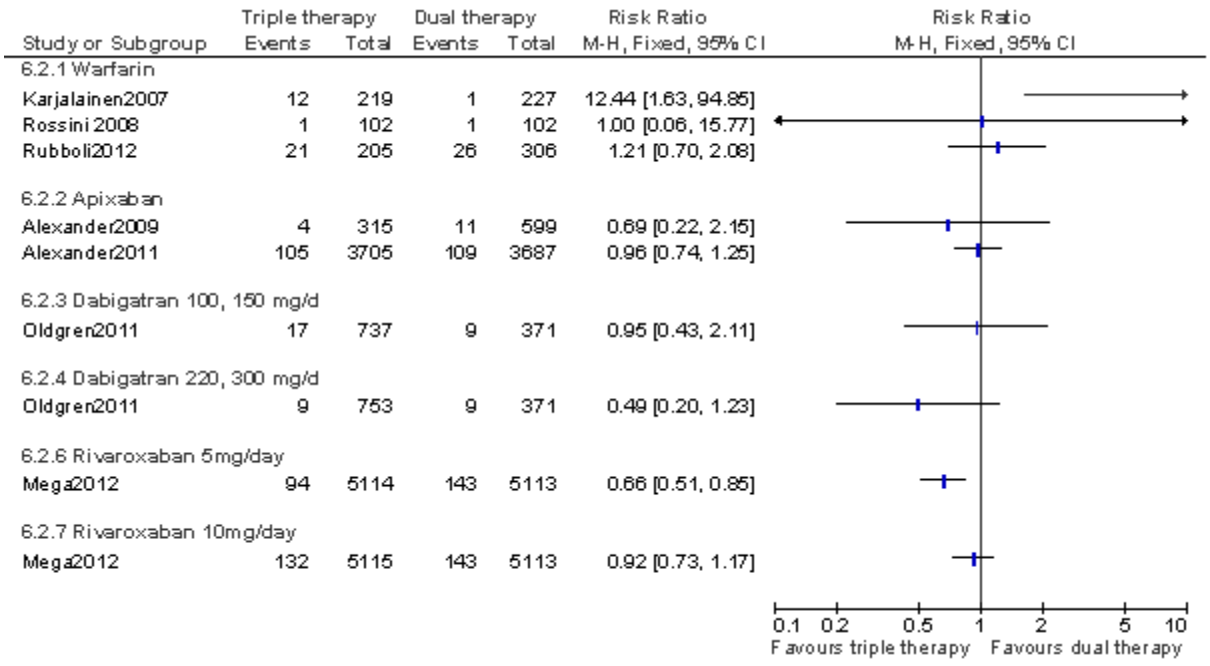


Figure 219: Triple therapy (oral anticoagulation and dual antiplatelet therapy) vs. dual antiplatelet therapy (Indirect population I) -reinfarction.

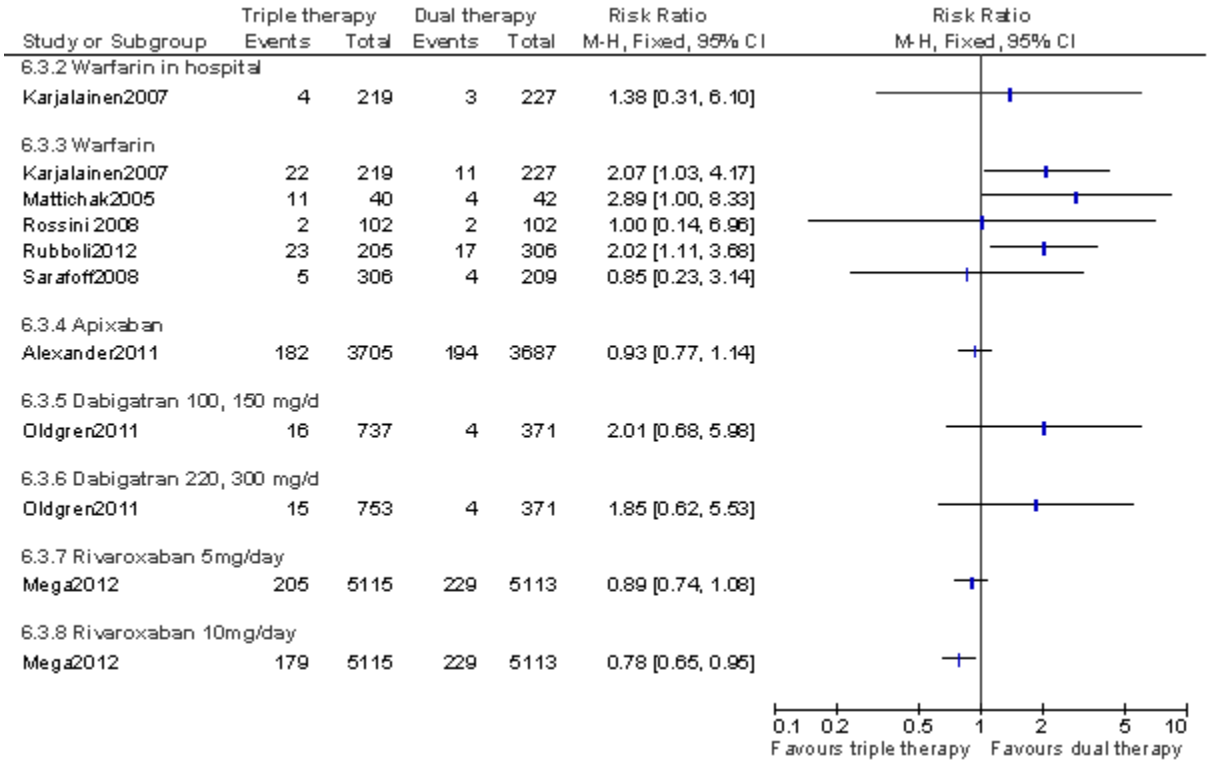


Figure 220: Triple therapy (oral anticoagulation and dual antiplatelet therapy) vs. dual antiplatelet therapy (Indirect population I) - revascularisation

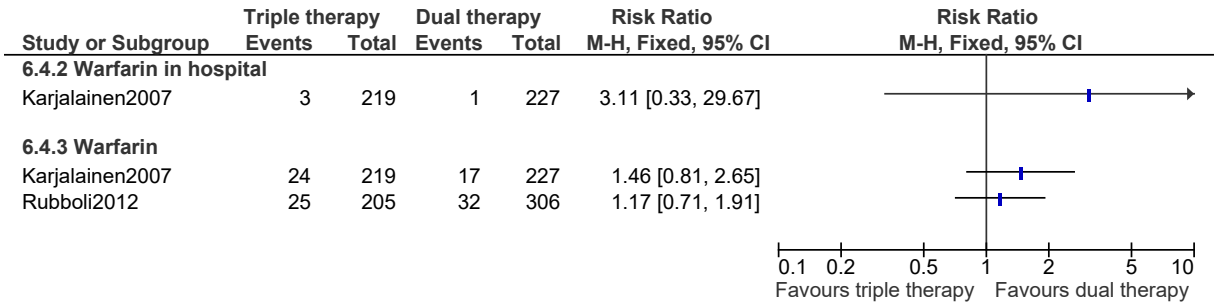


Figure 221: Triple therapy (oral anticoagulation and dual antiplatelet therapy) vs. dual antiplatelet (Indirect population I) - stroke

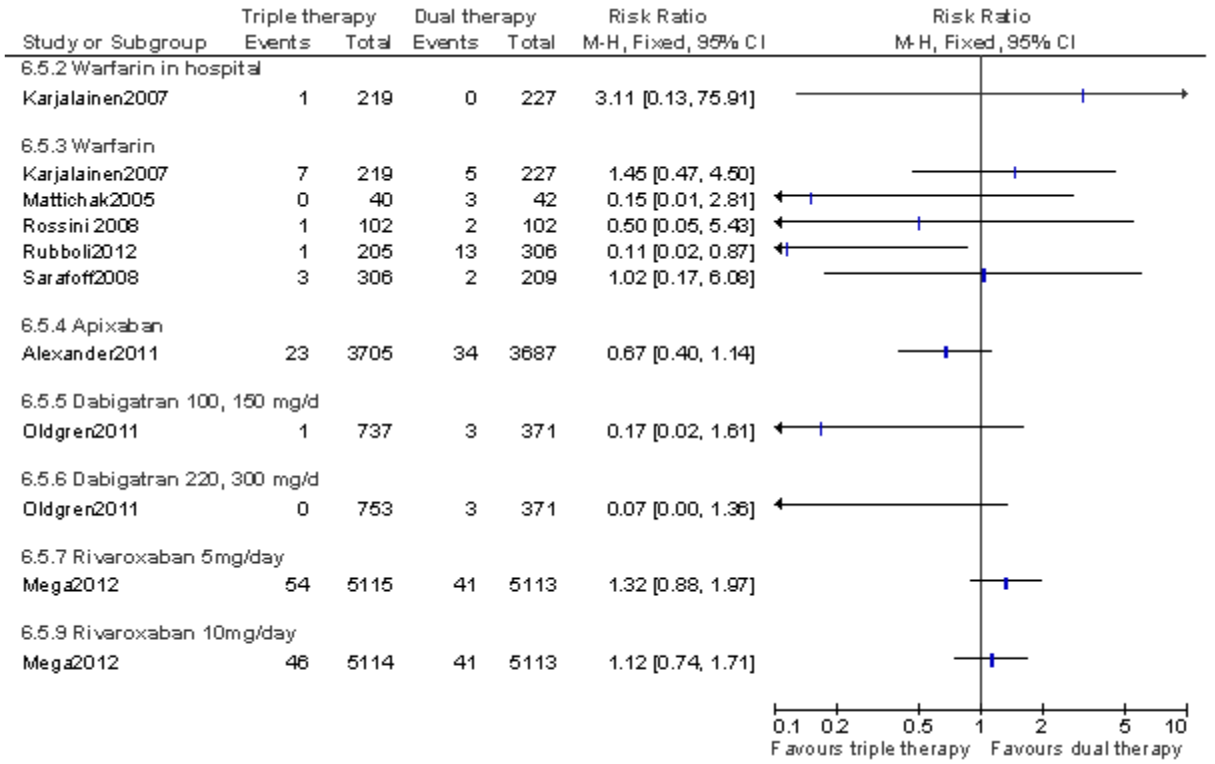

Triple therapy
Dual therapy
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
6.5.2 Warfarin in hospital
Karjalainen2007 1 219 0 227 3.11 [0.13, 75.91]
6.5.3 Warfarin
Karjalainen2007 7 219 5 227 1.45 [0.47, 4.50]
Mattichak2005 0 40 3 42 0.15 [0.01, 2.81]
Rossini 2008 1 102 2 102 0.50 [0.05, 5.43]
Rubboli2012 1 205 13 306 0.11 [0.02, 0.87]
Sarafoff2008 3 306 2 209 1.02 [0.17, 6.08]
6.5.4 Apixaban
Alexander2011 23 3705 34 3687 0.67 [0.40, 1.14]
6.5.5 Dabigatran 100, 150 mg/d
Oldgren2011 1 737 3 371 0.17 [0.02, 1.61]
6.5.6 Dabigatran 220, 300 mg/d
Oldgren2011 0 753 3 371 0.07 [0.00, 1.36]
6.5.7 Rivaroxaban 5mg/day
Mega2012 54 5115 41 5113 1.32 [0.88, 1.97]
6.5.9 Rivaroxaban 10mg/day
Mega2012 46 5114 41 5113 1.12 [0.74, 1.71]
0.1 0.2 0.5 1 2 5 10
Favours triple therapy
Favours dual therapy

Figure 222: Triple therapy (oral anticoagulation and dual antiplatelet therapy) vs. dual antiplatelet therapy (Indirect population I) – major bleeding

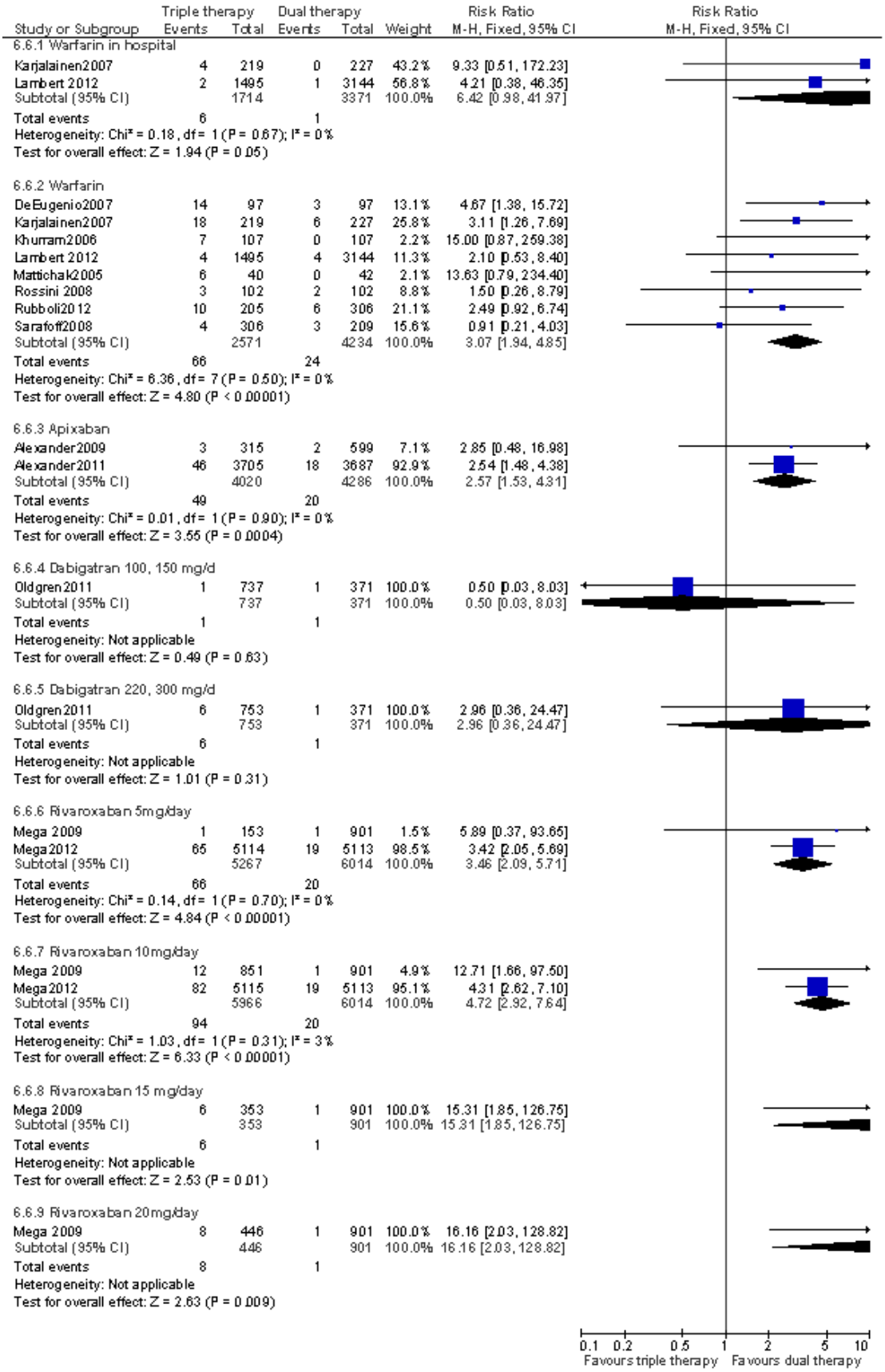
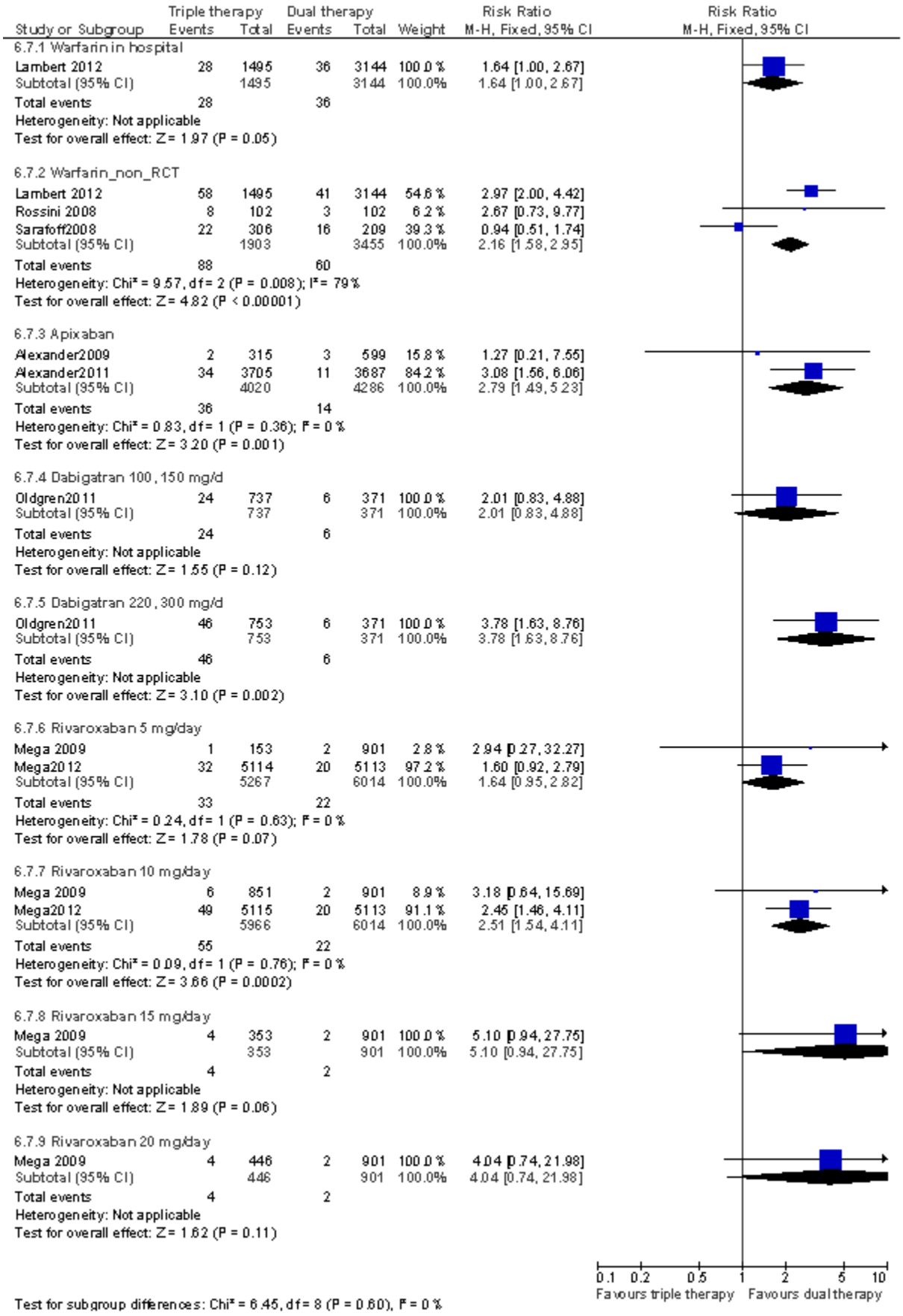


Figure 223: Triple therapy (oral anticoagulation and dual antiplatelet therapy) vs. dual antiplatelet therapy (Indirect population I) – minor bleeding



I.6.3.5 Warfarin + aspirin vs. aspirin (indirect population II)

Figure 224: Warfarin+ aspirin vs. aspirin (Indirect population II) – all-cause mortality

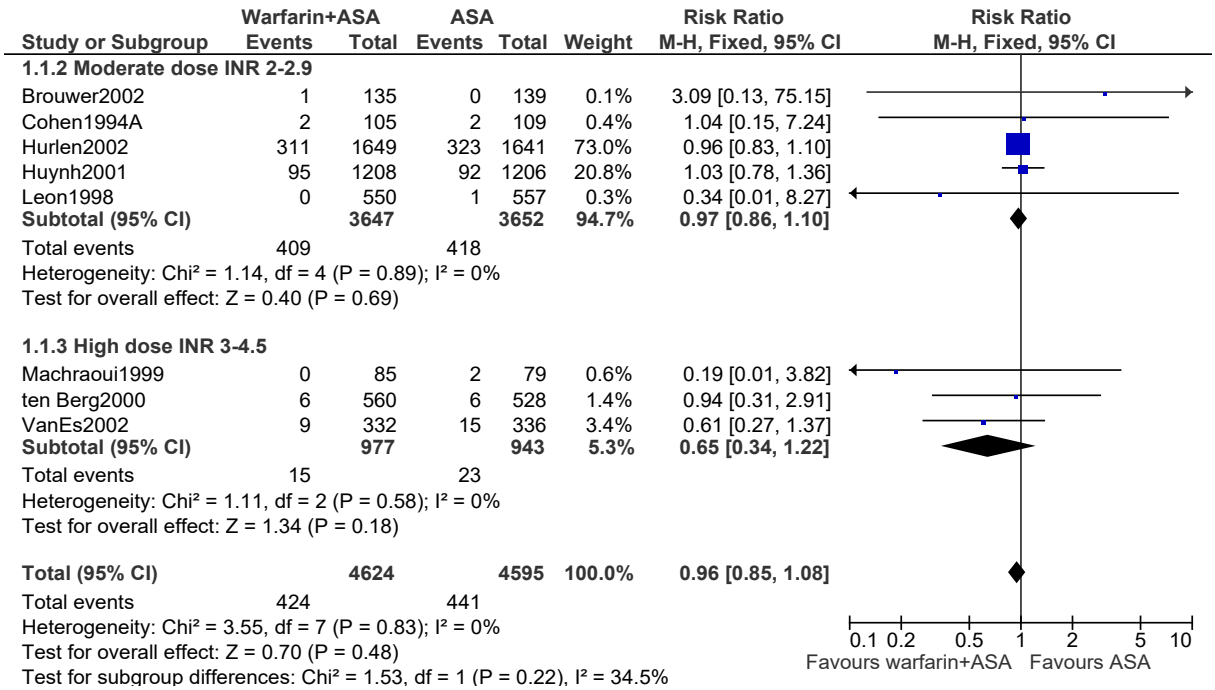


Figure 225: Warfarin + aspirin vs. aspirin (Indirect population II) – cardiovascular mortality

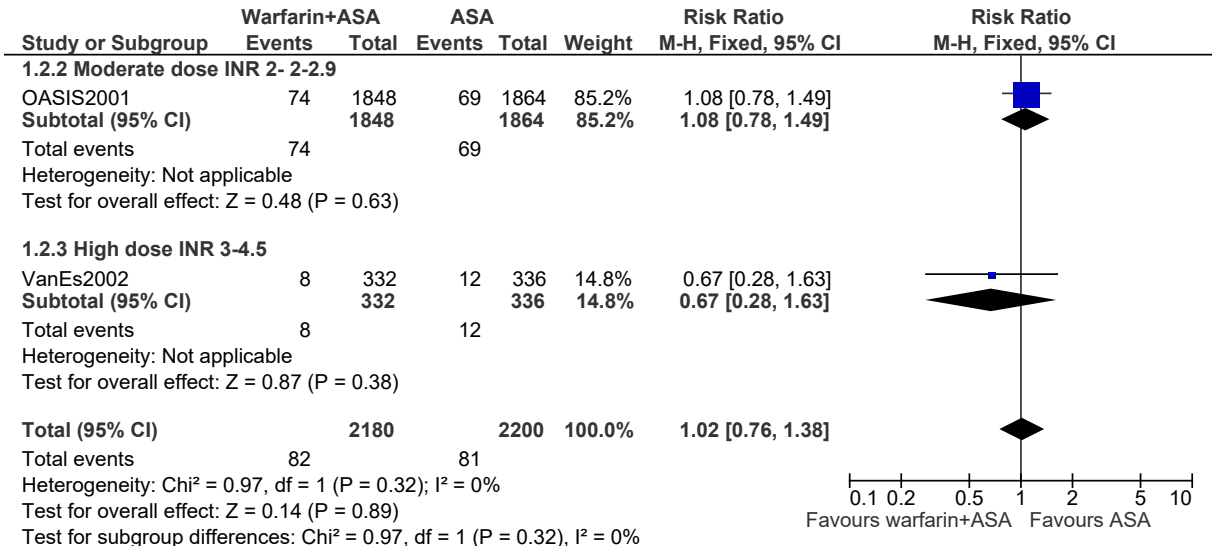


Figure 226: Warfarin + aspirin vs. aspirin (Indirect population II) - reinfarction

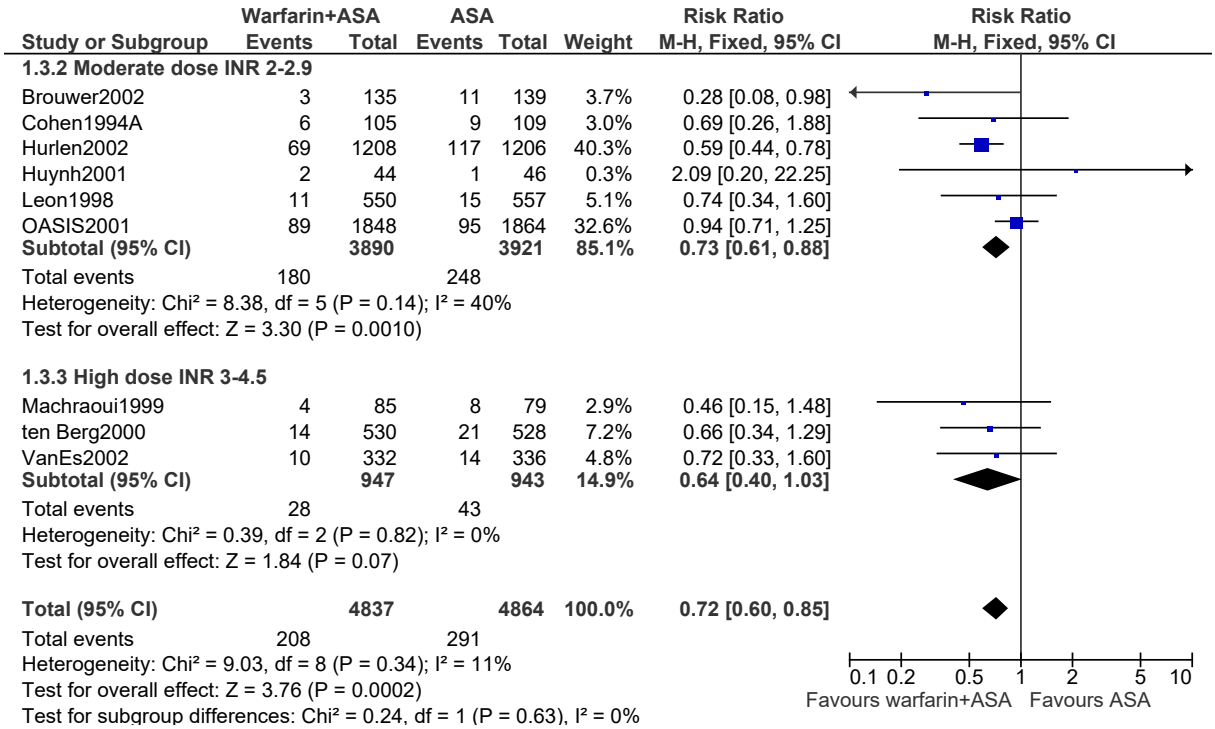


Figure 227: Warfarin + aspirin vs. aspirin (Indirect population II) - stroke

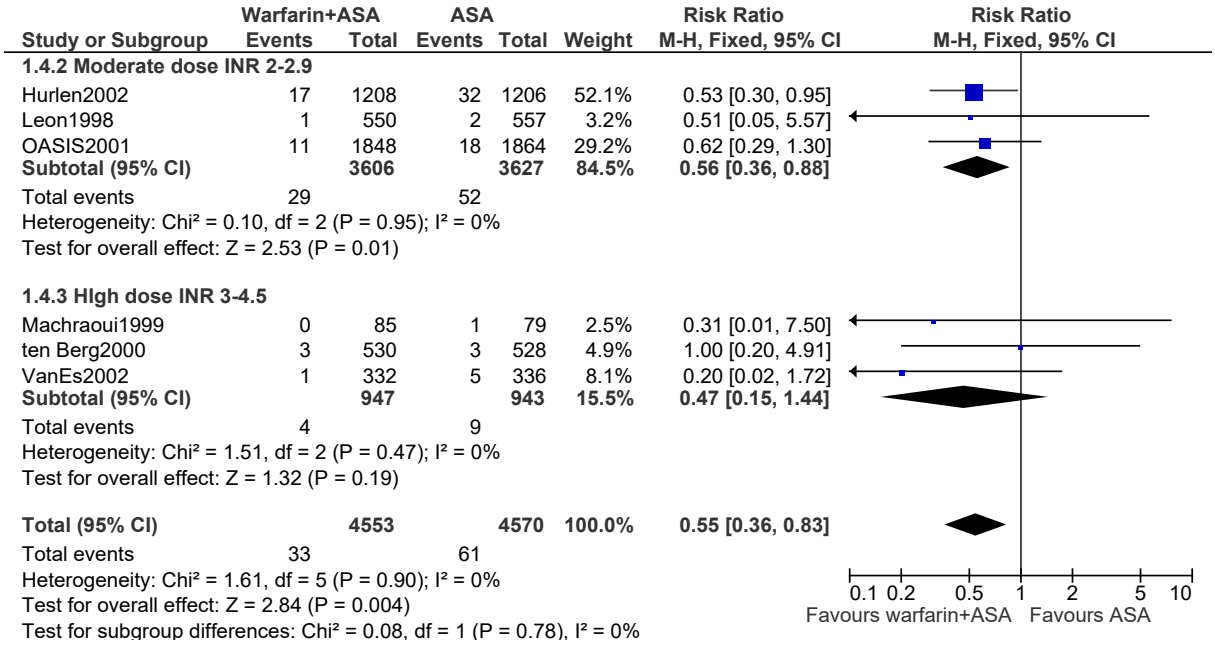
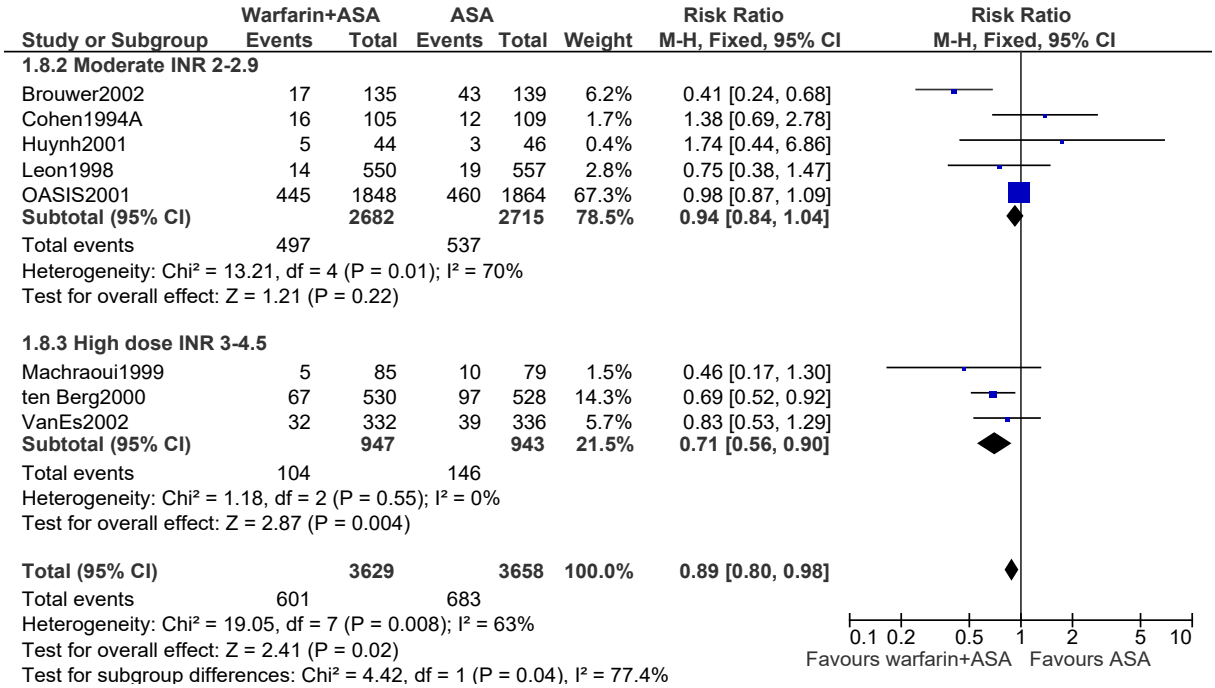


Figure 228: Warfarin + aspirin vs. aspirin (Indirect population II) - revascularisation



Heterogeneity

Heterogeneity was detected in the subgroup Moderate INR 2-2.9. This was first explored by looking at papers that carried a risk of bias. Cohen and Brouwer both published unclear methods of randomisation and it was unclear if they performed allocation concealment. When a sensitivity analysis was performed by removing these two studies heterogeneity still existed. There was a variation in the durations of follow-up, 1 paper was for 30 days (Leon et al.) the remainder were between 3 months-12 months, but this did not explain the heterogeneity. None of the patients had an indication for anticoagulation and all except Leon et al. appeared to treat the MI patients medically. Since none of the pre-selected subgroups explained the heterogeneity, the RR results are

presented as random effects, rather than fixed effects. See below for random effects RR result for moderate dose and total (high dose results did not change).

Figure 229: Warfarin + aspirin vs. aspirin – revascularisation (random effects)

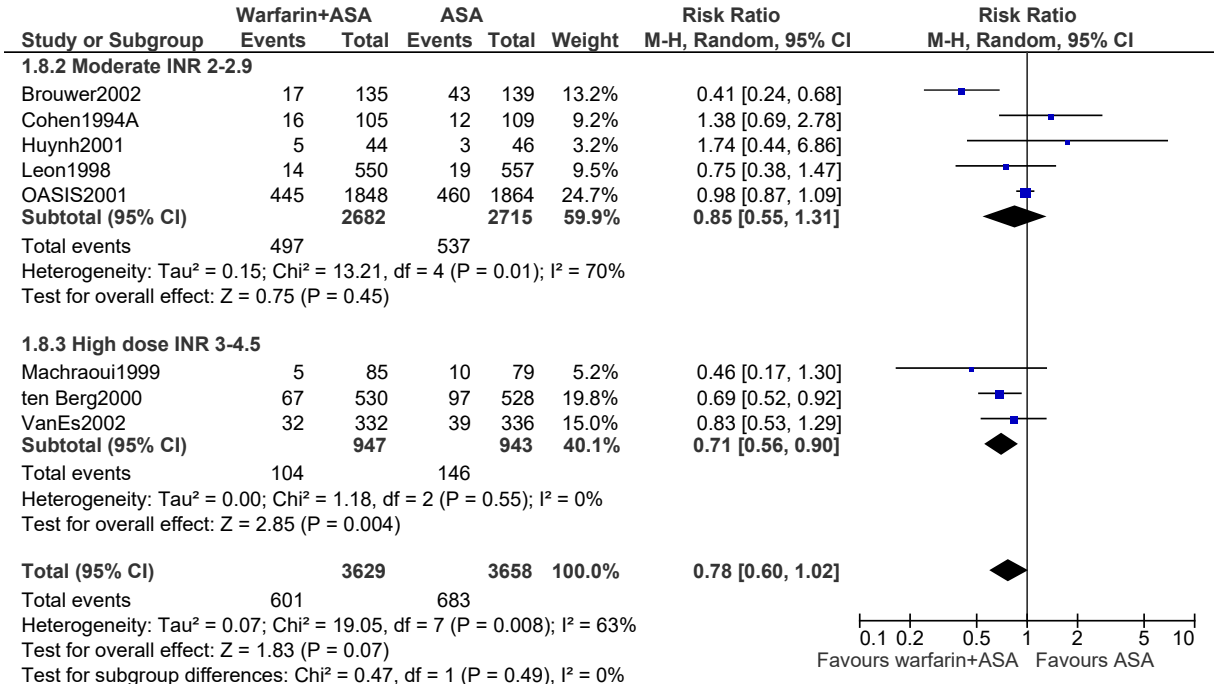


Figure 230: Warfarin + aspirin vs. aspirin (Indirect population II) - rehospitalisation

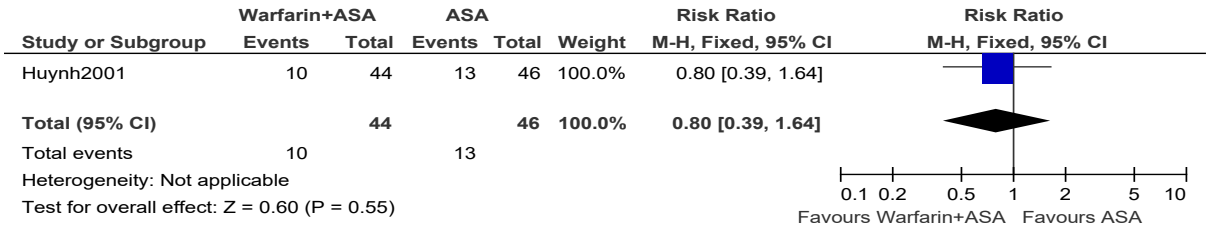


Figure 231: Warfarin + aspirin vs. aspirin (Indirect population II) – major bleeding

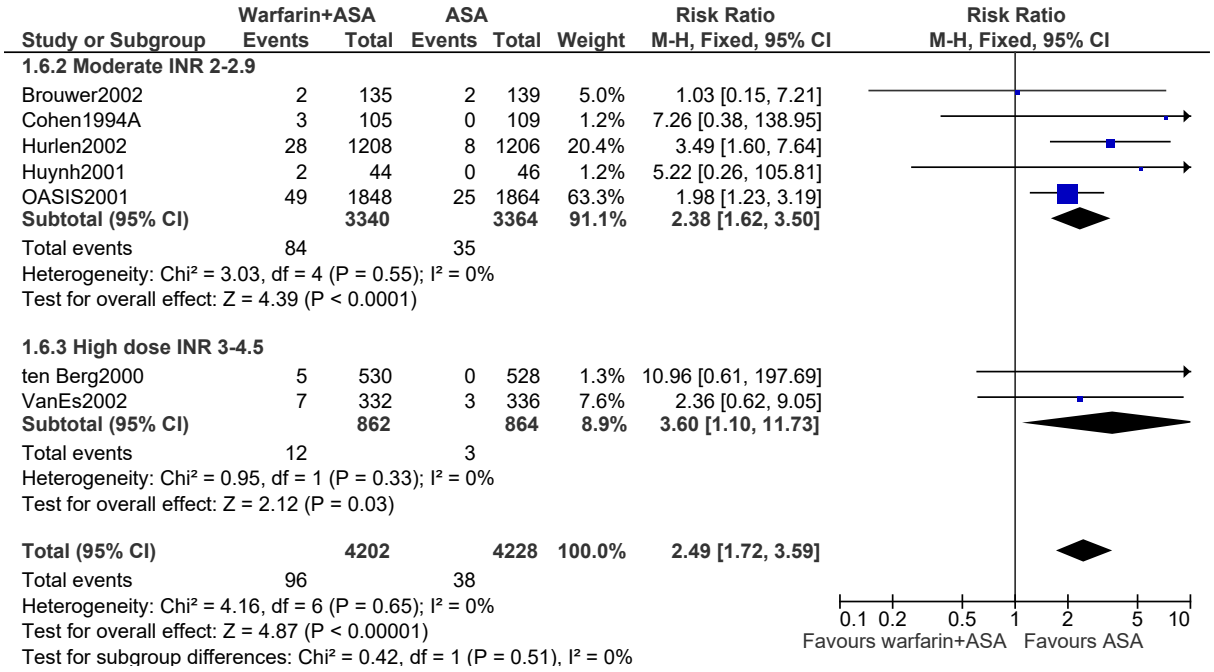
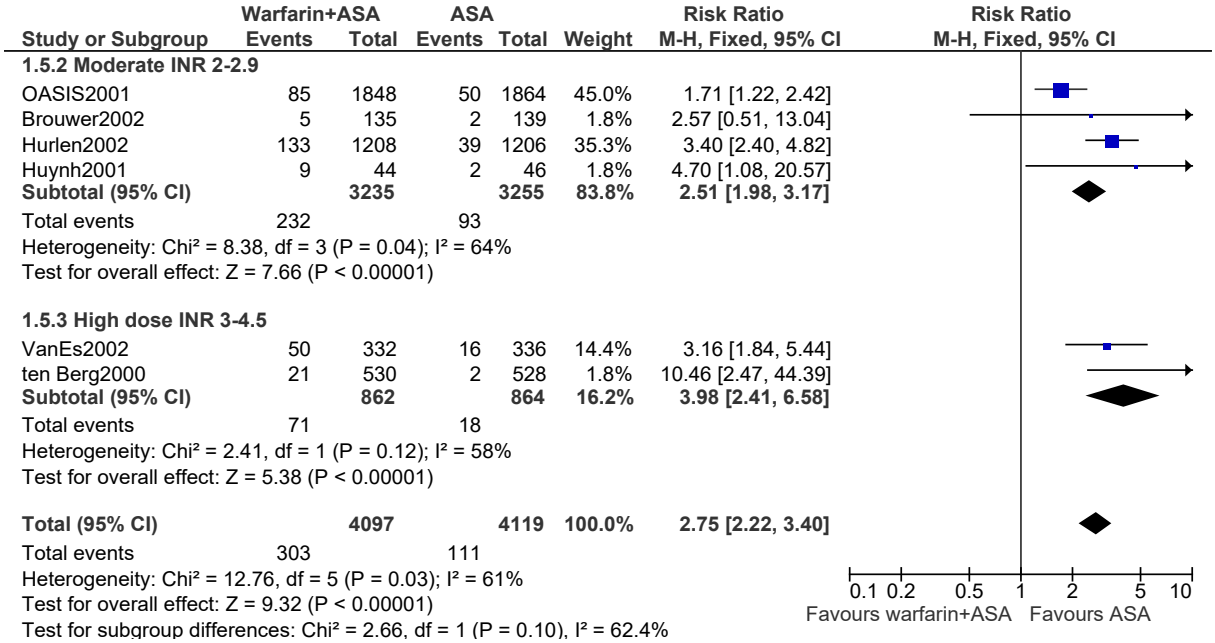


Figure 232: Warfarin + aspirin vs. aspirin (Indirect population II) – minor bleeding

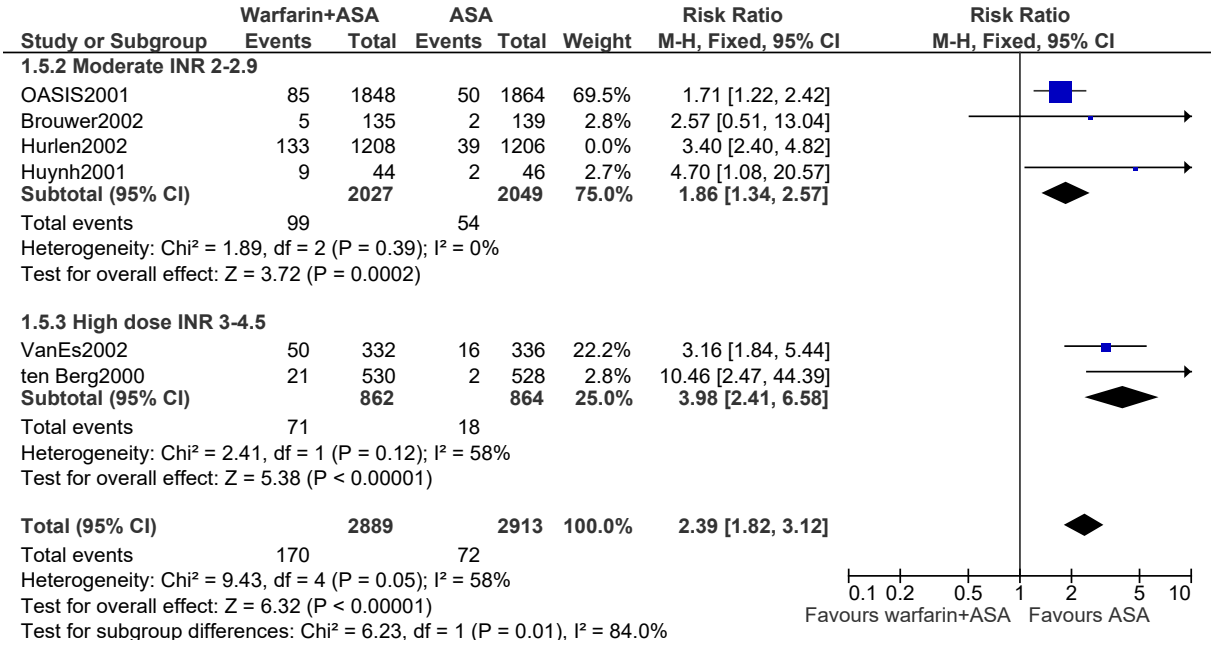


Heterogeneity

Heterogeneity was detected in the subgroup Moderate INR 2-2.9. This was first explored by looking at papers that carried a risk of bias. However, none of the papers carried a greater risk of bias compared with the others. There was a variation in the durations of follow-up, 1 paper (Hurlen et al) was for 5 years, while the remainder were between 30 day-12 months and when a sensitivity analysis was performed by removing this study heterogeneity no longer existed (see below). The other subgroups did not explain the heterogeneity: none of the patients had an indication for anticoagulation and all were treated medically. Although the longer follow-up period may explain

the heterogeneity, heterogeneity was also eliminated when the other larger study by Oasis et al. was removed. So it may be that the large variation in sample size is contributing towards the heterogeneity, more than anything else.

Figure 233: Warfarin and aspirin vs. aspirin - mild bleeding risk (sensitivity analysis)



Note: Hurlen et al. was removed since it was the only paper followed-up beyond one year.

I.6.4 Warfarin + aspirin vs. warfarin (indirect population II)

Figure 234: Warfarin + aspirin vs. warfarin (Indirect population II) – all-cause mortality

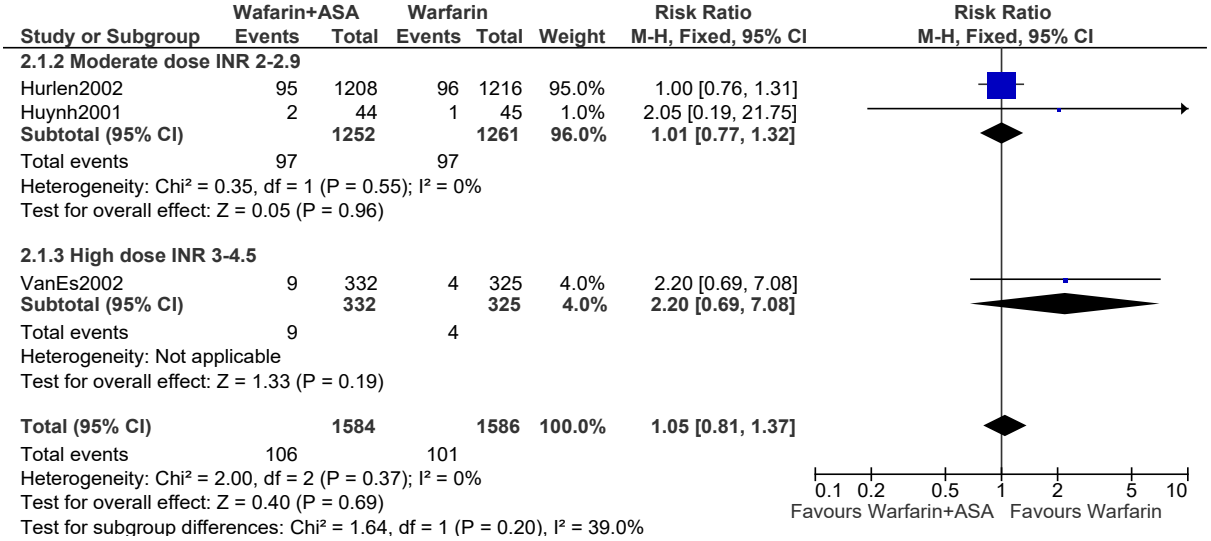


Figure 235: Warfarin + aspirin vs. warfarin (Indirect population II) – cardiac mortality

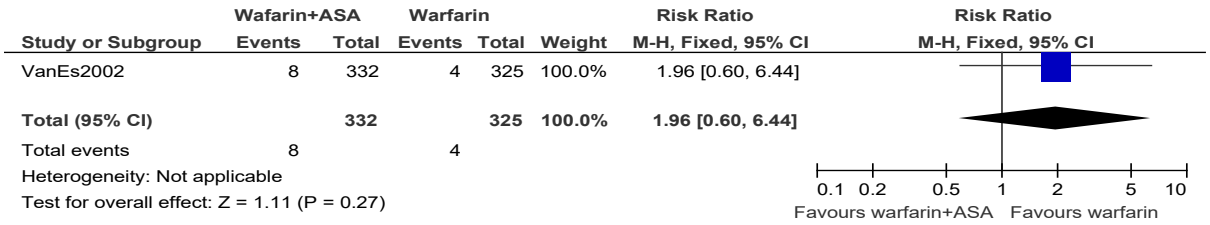


Figure 236: Warfarin + aspirin vs. warfarin (Indirect population II) - reinfarction

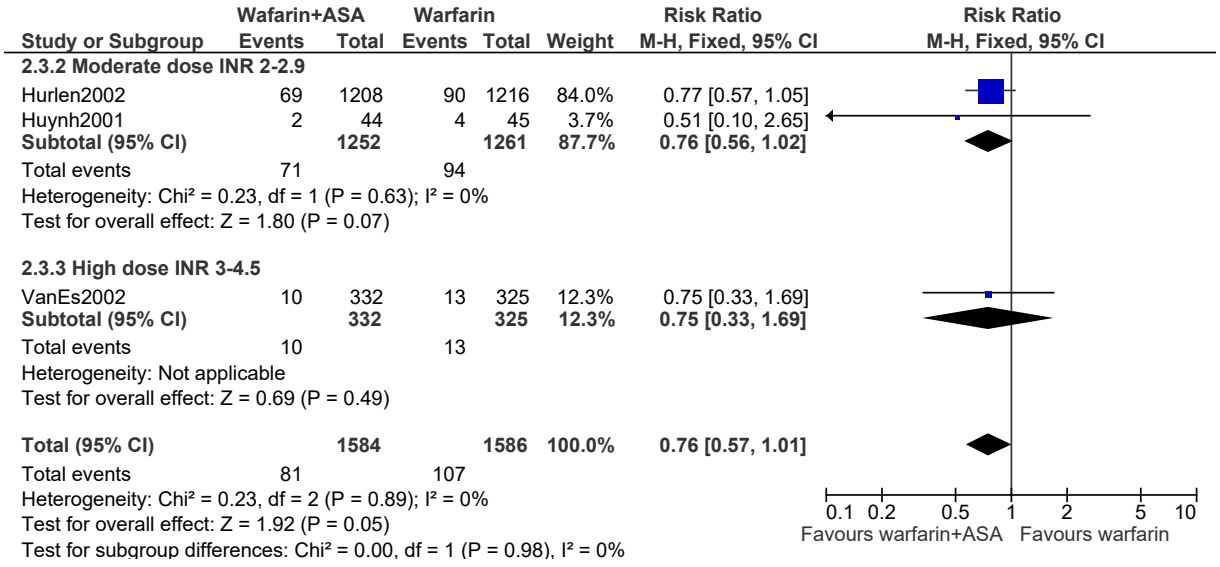


Figure 237: Warfarin + aspirin + clopidogrel vs. warfarin (Indirect population II) - stroke

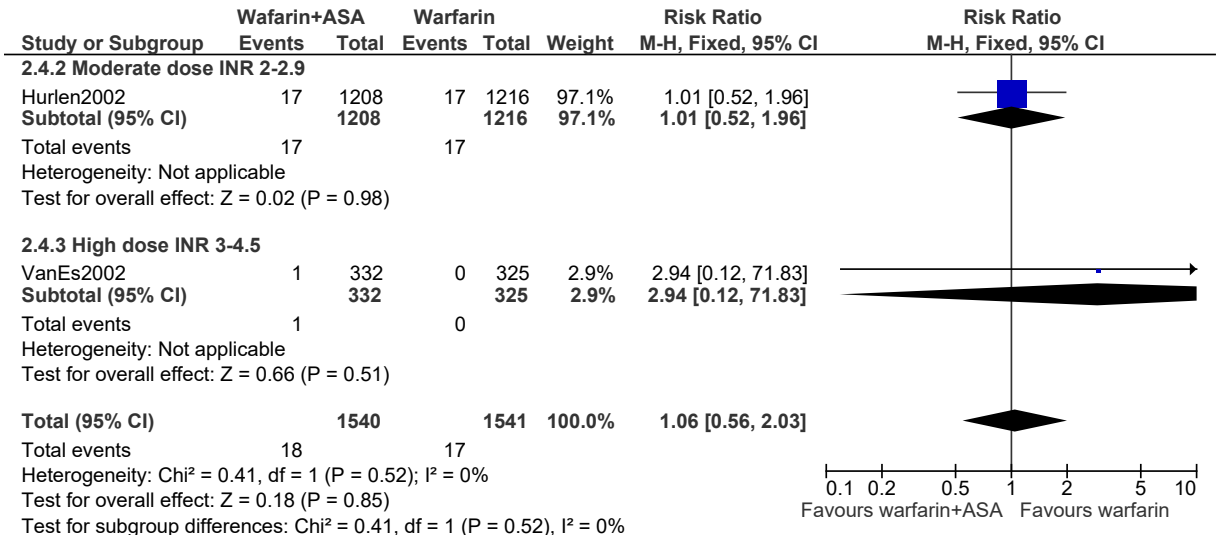


Figure 238: Warfarin + aspirin vs. warfarin (Indirect population II) - revascularisation

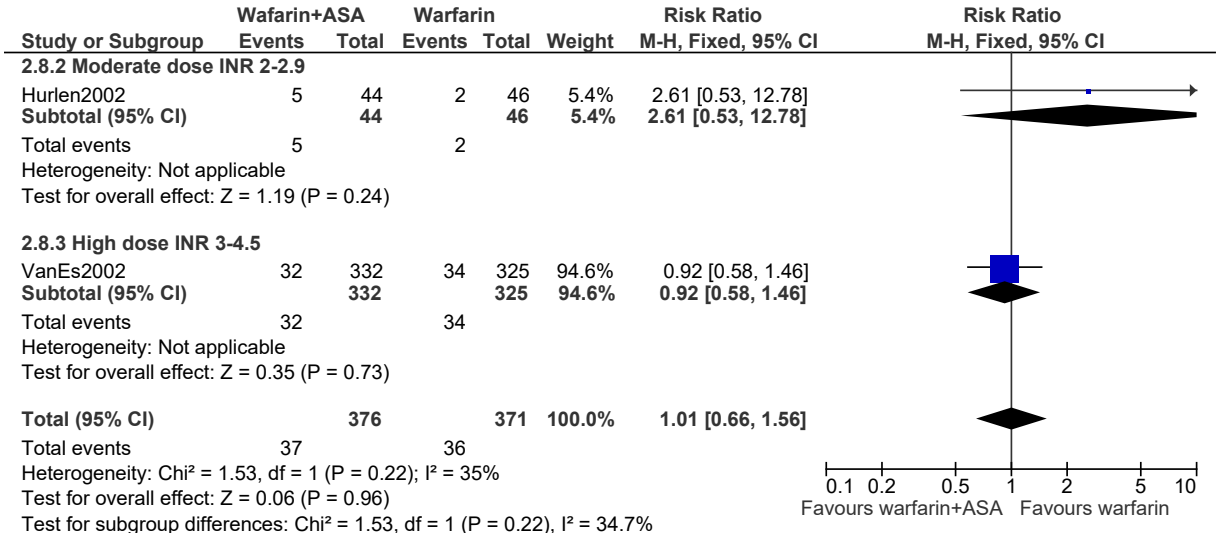


Figure 239: Warfarin + aspirin vs. warfarin (Indirect population II) - rehospitalisation

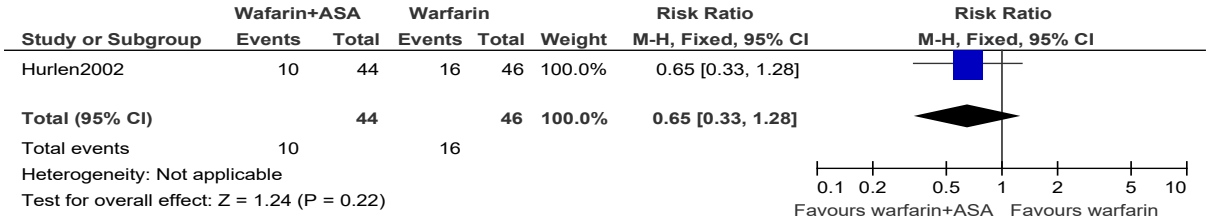


Figure 240: Warfarin + aspirin vs. aspirin (Indirect population II) – major bleeding

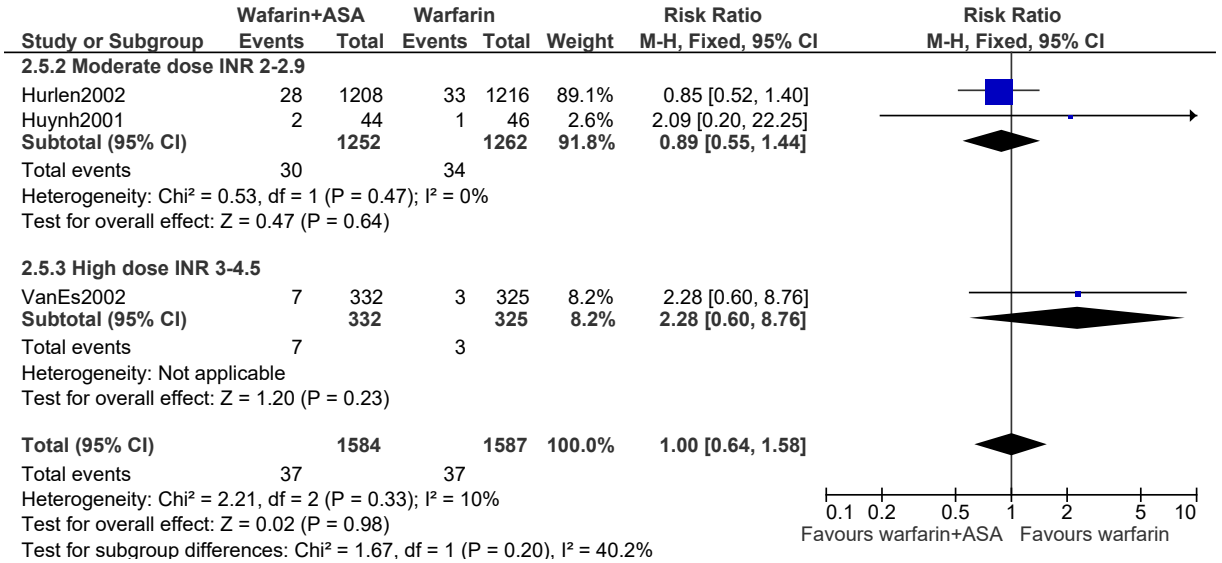
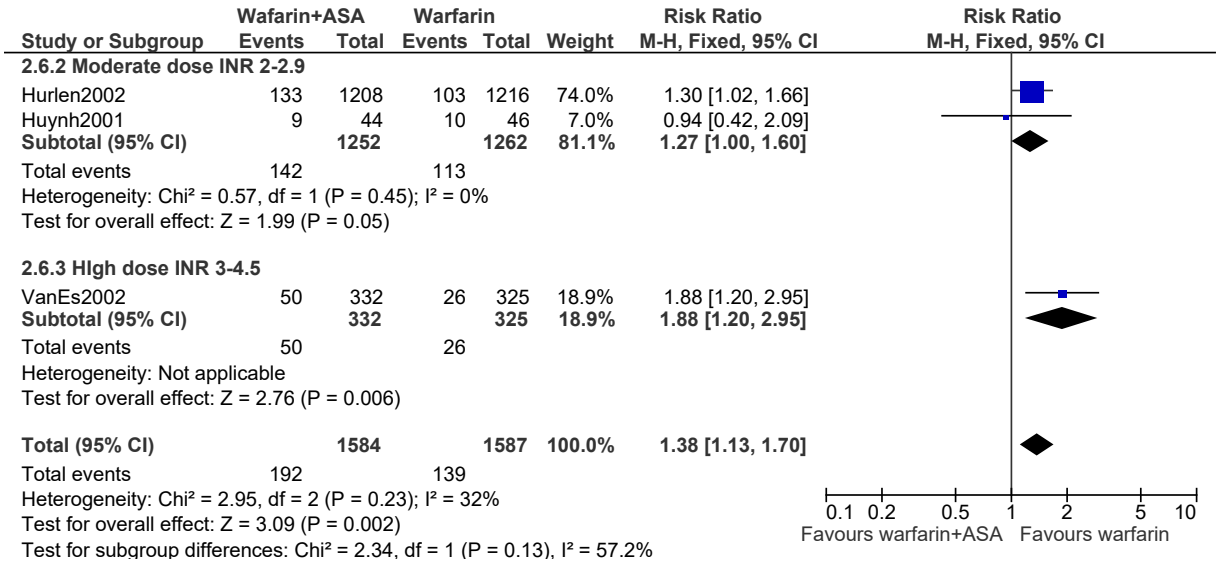


Figure 241: Warfarin + aspirin vs. aspirin (Indirect population II) – minor bleeding



I.6.5 Beta-blockers

This section was partially updated in 2020. See www.nice.org.uk/guidance/ng185 for the 2020 evidence review.

I.6.5.1 Beta-blocker vs. placebo (people who have had an MI and who have been initiated with treatment within 72 hours)

Figure 242: Beta-blocker vs. placebo – all-cause mortality (people who have had an MI and who have been initiated with treatment within 72 hours)

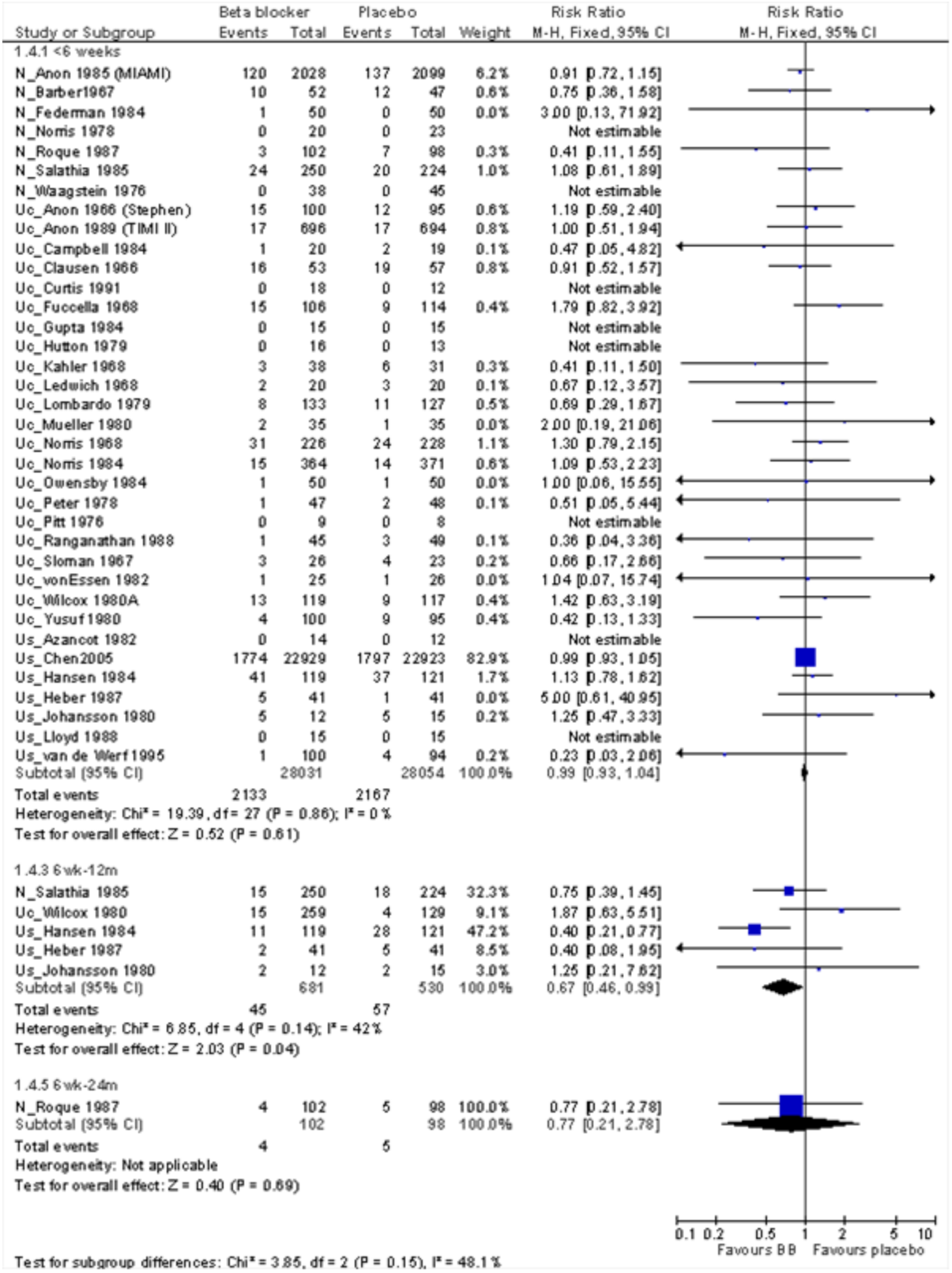


Figure 243: Beta-blocker vs. placebo – sudden death (people who have had an MI and who have been initiated with treatment within 72 hours) (distinct time periods).

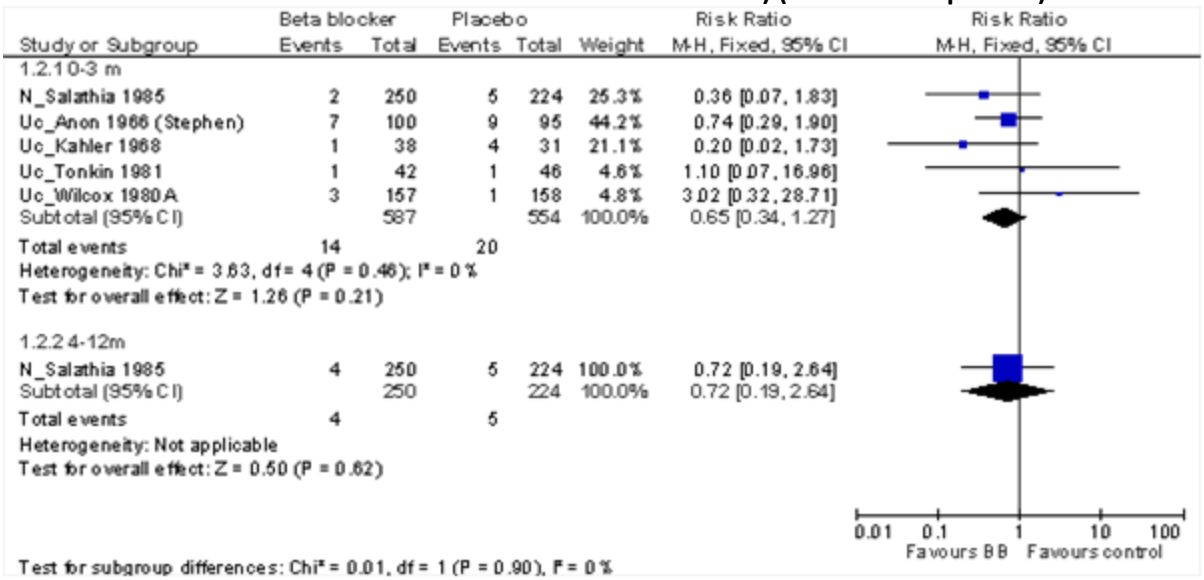


Figure 244: Beta-blocker vs. placebo – cardiac mortality (people who have had an MI and who have been initiated with treatment within 72 hours) (distinct time periods)

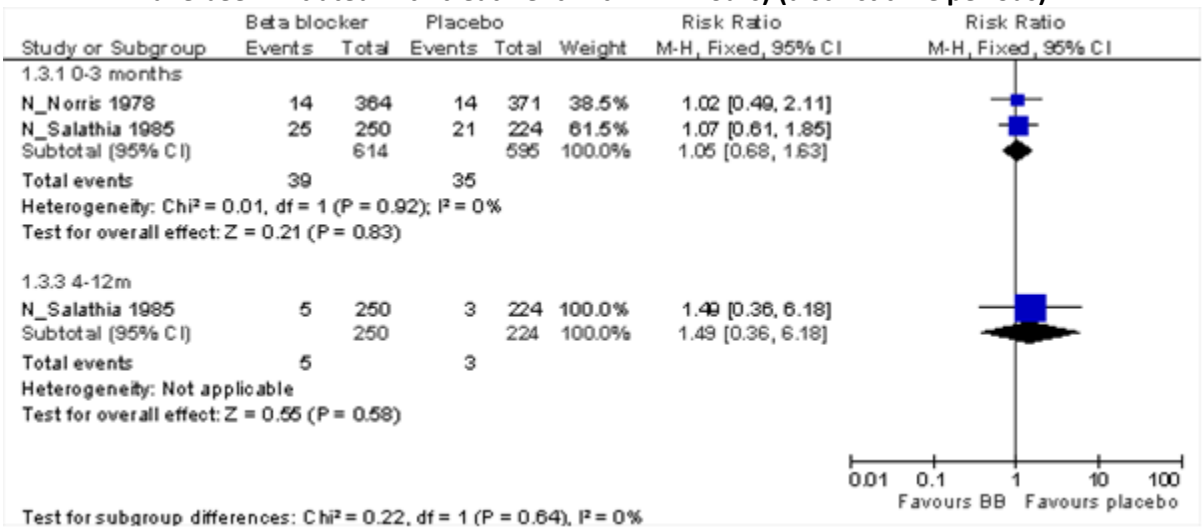


Figure 245: Beta-blocker vs. placebo – reinfarction (people who have had an MI and who have been initiated with treatment within 72 hours) (distinct time periods).

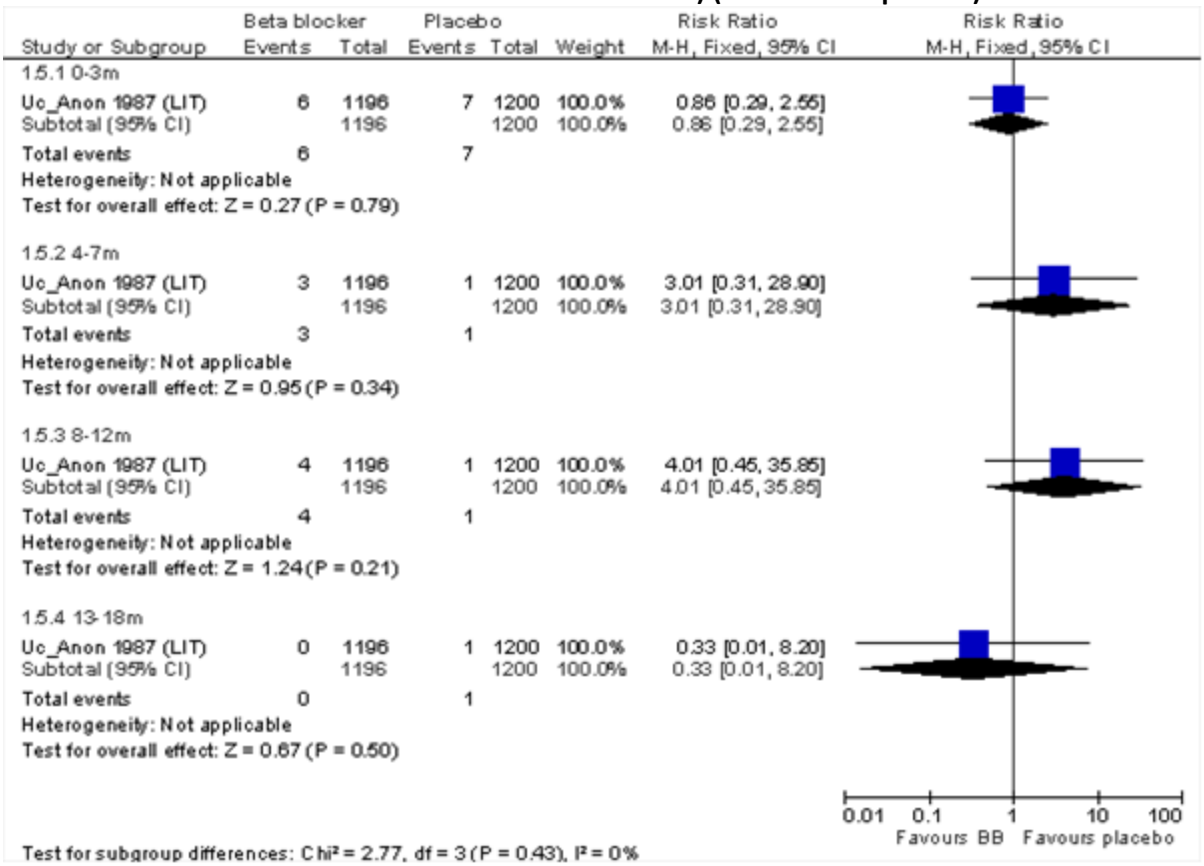


Figure 246: Beta-blocker vs. placebo – all-cause mortality (people who have had an MI and who have been initiated with treatment within 72 hours)

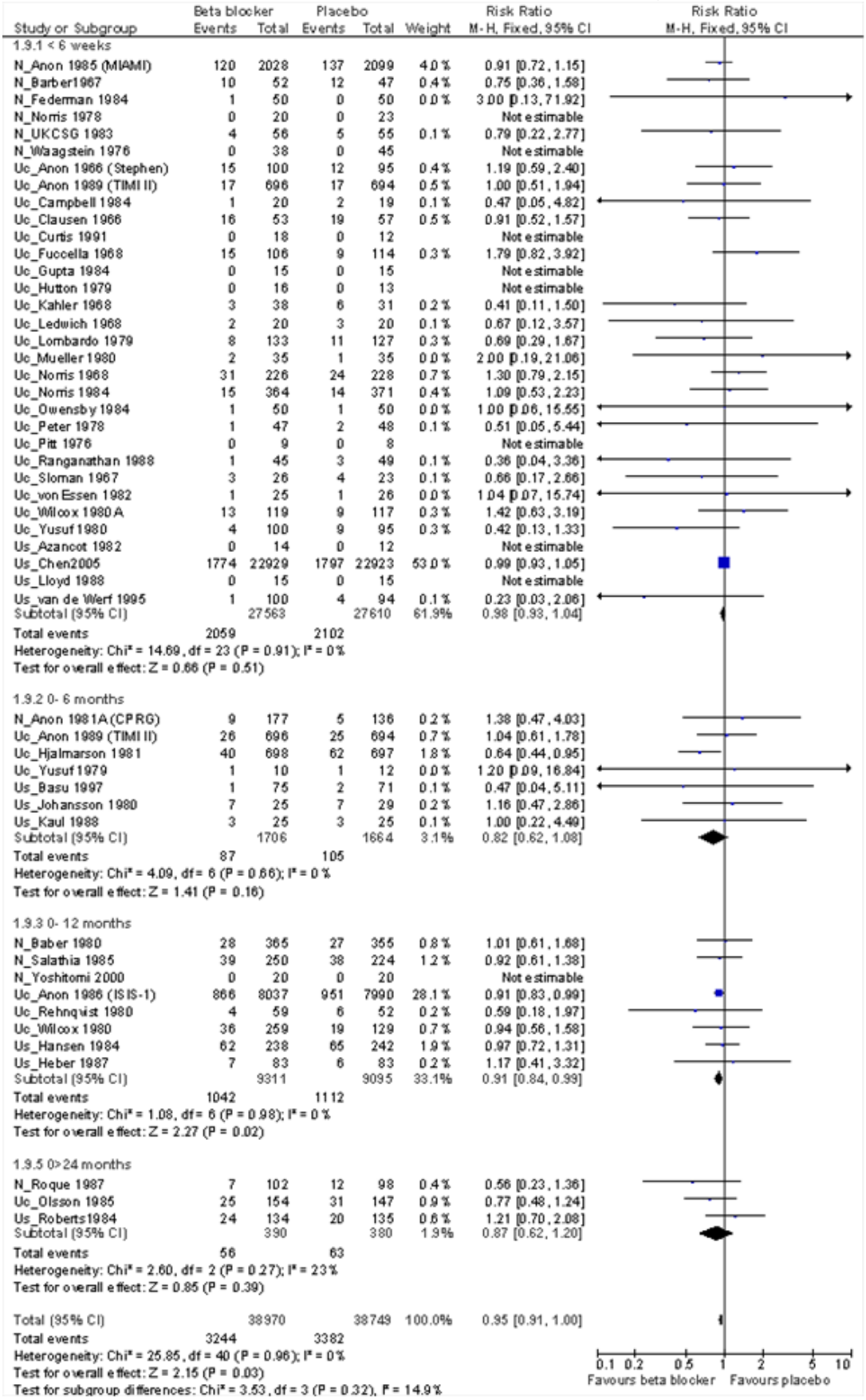


Figure 247: Beta-blocker vs. placebo – cardiac mortality (people who have had an MI and who have been initiated with treatment within 72 hours)

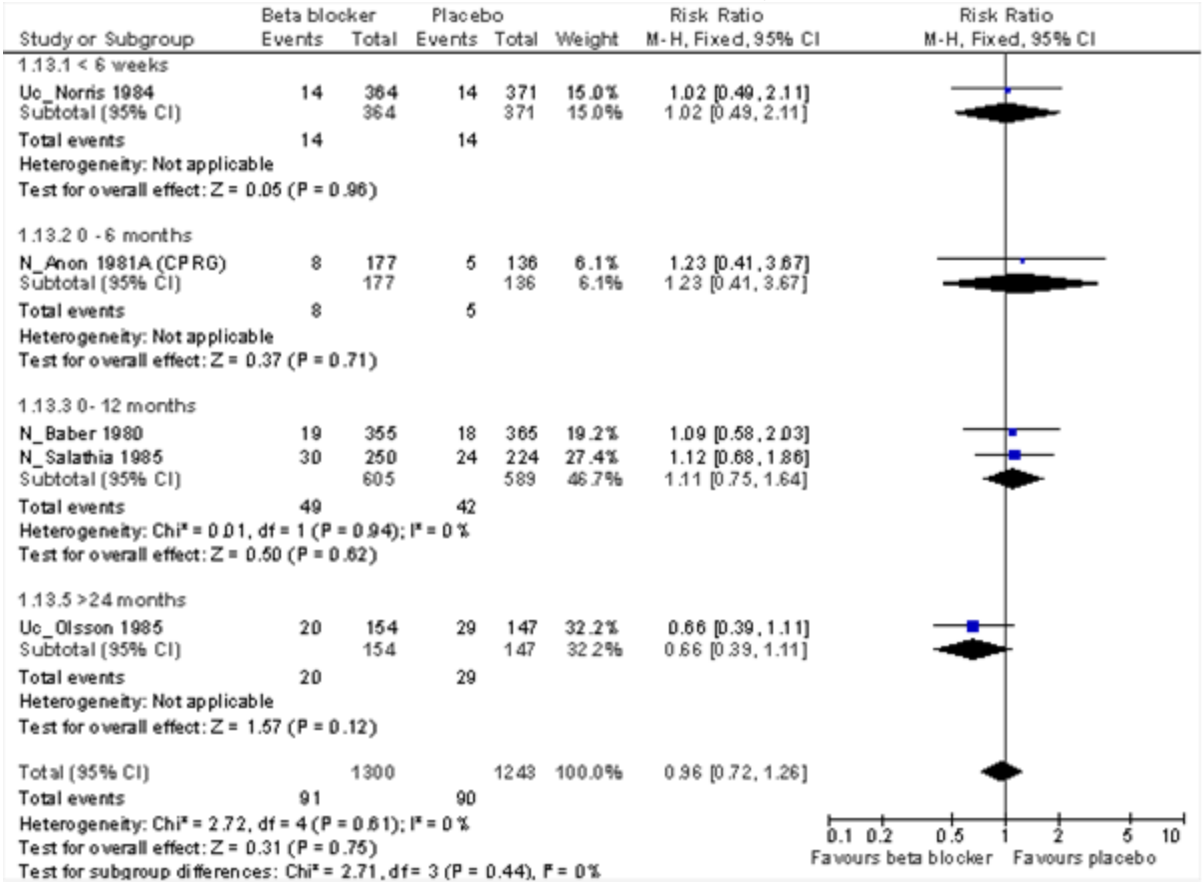


Figure 248: Beta-blocker vs. placebo – sudden cardiac death (people who have had an MI and who have been initiated with treatment within 72 hours)

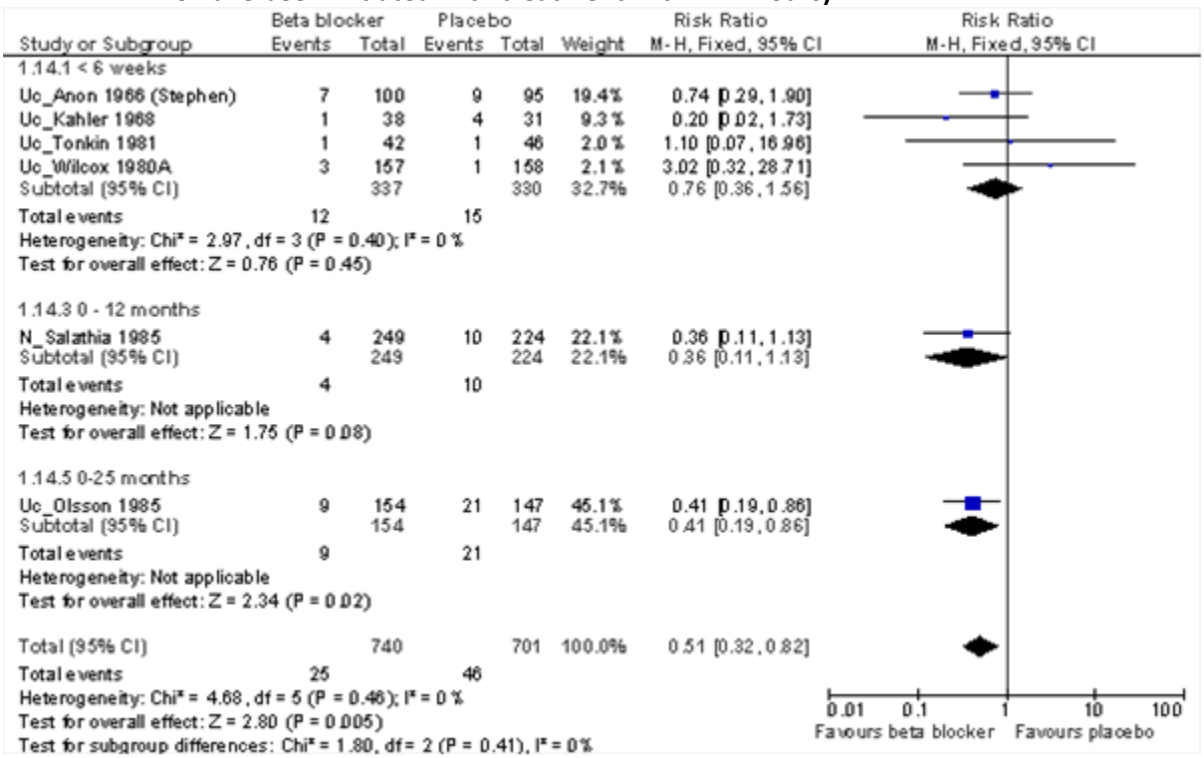
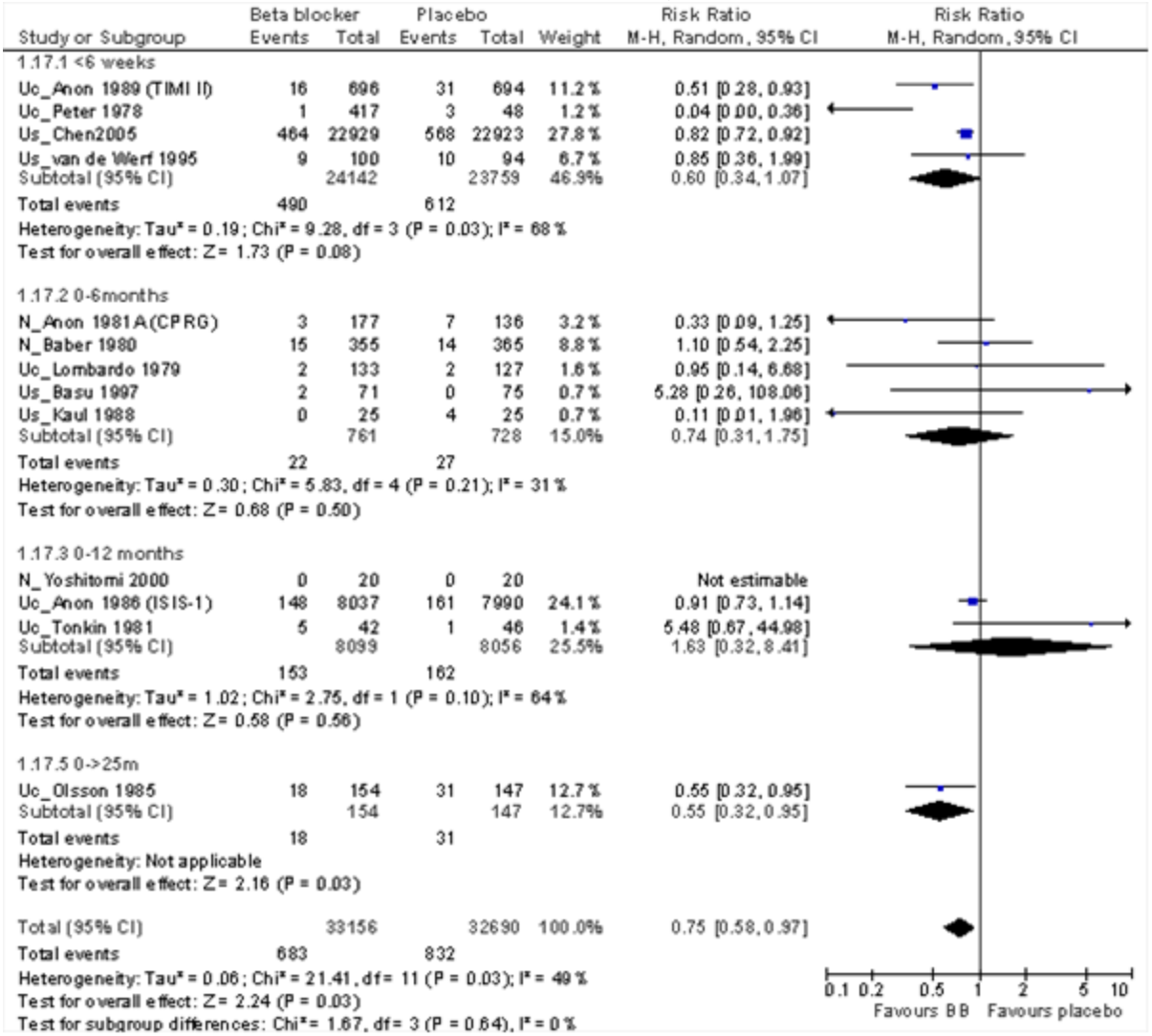


Figure 249: Beta-blocker vs. placebo - reinfarction (people who have had an MI and who have been initiated with treatment within 72 hours)



Heterogeneity was detected at <6 months, I^2=68% and 0-12 months, I2=64%. Investigating factors to ascertain whether they explain the heterogeneity is difficult because in some of the papers it is unclear what the patients LV function status was, ethnicity and age range. In the <6month data, the study by Van De Werf used a low lipid soluble beta-blocker (Atenolol), the others were moderate to highly soluble, but removing it had no effect on heterogeneity. In the 0-12m data, both studies used low lipid soluble beta-blockers and acute treatment was likely to be similar given they were published in the early 1980s. Heterogeneity in both sets of data is likely to be the result of few events recorded and low patient numbers in some of the studies. At 0-12 m if the study by Tonkin et al. was removed, heterogeneity is no longer present. Since heterogeneity could not be explained the results are presented as random effects, rather than fixed effects.

Figure 250: Beta-blocker vs. placebo - stroke (people who have had an MI and who have been initiated with treatment within 72 hours)

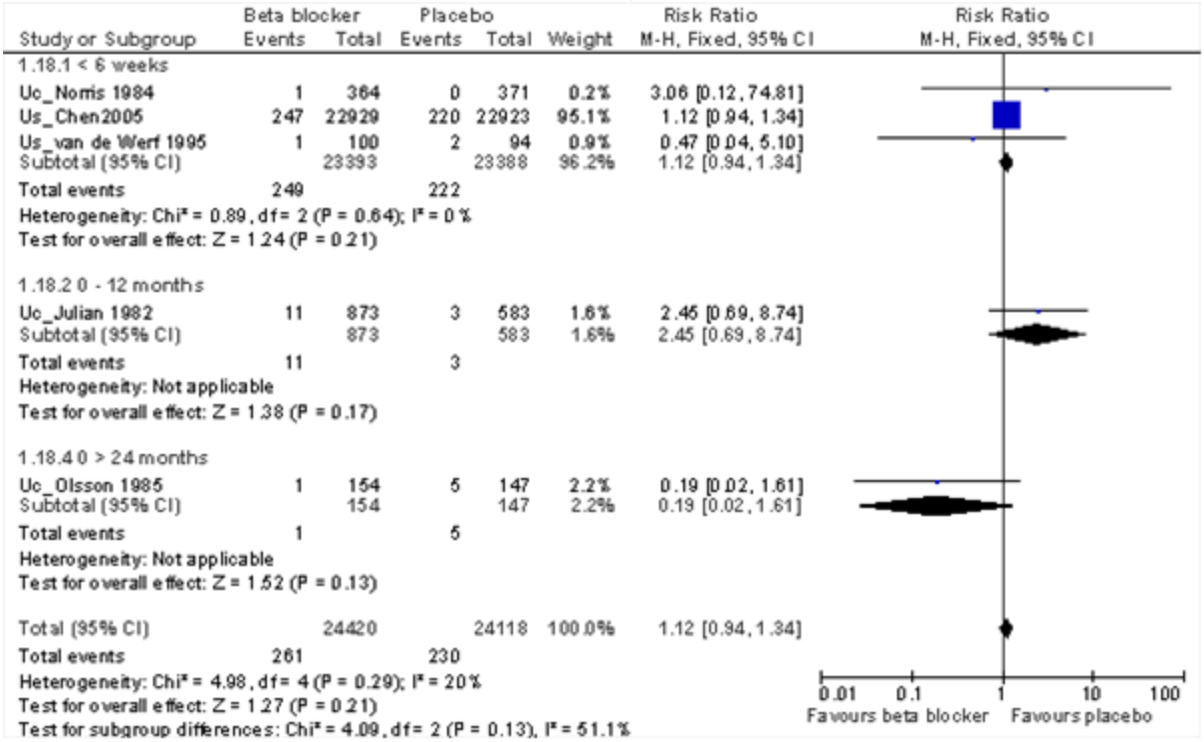


Figure 251: Beta-blocker vs. placebo - revascularisation (people who have had an MI and who have been initiated with treatment within 72 hours)

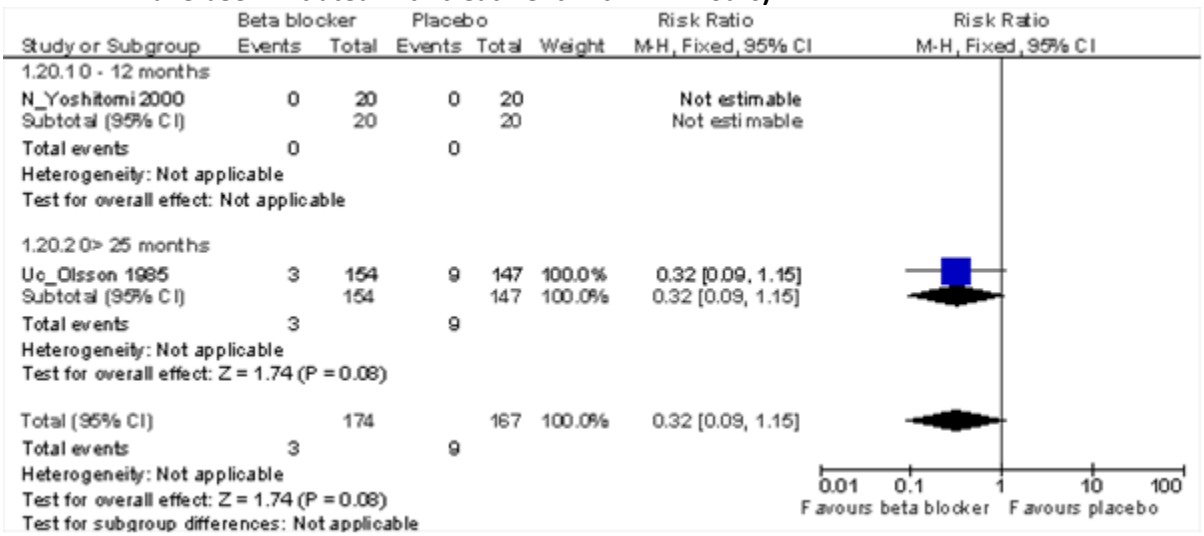


Figure 252: Beta-blocker vs. placebo – adverse events (people who have had an MI and who have been initiated with treatment within 72 hours)

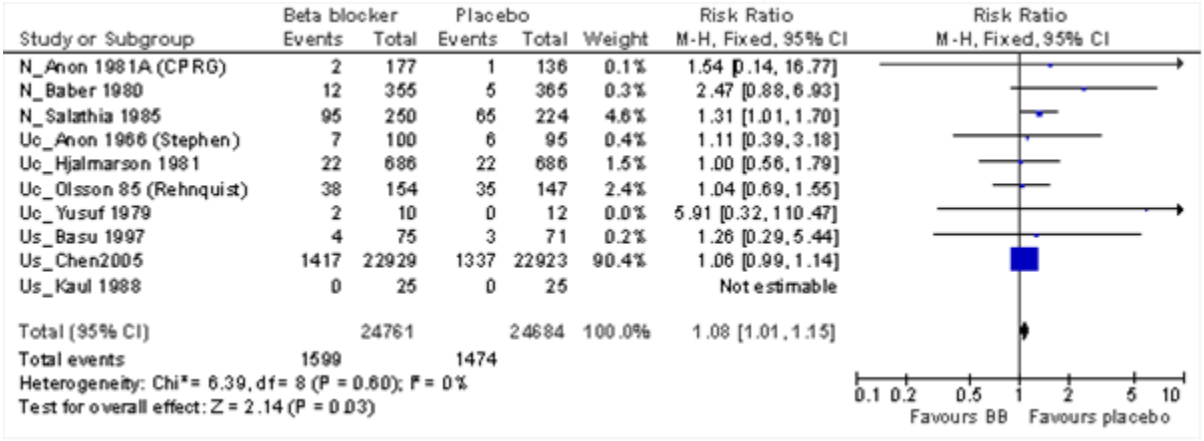


Figure 253: Beta-blocker vs. placebo - dizziness (people who have had an MI and who have been initiated with treatment within 72 hours)

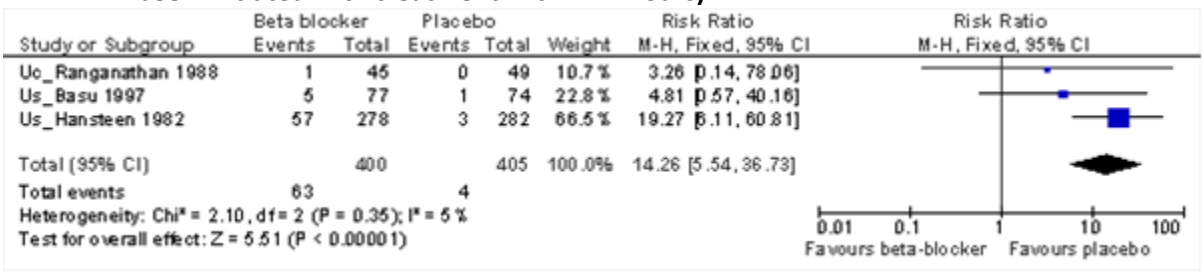


Figure 254: Beta-blocker vs. placebo - fatigue/tiredness (people who have had an MI and who have been initiated with treatment within 72 hours)

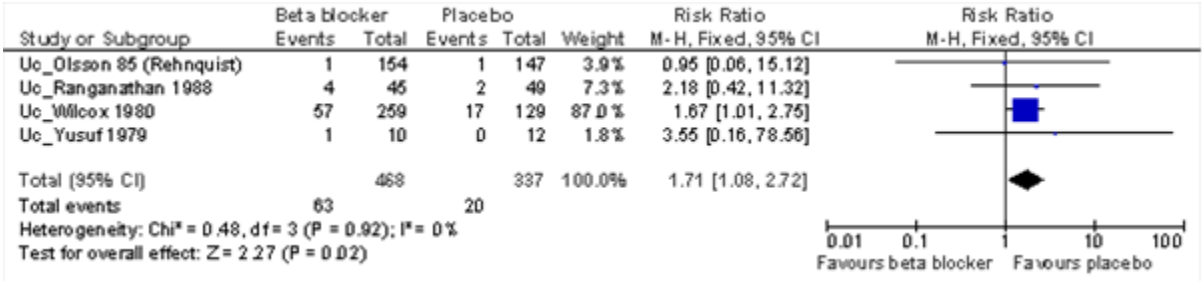


Figure 255: Beta-blocker vs. placebo – bradycardia (people who have had an MI and who have been initiated with treatment within 72 hours)

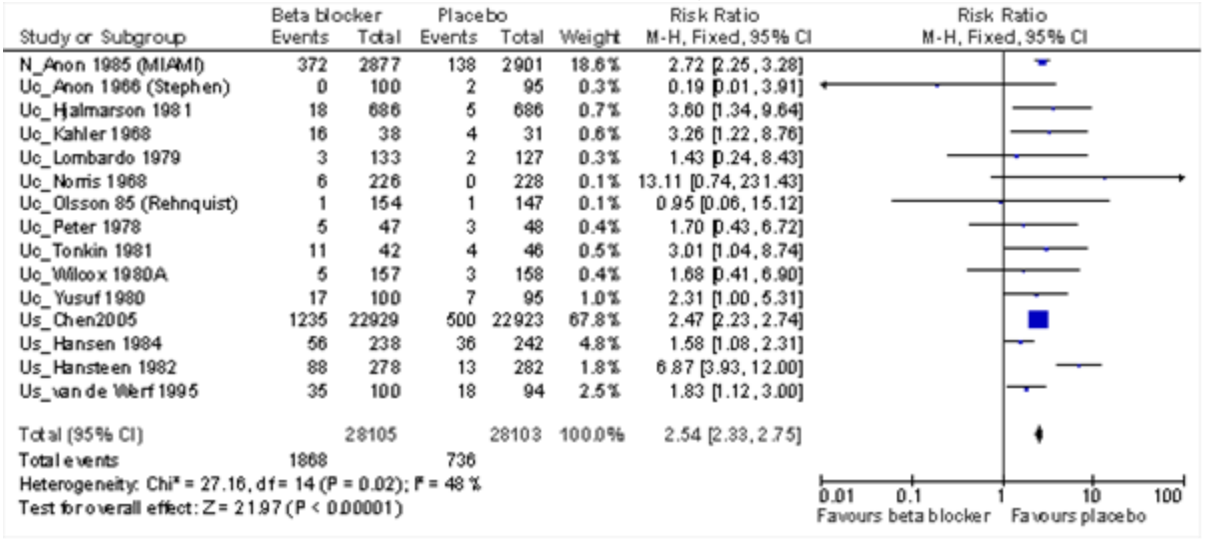


Figure 256: Beta-blocker vs. placebo – libido decrease (people who have had an MI and who have been initiated with treatment within 72 hours)

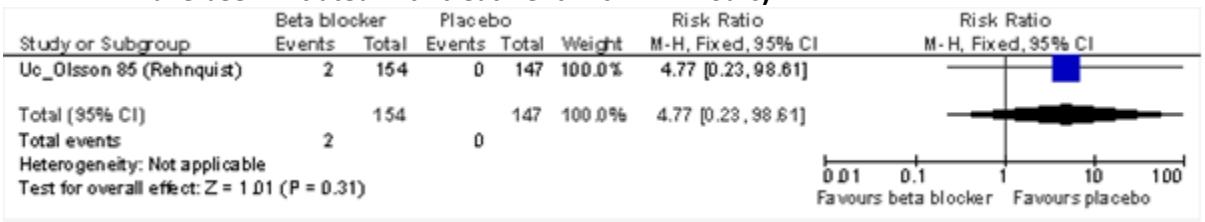
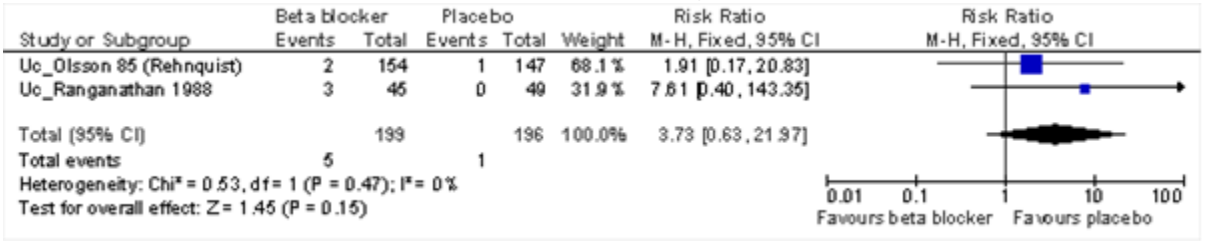
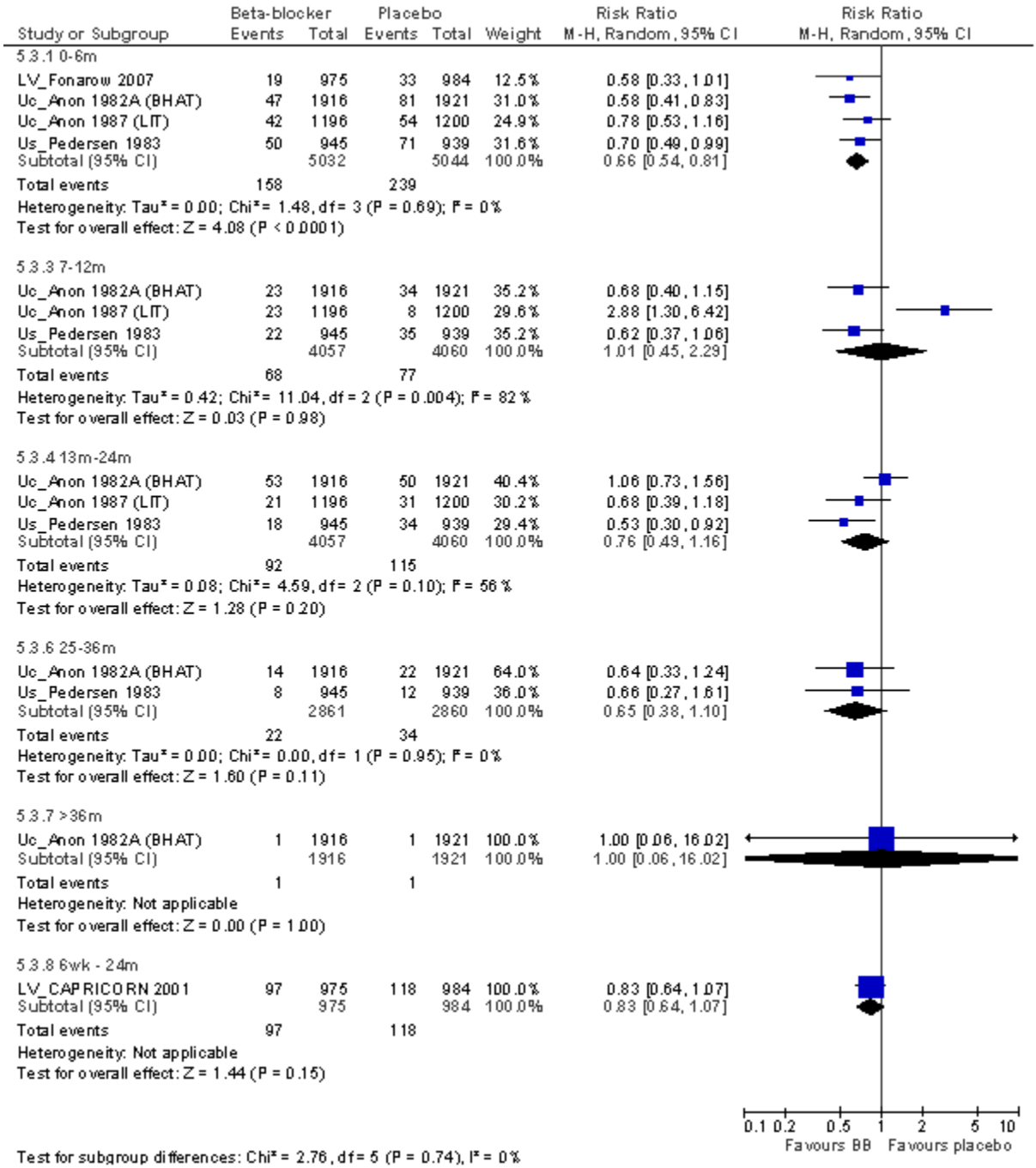


Figure 257: Beta-blocker vs. placebo - nightmares (people who have had an MI and who have been initiated with treatment within 72 hours)



I.6.5.2 Beta-blocker vs. placebo (people who have had an MI and who have been initiated with treatment between 72 hours and 12 months)

Figure 258: Beta-blocker vs. placebo -all-cause mortality (distinct time periods) (people who have had an MI and who have been initiated with treatment between 72 hours and 12 months)



Heterogeneity was detected at 7-12 months, I^2=82%. This appears to be the result of the findings by Anon_(LIT) that is an outlier. The numbers have been checked and are correct. There is no obvious risk of bias, patients were blinded and they had few HF patients, 2.1%. Other factors that may explain the heterogeneity are difficult to isolate since both the study by Anon_LIT and the study by Anon_BHAT, that is not an outlier, had unclear LV function status, patients did not have COPD, a similar age range, treatments are likely to be similar given the date of publication of early 80's and Anon_LIT used a moderately soluble beta-blocker, while the others used a high and low lipid soluble beta blockers. Heterogeneity was also detected at 13-24m, I^2=57%. The same three studies were

used hence no explanation could be found. Since heterogeneity could not be explained, the results are shown as random effects, rather than fixed effects.

Figure 259: Beta-blocker vs. placebo - sudden death (distinct time periods) (people who have had an MI and who have been initiated with treatment between 72 hours and 12 months)

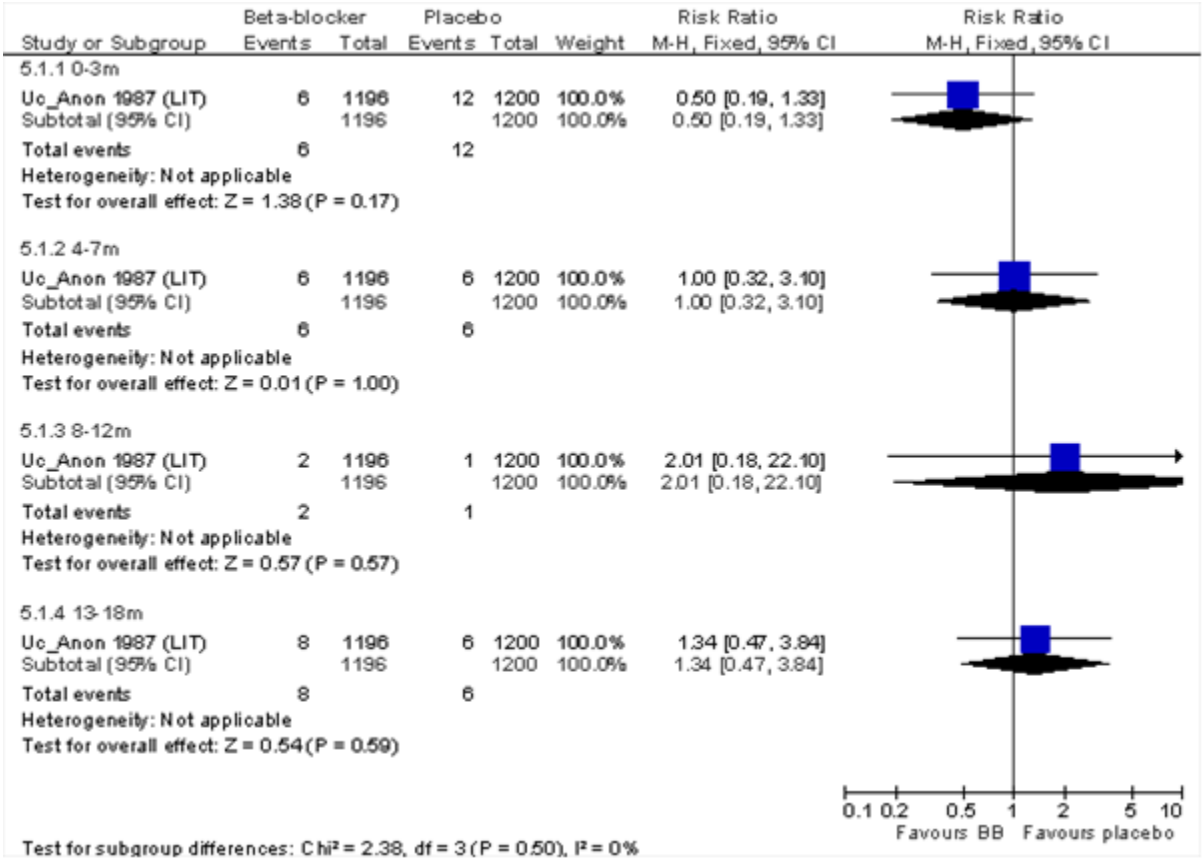


Figure 260: Beta-blocker vs. placebo - cardiac death(distinct time periods) (people who have had an MI and who have been initiated with treatment between 72 hours and 12 months)

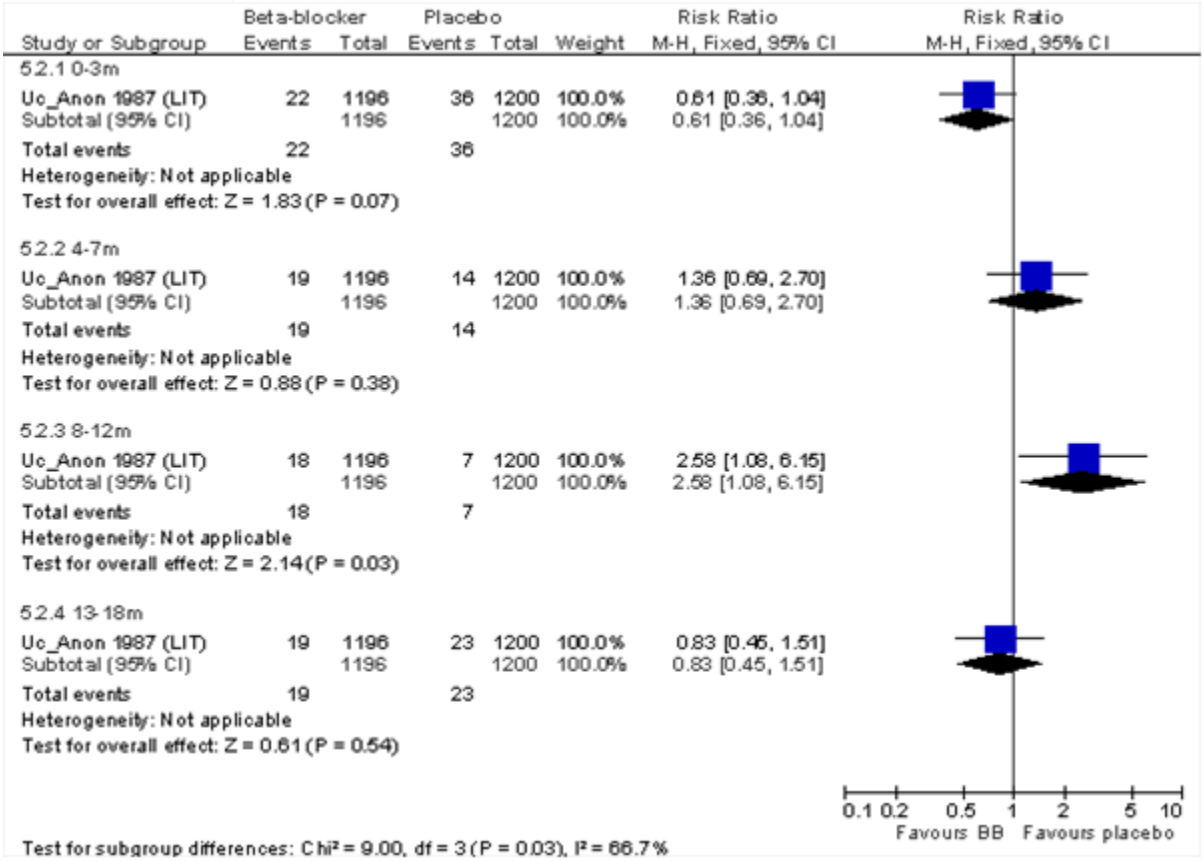


Figure 261: Beta-blocker vs. placebo - reinfarction(distinct time periods) (people who have had an MI and who have been initiated with treatment between 72 hours and 12 months)

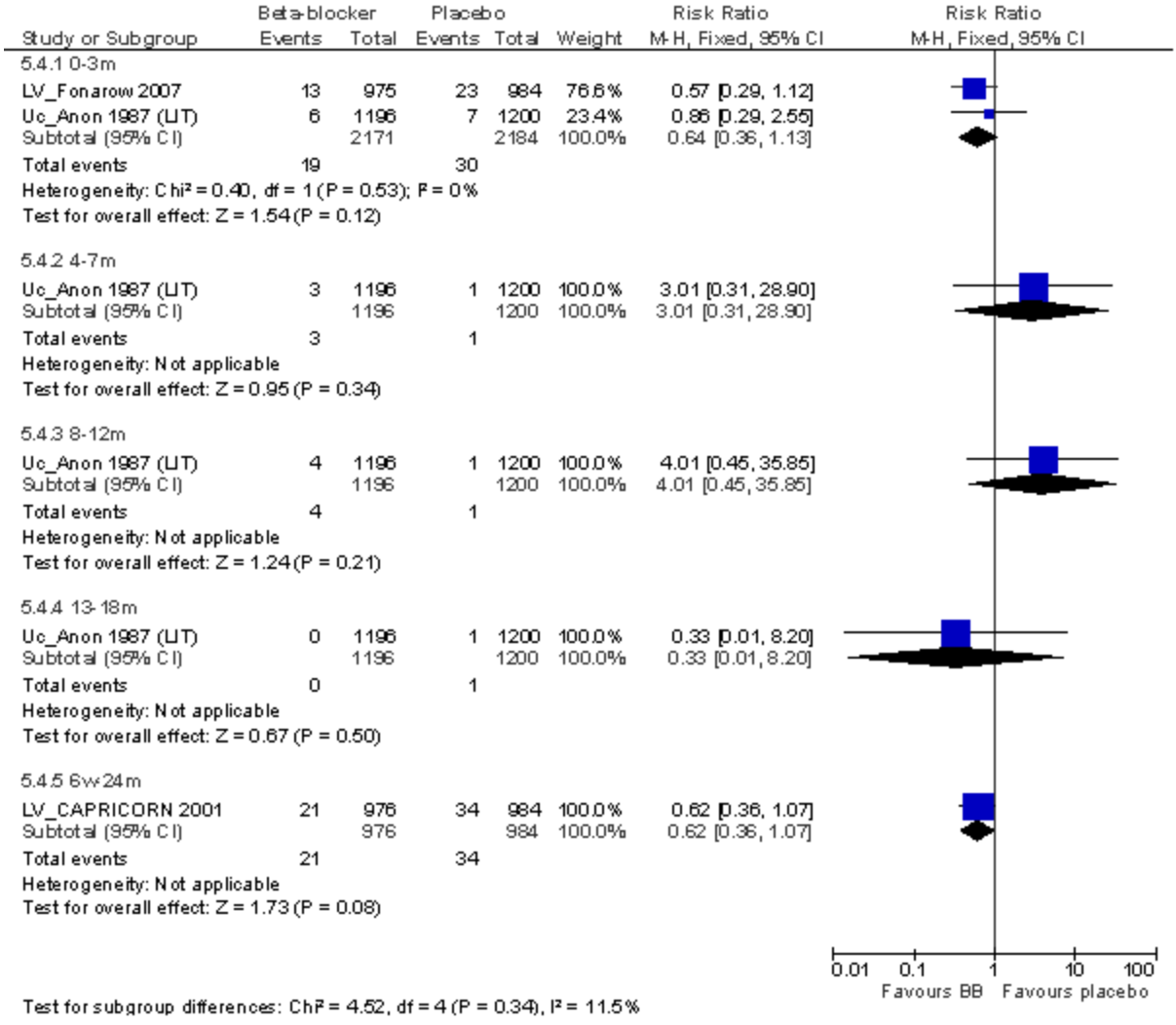
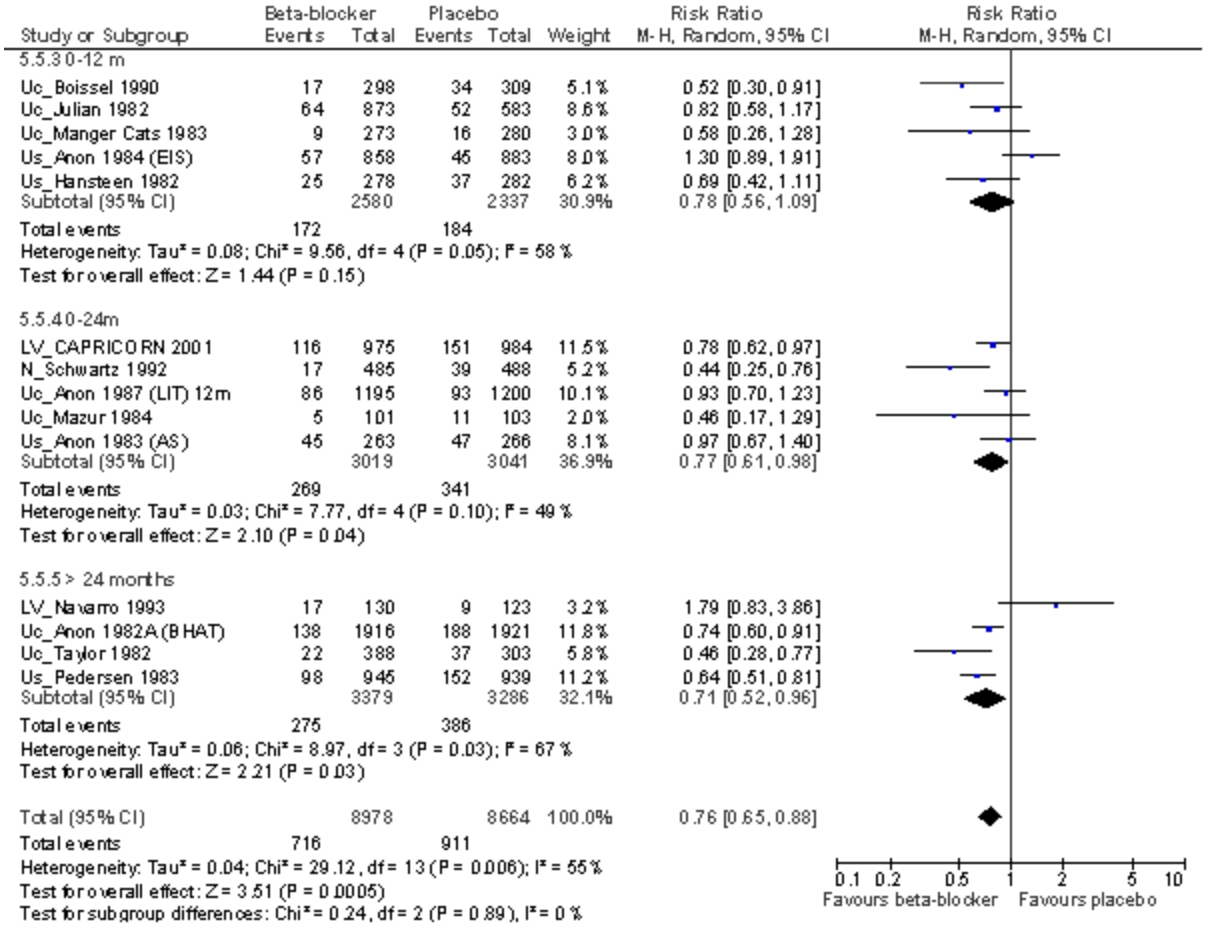
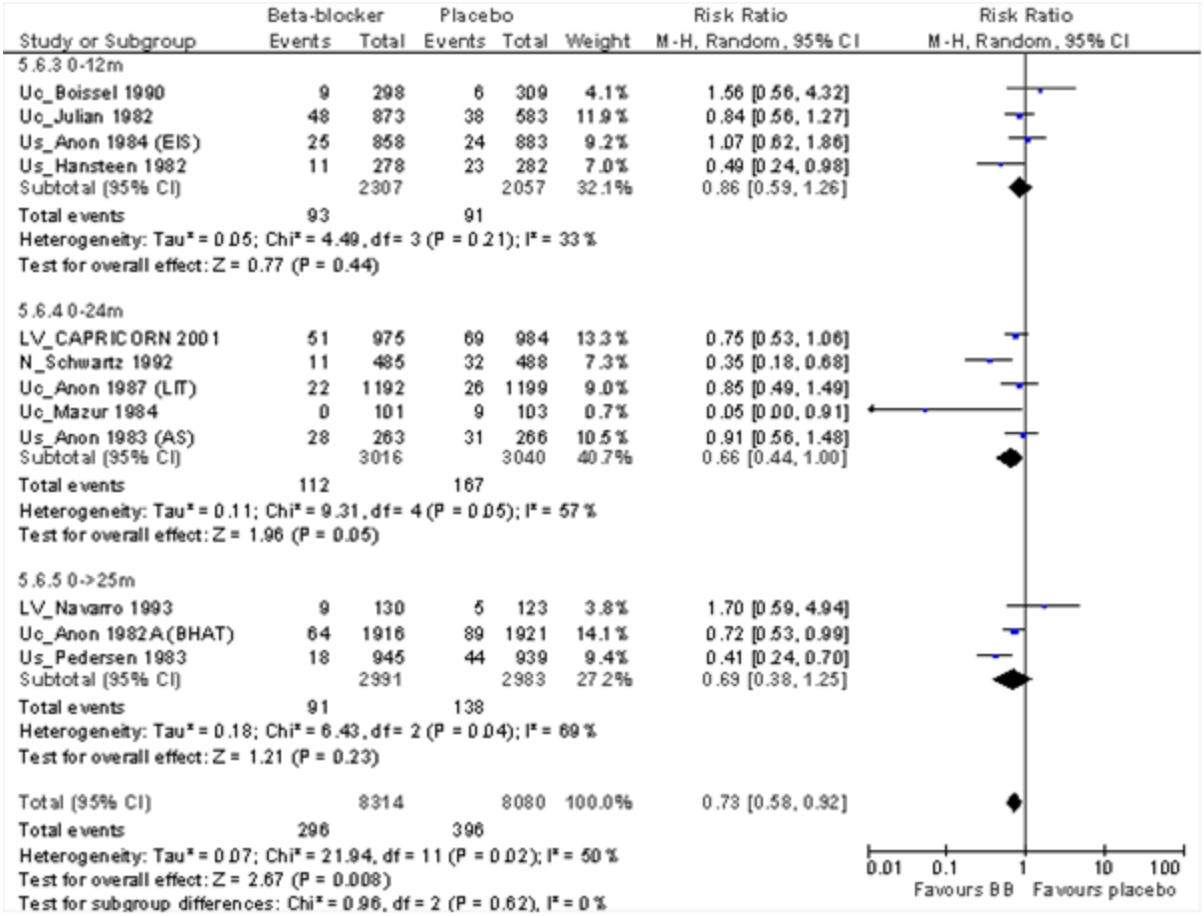


Figure 262: Beta-blocker vs. placebo -all-cause mortality (people who have had an MI and who have been initiated with treatment between 72 hours and 12 months)



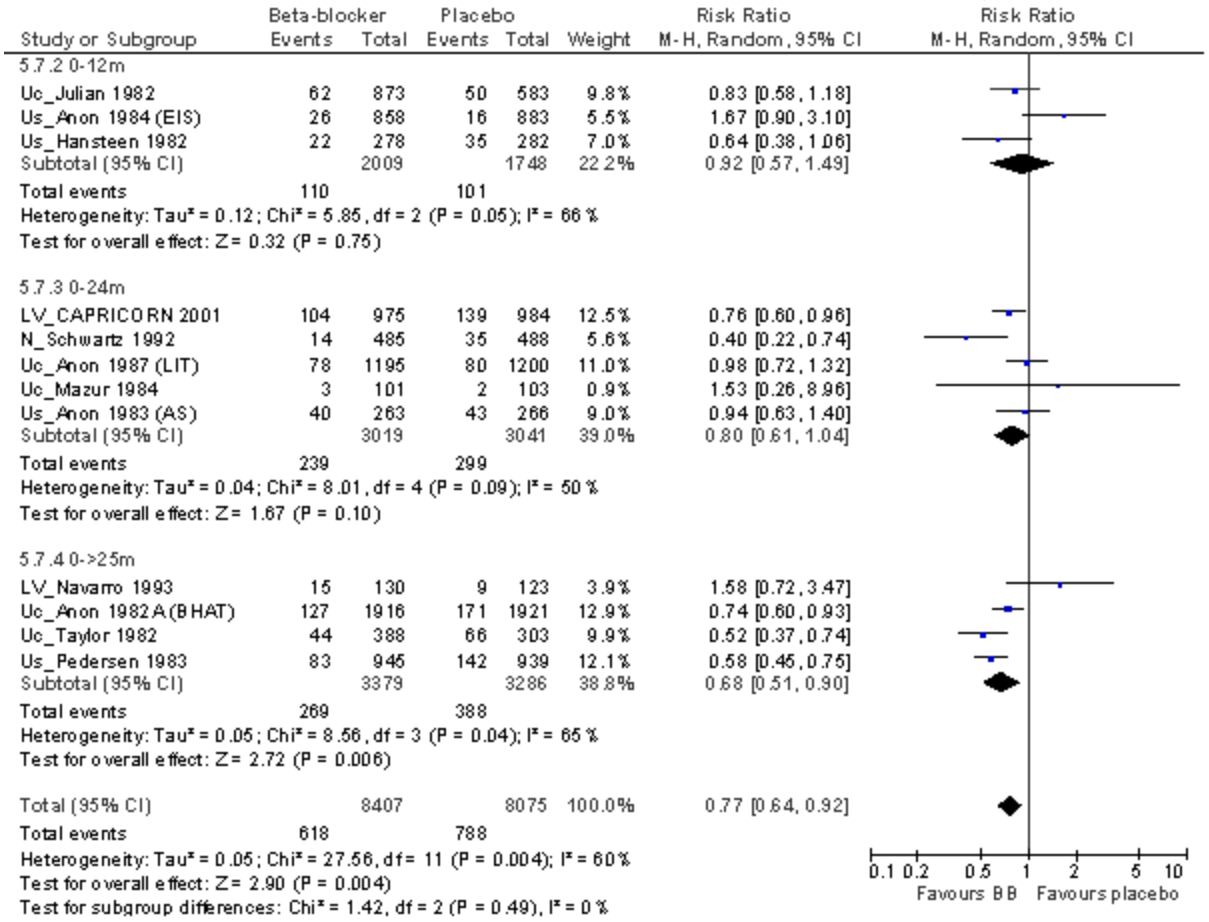
Heterogeneity was detected at 0-12 months, I^2=58%, this appears to be the result of the paper by Anon_EIS, when this is removed heterogeneity is no longer present. Investigating the other factors that may explain why heterogeneity is present, does not show any one reason why this paper is an outlier since other papers can fall into the same category as it does for the following: COPD status, LV function, beta-blocker solubility, age range. It is unclear in this paper, as in others what the ethnicity status is or what treatment was used. However since they are all published before 1990 it is likely they had similar treatments. As such this meta-analysis is presented as random effects instead of fixed effects. Heterogeneity was also detected at over 24 months, I^2=67%. Again, this appears to be due to one paper appearing as an outlier, Navarro. If this paper is removed, so is the heterogeneity. This paper has a risk of bias since it's the only study that does not appear to have blinded the patients. It has few events and low patient numbers, resulting in a large 95% CI. No other factor investigated appears explain the heterogeneity. As such the results as shown as a random effects model.

Figure 263: Beta-blocker vs. placebo – sudden death (people who have had an MI and who have been initiated with treatment between 72 hours and 12 months)



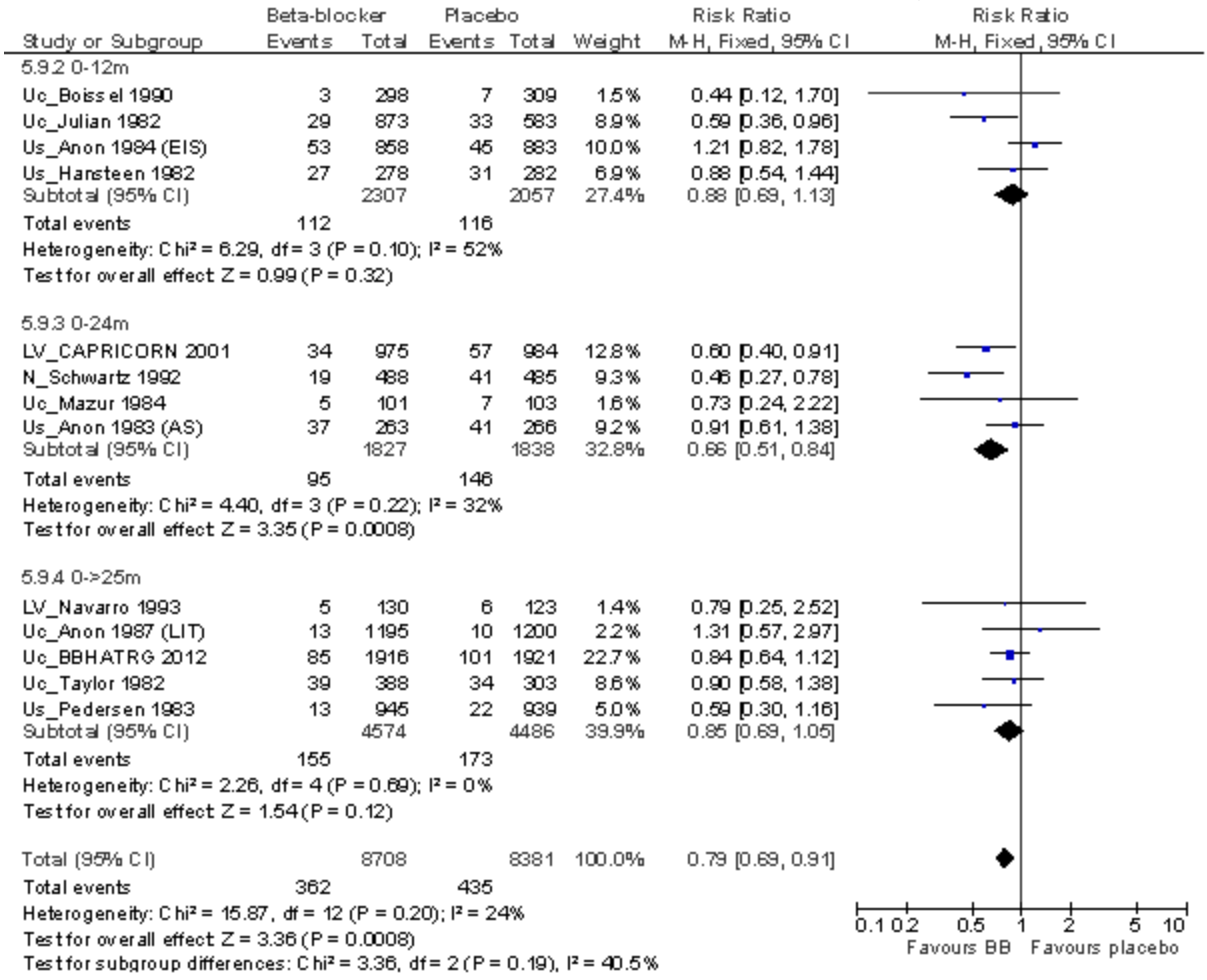
Heterogeneity was detected, I^2= 57%, at 0-24 months subgroup. This is eliminated when the paper with few events and patient numbers by Mazur et al. is removed. It is also eliminated when Schwartz et al. is removed. Investigating the other factors that may explain heterogeneity, there is nothing in the risk of bias, COPD status, age, ethnicity, LV function status. Mazur is the only paper that uses a highly lipid soluble form of beta-blocker, propranolol compared with the other papers that used a moderately soluble beta-blocker, hence this may explain the heterogeneity. In the 0 to 25 month subgroup, heterogeneity is again detected at I^2=69%. The paper by Navarro appears to be an outlier and may carry a risk of bias since, compared with the other, papers is the only on that did not blind the patients to the aim of the study. It is also has few patients and few events recorded.

Figure 264: Beta-blocker vs. placebo - cardiac mortality (people who have had an MI and who have been initiated with treatment between 72 hours and 12 months)



Heterogeneity was detected at 0-12 months, I^2=66%, this appears to be the result of the paper by Anon_EIS, when this is removed heterogeneity is no longer present. Investigating the other factors that may explain why heterogeneity is present, does not show any one reason why this paper is an outlier since other papers can fall into the same categorised for the following: COPD status, LV function, beta-blocker solubility, age range. It is unclear in this paper, as in others what the ethnicity status is or what treatment was used. However since they are all published before 1990 it is likely they had similar treatments. As such this meta-analysis is presented as random effects instead of fixed effects. Heterogeneity was also detected at over 25months, I^2=65%. Again, this appears to be due to one paper appearing as an outlier, Navarro. If this paper is removed, so is the heterogeneity. This paper has a risk of bias since it's the only study that does not appear to have blinded the patients. It has few events and low patient numbers, resulting in a large 95% CI. No other factor investigated appears explain the heterogeneity. As such the results as shown as a random effects model.

Figure 265: Beta-blocker vs. placebo – reinfarction (people who have had an MI and who have been initiated with treatment between 72 hours and 12 months)



Heterogeneity was just detected, I^2= 52%, at 0-12 months subgroup. This appears to be the result of the paper by Anon_EIS, when this is removed heterogeneity is no longer present. Investigating the other factors that may explain why heterogeneity is present, does not show any one reason why this paper is an outlier since other papers can fall into the same categorised for the following: COPD status, LV function, beta-blocker solubility, age range. It is unclear in this paper, as in others what the ethnicity status is or what treatment was used. However since they are all published before 1990 it is likely they had similar treatments. As such this meta-analysis is presented as random effects instead of fixed effects.

Figure 266: Beta-blocker vs. placebo – stroke (people who have had an MI and who have been initiated with treatment between 72 hours and 12 months)

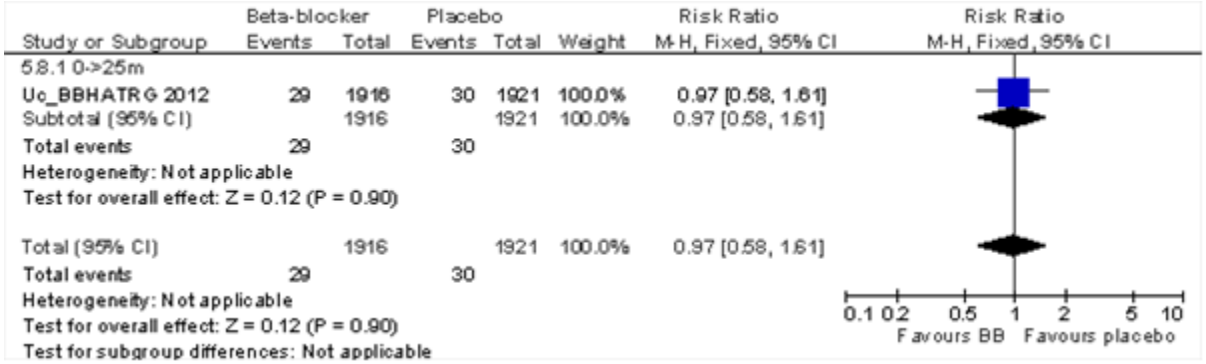


Figure 267: Beta-blocker vs. placebo – rehospitalisation (people who have had an MI and who have been initiated with treatment between 72 hours and 12 months)

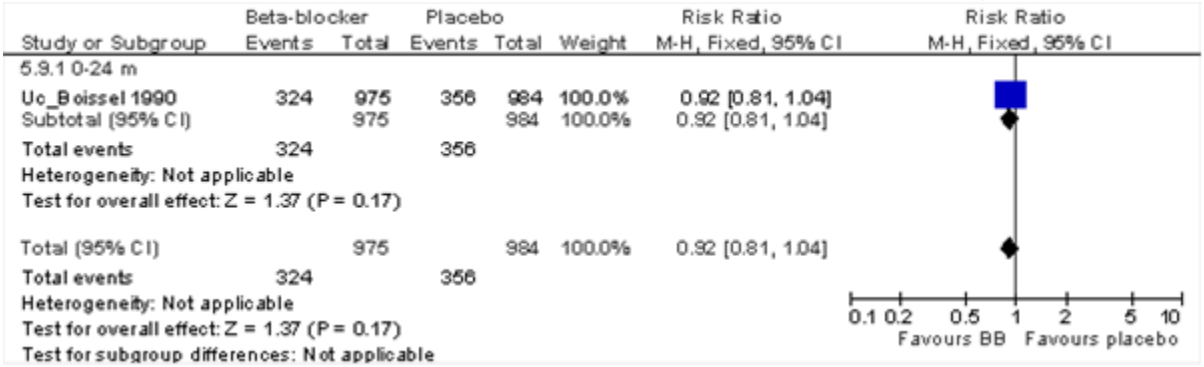


Figure 268: Beta-blocker vs. placebo – fatigue (people who have had an MI and who have been initiated with treatment between 72 hours and 12 months)

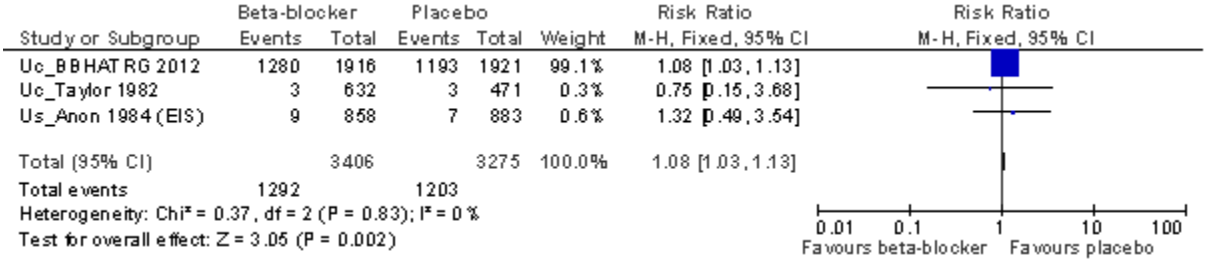
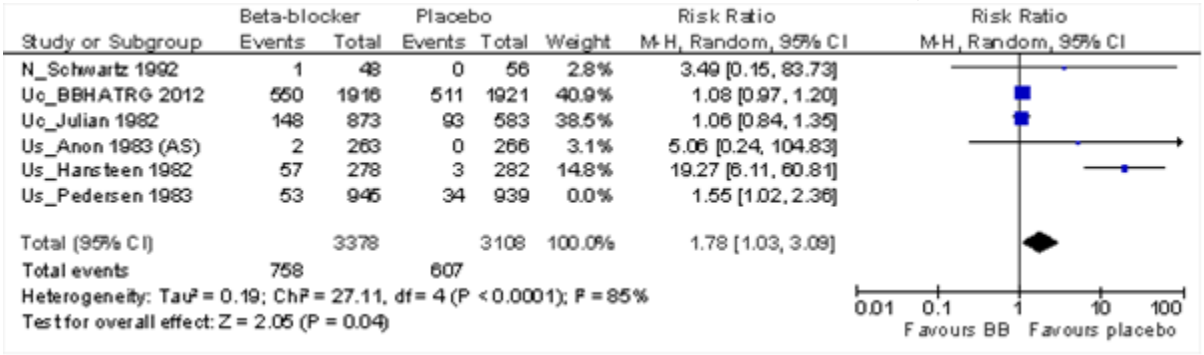
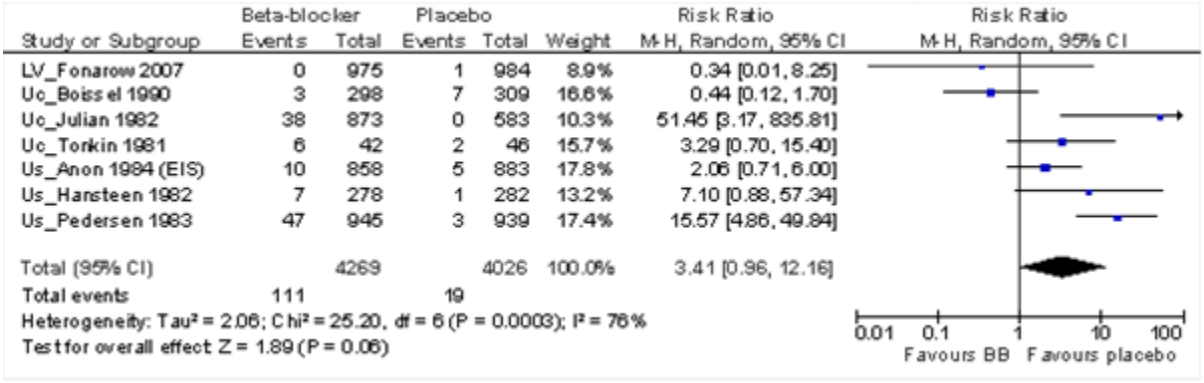


Figure 269: Beta-blocker vs. placebo – dizziness (people who have had an MI and who have been initiated with treatment between 72 hours and 12 months)



Heterogeneity was detected, I^2= 85%. This does not appear to be the result of an obvious outlier or a risk of bias. Nor when investigating other factors does heterogeneity appear to be explained i.e. by separating the papers into their groups based on their COPD and LV function status or beta-blocker solubility. Age did not explain it. Nor is it clear in these papers what the ethnicity status is or what treatment was used. However since they are all published before 1990 it is likely they had similar treatments. Because heterogeneity could not be explained, this meta-analysis is presented as random effects instead of fixed effects.

Figure 270: Beta-blocker vs. placebo – bradycardia (people who have had an MI and who have been initiated with treatment between 72 hours and 12 months)



Heterogeneity was detected, I^2= 76%. This does not appear to be the result of an obvious outlier or a risk of bias. Nor when investigating other factors does heterogeneity appear to be explained i.e. by separating the papers into their groups based on their COPD and LV function status or beta-blocker solubility. Age could not explain it. Nor is it clear in these papers what the ethnicity status is or what treatment was used. However since most of them are published before 1990 it is likely they had similar treatments, except Fonarow where 13% of the patients had angioplasty. Because heterogeneity could not be explained, this meta-analysis is presented as random effects instead of fixed effects.

Figure 271: Beta-blocker vs. placebo - change in dreaming (people who have had an MI and who have been initiated with treatment between 72 hours and 12 months)

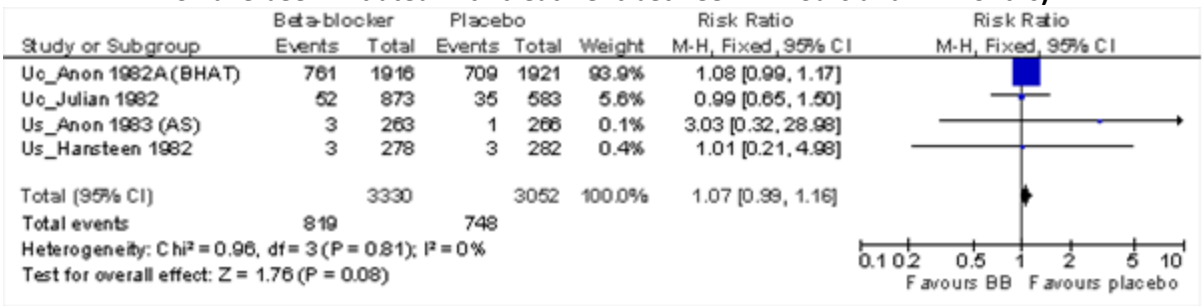


Figure 272: Beta-blocker vs. placebo – revascularisation (people who have had an MI and who have been initiated with treatment between 72 hours and 12 months)

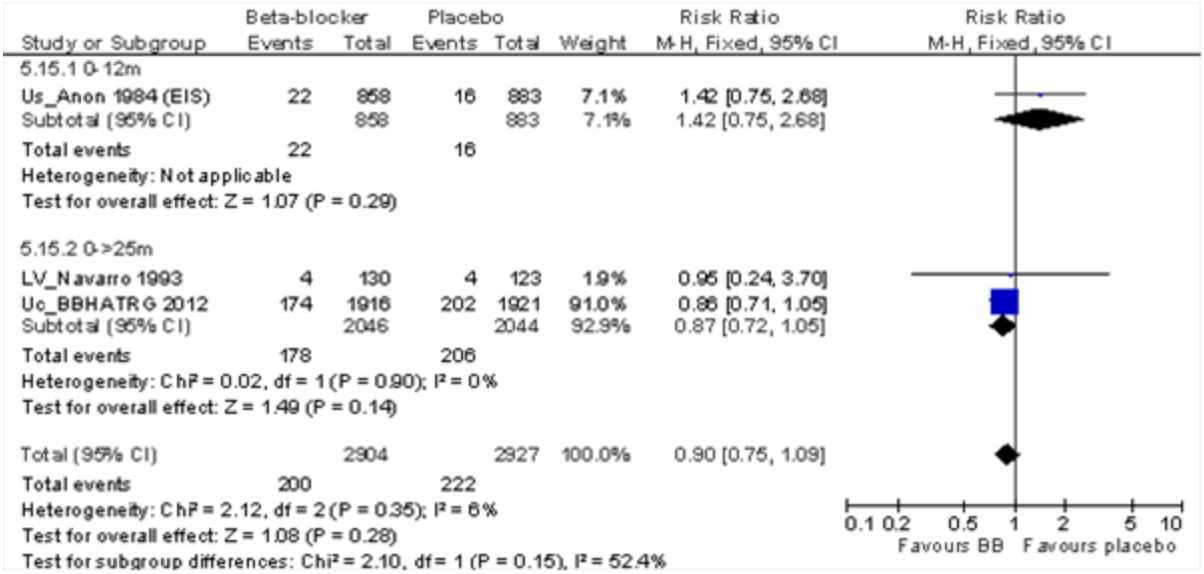
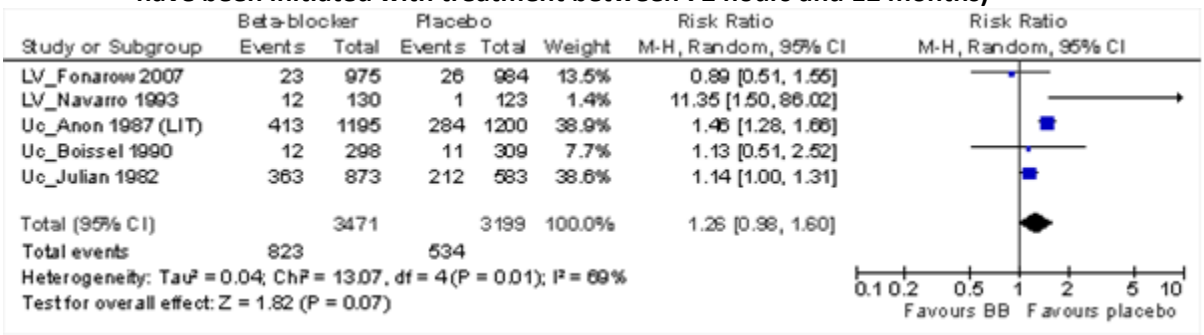
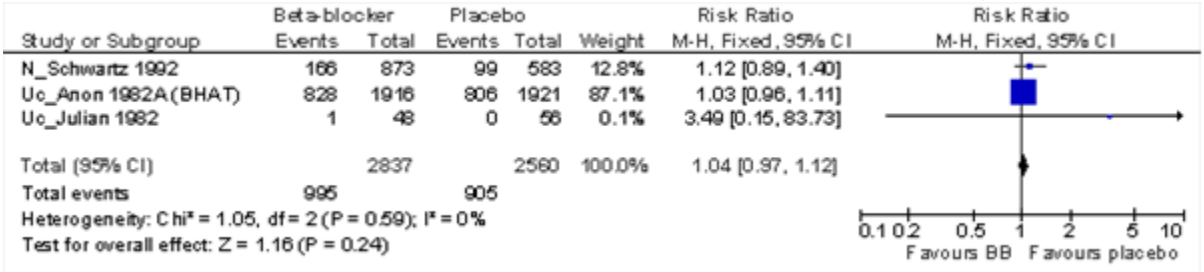


Figure 273: Beta-blocker vs. placebo - adverse events (people who have had an MI and who have been initiated with treatment between 72 hours and 12 months)



Heterogeneity was detected, I^2= 69%. This does not appear to be the result of an obvious outlier or a risk of bias. The only paper that when eliminated reduces the risk of bias is by Anon_LIT. When investigating other factors heterogeneity is not explained i.e. by separating the papers into their groups based on their COPD and LV function status or beta-blocker solubility. Age could not explain it. Nor is it clear in these papers what the ethnicity status is or what treatment was used. However since most of them are published before 1990 it is likely they had similar treatments, except Fonarow where 13% of the patients had angioplasty. Because heterogeneity could not be explained, this meta-analysis is presented as random effects instead of fixed effects.

Figure 274: Beta-blocker vs. placebo - libido decrease(people who have had an MI and who have been initiated with treatment between 72 hours and 12 months)



I.6.5.3 Beta-blocker vs. placebo (in those who have had an MI in the past (over 12 months ago))

Figure 275: Beta-blocker vs. placebo - all-cause mortality (people who have had an MI in the past)

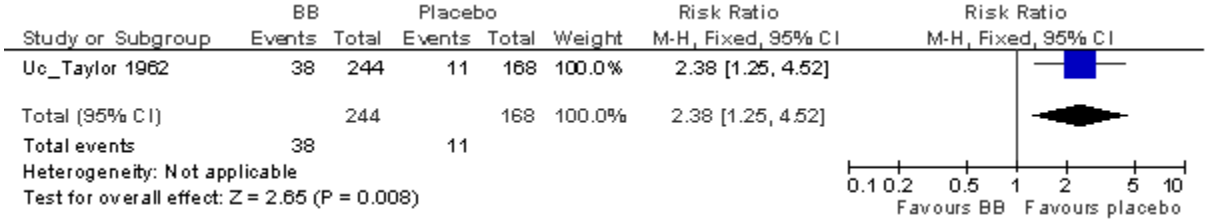


Figure 276: Beta-blocker vs. placebo - cardiac mortality (people who have had an MI in the past)

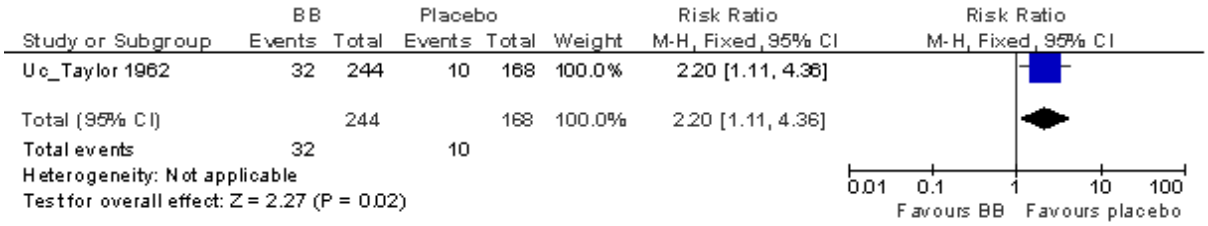
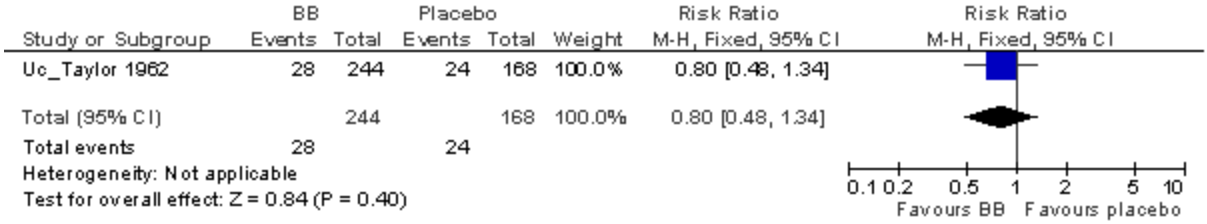


Figure 277: Beta-blocker vs. placebo – reinfarction (people who have had an MI in the past)



I.6.5.4 Beta-blocker (early initiation) vs. beta-blocker (late initiation)

Figure 278: Beta-blocker (early initiation) vs. beta-blocker (late initiation) – long term survival (over 45 days) (people with left ventricular dysfunction) (hazard ratio)

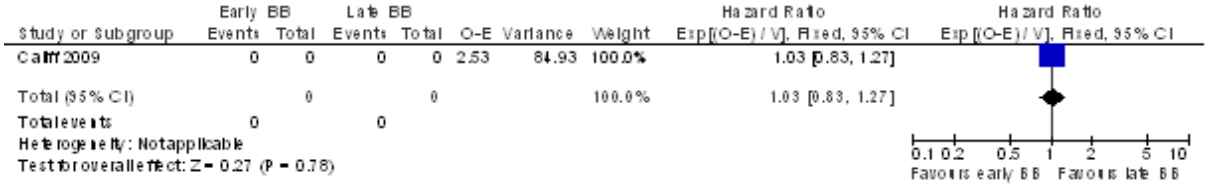


Figure 279: Beta-blocker (early initiation) vs. beta-blocker (late initiation) – all-cause mortality (people without LVSD) (relative risk)

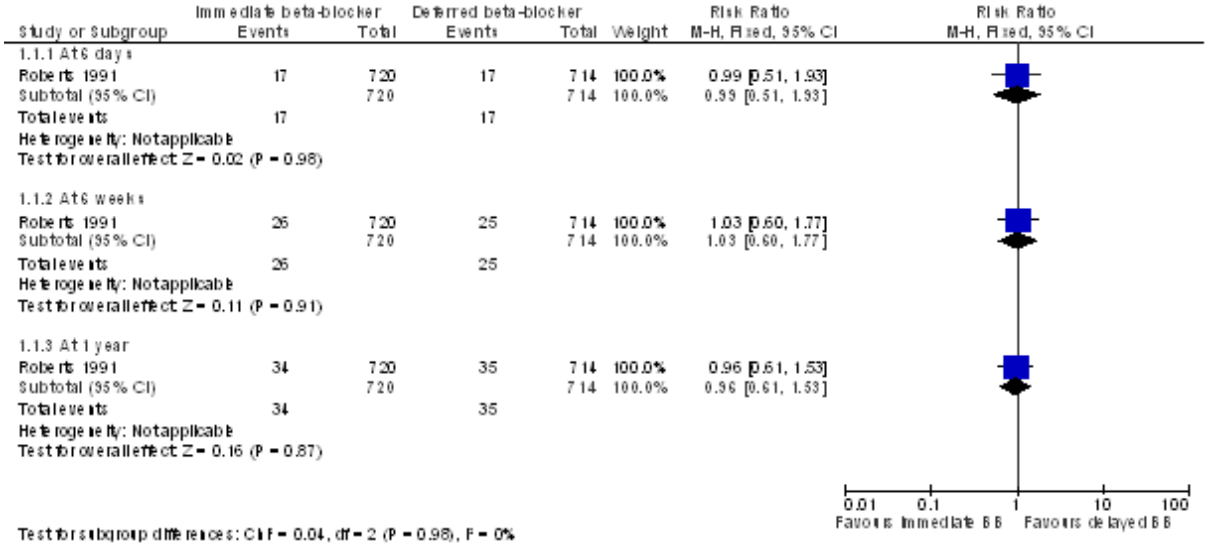


Figure 280: Beta-blocker (early initiation) vs. beta-blocker (late initiation) – reinfarction (people without l LVSD) (relative risk)

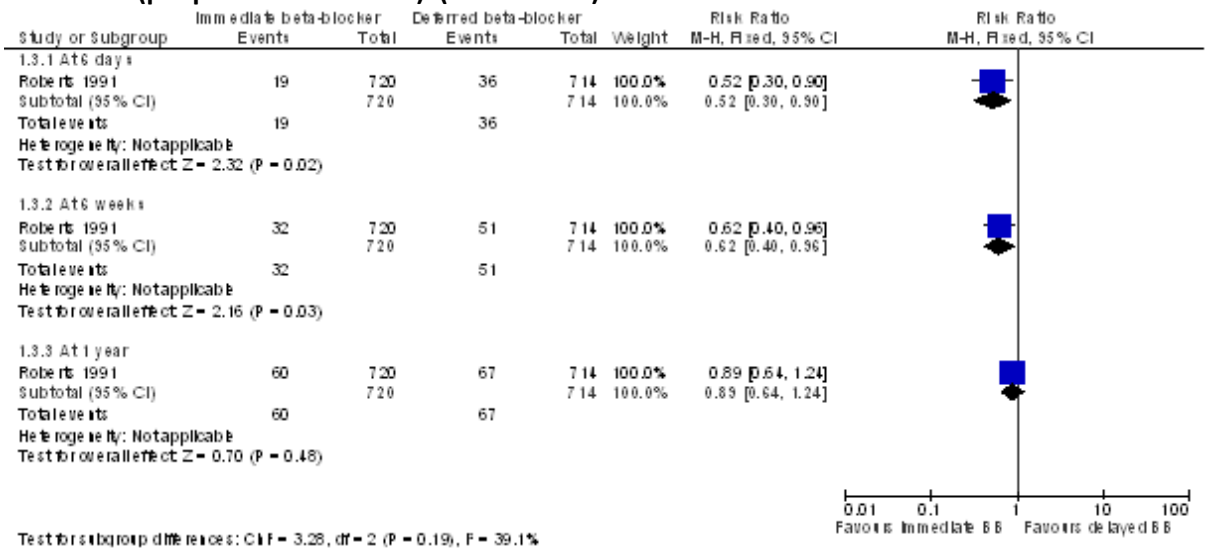
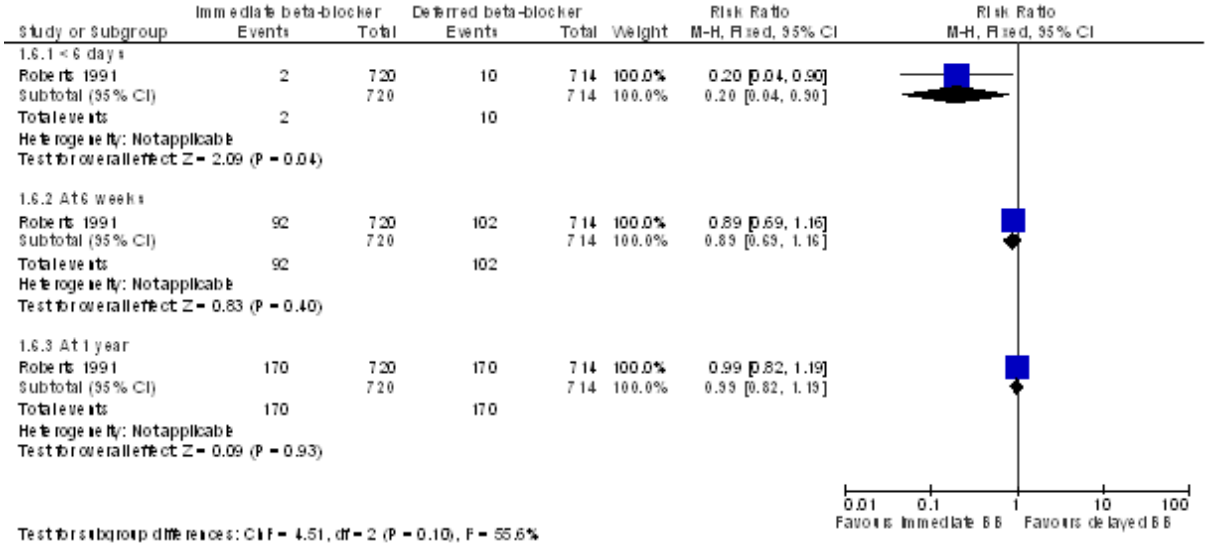


Figure 281: Beta-blocker (early initiation) vs. beta-blocker (late initiation) – severe ischaemic event (people without LVSD)(relative risk)



Appendix J: Excluded clinical studies

J.1 Lifestyle

J.1.1 Omega-3 fatty acids

Reference	Reason for exclusion
Aarsetøy H 2008 [11]	Not secondary prevention.
Athyros 2011 [35]	Not relevant outcomes.
Bosch 2012 [74]	Not relevant population.
Brouwer 2006 [80]	Patients with implantable cardioverter.
BURR2003 [87]	Indirect population <75% MI.
Carrero 2007 [93]	Insufficient information on relevant outcomes – not in Cochrane.
Castro 2007 [98]	Not relevant outcomes.
Einvik 2010 [172]	Included primary prevention patients.
Eritsland 1996 [175]	Indirect population (unclear exactly why they needed CABG but mostly angina patients).
Erkkilä 2008 [176]	Fish diet and not RCT.
Galan 2008 [205]	Methods paper.
Garbagnati 2009 [212]	Stroke patients.
Hamaad 2006 [253]	Single blind, not relevant outcomes.
Hansen 2007 [258]	Review
Jump 2012 [304]	Review
Leaf 2005 [336]	Included patients with implanted cardioverter/defibrillators (ICDs).
Levitan 2009 [342]	Primary prevention of MI
Madsen 2007[355]	Not relevant outcomes
Marinsek 2009 [367]	Not relevant outcomes
O'Keefe 2006 [433]	Not relevant outcomes
Pascho 2007 [454]	Not secondary prevention and only 12 week intervention
Patel 2008 [456]	Not relevant outcome. Patients with implantable cardioverter defibrillators:
Raitt 2005 [490]	Patients with implantable cardioverter
Rizos 2012 [501]	Systematic review, included primary prevention
Seierstad 2005[532]	Fish diet
Smith 2012 A[546]	Review
Tanaka2008[568]	Subgroup analysis of patients from the JELIS trial. Looked at primary and secondary prevention of stroke. Mixed CAD population.
Tang 2009 [569]	Not in English and abstract
Tavazzi 1989 [570]	Heart failure patients
Weber 2006 [611]	Review
WIlk 2012 [619]	Prospective cohort study
Yokoyama 2007 [628]	JELIS study but used a mixed population. Matsukai uses the patients from this study to look at secondary prevention

J.1.2 Oily fish consumption

Reference	Reason for exclusion
Alforaih 2011 [18]	Non-RCT. No relevant outcomes.
Buckland 2009 [84]	Primary prevention of CHD.
Carrero 2007 [93]	Fish oil intervention.
Galli 2009 [211]	Systematic review.
Gardener 2011 [213]	Population 80% no history of heart disease.
Geleijnse 2010B [216]	Literature review.
Geleijnse 2010A [217]	Methods paper for a trial not included in this review.
Geleijnse 2011 [215]	No relevant outcomes.
Giannuzzi 2009 [225]	Abstract.
Iestra 2006 [282]	Cohort study.
Jump 2012 [304]	Review.
Manger 2010 [362]	Cohort study.
Mead 2006A [380]	Systematic review.
Mozaffarian 2006 [405]	Cohort study.
Serramajem2006 [533]	Systematic review.
Trichopoulou 2007A [586]	Mediterranean diet, couldn't isolate fish effect.
Tuttle 2008 [588]	Mediterranean diet, couldn't isolate fish effect.
Wang 2006 [608]	Systematic review.
WIlk 2012 [619]	Prospective cohort study.

J.2 Cardiac rehabilitation

J.2.1 Barriers to the uptake of and adherence to cardiac rehabilitation

Reference	Reason for exclusion
Ali 2012 [22]	Non-UK.
Arnetz 2010[28]	Non-UK.
Astin2008[32]	South Asian patients – not needed as have SR.
Baigi 2011 (Almerud-Osterberg)[39]	Not uptake/adherence to CRP.
Banerjee 2010[42]	Non-UK; South Asian patients – not needed as have SR.
Blanchard 2006 [68]	Non-UK.
Blanchard 2007 [70]	Non-UK.
Blanchard 2010 [71]	Non-UK.
Blanchard 2012 [69]	Non-UK.
Brezinka 1998 [77]	Non-UK; not uptake/adherence to CRP.
Brual 2010[82]	Non-UK.
Caldwell 2009[90]	Non-UK.
Casey2008[96]	Non-UK.
Caulin-Glaser2000[99]	Non-UK.
Chauhan 2010[103]	South Asian patients – not needed as have SR.

Reference	Reason for exclusion
Clark 2012 [111]	Non-UK.
Concepcion 2010[117]	Non-UK.
Cooper 2007 [121]	Only quantitative data.
Courtney 2011 [127]	Not all MI patients.
Dalal 2012 [131]	Heart failure not MI; not uptake/adherence to CRP.
Dankner 2011[133]	Elective CABG patient; not all MI.
Deskur-Smielecka 2009[149]	Non-UK.
Ding 2012 [158]	Conference abstract, full paper is needed to get all relevant data.
Dolansky 2006 [160]	Non-UK.
Dunlay2009[166]	Non-UK.
Dunn2009 [167]	Non-UK.
Eftekhari 2005[171]	South Asian patients – not needed as have SR.
Fernandez 2008A [184]	Non-UK.
Fernandez 2010[183]	Non-UK.
Fernandez 2011 [185]	Non-UK.
Fleig 2011	Non-UK.
French 2005[201]	No qualitative factors. Closer to a quantitative study design and did not meet our inclusion criteria.
Galdas 2010 [209]	Included in Galdas 2012 SR.
Gharacholou 2011[222]	Quantitative data only.
Goulding 2010[236]	Not all MI patients; no data on qualitative factors helping/hindering attendance/completion of CRP.
Grace2008[239]	Non-UK.
Grace 2009 [238]	Non-UK.
Grewal 2010[245]	South Asian patients – not needed as have SR.
Hagan 2007[249]	Non-UK.
Haghshenas 2011[250]	Non-UK.
Johnson 2010[293]	Non-UK.
Kolman 2011[317]	Non-UK.
Lau-Walker 2007[333]	Not all MI patients; no data on qualitative factors helping/hindering attendance/completion of CRP.
Le Grande 2006[335]	Not all MI patients.
McDonnell 2008[375]	Non-UK.
McGrady2009[376]	Non-UK.
Mead 2010 [381]	Non-UK.
Melville 1999 [385]	Not qualitative study.
Miller 1989 [391]	Long term results.
Molloy 2008[394]	Not all MI patients.
Molloy2008[393]	Not all MI patients.
Moore2006[399]	Gave description of non-attendees not reasons for withdrawing. Non-UK.
Moore2011[398]	Non-UK.
Moore 1996[397]	Non-UK.

Reference	Reason for exclusion
Moradi 2011 [400]	Non-UK.
Murie 2006[409]	Not uptake/adherence to CRP.
Nielsen2012[425]	Non-UK.
Oldridge[440]	Gave description of non-attendees not reasons for withdrawing.
Paquet 2005 [450]	Non-UK.
Pollard 2009[480]	No qualitative data.
Rolfe 2010[508]	Non-UK.
Russell 2011[514]	Non-UK.
Sanderson 2010 [520]	Non-UK.
Sarkar 2011[523]	Non-UK.
Shanks 2007[536]	Non-UK.
Sharp 2009 [537]	Not all MI patients; no qualitative factors.
Shaw 2012 [540]	Not all MI patients.
Sniehotta 2006[548]	Gave description of non-attendees not reasons for withdrawing.
Sniehotta 2010[547]	Not all MI patients.
Soleimani2009[552]	Non-UK.
Sriskantharajah2007 [557]	Not all MI patients.
Swardfager 2011[562]	Non-UK.
Sweet 2011[564]	Non-UK.
Thow 2008[578]	Not all MI patients.
Tod 2001[581]	Included in Galdas 2012 SR Not MI population – stable angina.
Toobert 1998[585]	Non-UK; not all MI patients.
van Riezen[599]	Non-UK
Visram 2007 [605]	South Asian patients – not needed as have SR.
Visram 2008[606]	South Asian patients – not needed as have SR.
Wang 2011[609]	Non-UK.
Webster 2002 [612]	Included in Galdas 2012 SR.
Wyer2001 [622]	Gave description of non-attendees not reasons for withdrawing.
Yalfani 2006 [623]	No qualitative data.
Yohannes 2007[627]	Not all MI patients; no data on qualitative factors helping/hindering attendance/completion of CRP.
Young 1989[631]	Non-UK.

J.2.2 Interventions to increase the uptake of and adherence to cardiac rehabilitation

Reference	Reason for exclusion
Ali 2012 [21]	Medication adherence.
Aish 1996 [15]	Measured improvement in food habits, no exercise component.
Ashe 1993 [31]	US PhD and not readily available. Also <80 patients.
Chase 2011 [101]	Systematic review to increase exercise after CRP.
Cossette 2009 [123]	Pilot study and small numbers.

Reference	Reason for exclusion
Cossette 2010 [124]	Abstract.
Deligiannis 2010 [144]	Abstract only.
Dressler 2012 [163]	Systematic review.
Duncan 2002 [165]	<80 patients in total.
Duncan 2001 [164]	Abstract only.
Erling 1985[177]	Abstract only.
Eder 2010 [169]	No relevant outcomes. Compares CRP vs none.
Giallauria 2006[223]	<80 patients in total.
Giannuzzi 2008 [226] et al. 2008	Did not measure adherence or uptake.
Giraud2012 [247]	Assessing usefulness of different tools to measure exercise levels.
Goulding 2010[236]	No relevant outcomes.
Hoopper 1995[272]	<80 patients in total.
Houle 2009 [275]	Abstract only.
Hillebrand 1995 [270]	Not in English.
Imich 1997 [283]	<80 patients in total.
Izawa 2005 [286]	<80 patients in total.
Jiang 2006 [291]	CR vs none.
Krasemann 1988 [323]	Not in English.
Lack 1985 [328]	<80 patients in total.
Leslie 1991 [340]	<80 patients in total.
Macchi 2007 [351]	Adherence to CRP was not measured. Rather 1 year after CRP.
Maher 1999 [359]	Measured exercise habits after discharge –not related to CRP per se.
Marshall 1986 [368]	<80 patients in total.
McKenna 1988[377]	PhD thesis, not available.
McPaul 2008 [379]	No raw data.
Michie 2009 [388]	Review .
Miller 1989 [391]	Long-term follow up .
Moore 2011 [398]	Abstract only.
Mosleh 2009 [403]	Model paper.
Moulaert 2007 [404]	Methods paper only.
Mueller 2009 [407]	Retrospective study.
Osika 2001 [445]	PhD thesis. Not available.
Patrick 2010 [458]	Abstract.
Pischke 2008 [476]	Outcomes not relevant: well being and correlations.
Price 2012 [485]	Conference abstract with no numbers that could be extracted.
Reid 2012 A[494]	Aim to increase physical activity levels. No relevant outcomes.
Robinson 2011 [503]	No intervention to increase uptake or adherence.
Sadeghzadeh 2011 [518]	Abstract only.
Scott 2012 [531]	Conference abstract and full papers on this topic are available.

Reference	Reason for exclusion
Throndson 2009[579]	Review.
Wolkanin 2010 [620]	No relevant outcomes. Intervention to increase health outcomes.
Varnfield 2012 [601]	Conference abstract and another full paper on this topic is available.

J.3 Drug therapy

J.3.1 ACE inhibitor vs. placebo and optimal duration

Reference	Reason for exclusion
BORGHI2007[73]	Intervention does not match protocol. The ACE is not licensed in the UK.
Borghi 2012 [72]	Not relevant comparison. ACEi vs. ACEi.
BRAUNWALD2004[76]	No numbers for the relevant outcome available, text only.
NABEL1991[410]	Treated patients acutely with intravenous ACE inhibitors .
BUCH2005[83]	Long-term follow up of patients no longer taking ACEi.
SOGAARD1994[550]	No relevant outcomes.
Anon(EDEN)1997 [8]	No relevant outcomes.
JANSSON1993 [290]	Treated patients acutely with intravenous ACE inhibitors .
JONG2003(SOLVD)[299]	Indirect population with no subgroup analysis.
MACMAHON2000(PART 2) [353]	Indirect population with no subgroup analysis.
NISSEN [428]2004(CAMELOT)	Indirect population with no subgroup analysis.
MORTARINO1990[401]	No relevant outcomes.
ANON1987(CONSENSUS) [6]	Indirect population, HF with no subgroup analysis.
SHEN[541]	No relevant outcomes.
SCHULMAN1995[528]	Treated patients acutely with intravenous ACE inhibitors.
SWEDBERG1992 [563]	Treated patients acutely with intravenous ACE inhibitors
QUIET[478]	ACE inhibitor not licenced in the UK.
YUSUF1991(SOLVD)[553]	Indirect population with no subgroup analysis.

J.3.2 Initiation of ACE inhibitors

Reference	Reason for exclusion
Ball1995[41]	Study design does not match the protocol. This was a non-systematic review.
Bazzino1997[47]	Outcomes do not match the protocol.
Beckwith1993[50]	Study design does not match the protocol. This was a non-systematic review.
Deedwania1990[142]	Study design does not match the protocol. This was a non-systematic review.
DiPasquale1990 [153]	Outcomes do not match the protocol.
DiPasquale1994 [154]	Same study as DiPasquale1994A but only showed part of the results.
Flather1995[190]	Comparison does not match the protocol. Study design does not match the protocol. This was a non-systematic review.

Reference	Reason for exclusion
Goa1996[229]	Study design does not match the protocol. This was a non-systematic review.
Greaves1997 [244]	Outcomes do not match the protocol.
Jugdutt1993[301]	Study design does not match the protocol. This was a non-systematic review.
Lindsay1995[345]	Study design does not match the protocol. This was a non-systematic review.
Lubarsky2007[349]	Study design does not match the protocol. This was a non-systematic review.
Maggioni1998[357]	Study design does not match the protocol. This was a non-systematic review.
Maggioni1999[356]	Study design does not match the protocol. This was a non-systematic review.
Pasquale1999B [455]	Comparison does not match the protocol.
Perez2009 [464]	Comparison does not match the protocol.
Plosker 1995[479]	Study design does not match the protocol. This was a non-systematic review.
Renkin1996[495]	Study design does not match the protocol. This was a non-systematic review.
Ricci1999[496]	Study design does not match the protocol. This was a non-systematic review.
Rich2001 [497]	Study design does not match the protocol. This was a review of guidelines.
Rodrigues2003[505]	Comparison does not match the protocol. Study design does not match the protocol. This was a non-systematic review.
Salam2003 [519]	Study design does not match the protocol. This was a non-systematic review.
Schulman2001[527]	Comparison does not match the protocol. Study design does not match the protocol. This was a non-systematic review.
Syed1996[565]	Study design does not match the protocol. This was a non-systematic review.
Tognoni1994[582]	Study design does not match the protocol. This was a non-systematic review.
Waring2000[610]	Study design does not match the protocol. This was a non-systematic review.
White2000[616]	Study design does not match the protocol. This was a non-systematic review.
Yan2011[624]	Study design does not match the protocol. This was a non-systematic review.
Young1995[630]	Study design does not match the protocol. This was a non-systematic review.

J.3.3 Titration of ACE inhibitors

Reference	Reason for exclusion
Dews 2001. [151]	Not a relevant comparison. All patients received the same

Reference	Reason for exclusion
	treatment.
De Young 1987. [152]	No relevant outcomes. Cross over study design.
Dollow 1994 [161]	Not a relevant comparison. All patients received the same treatment.
Tytus 2009 [589]	Not a titration comparison.
Weir 1994 [613]	Not a relevant population – hypertensive patients.
Welton 1990. [615]	No relevant outcomes.
Van den Berg 2009 [597]	Abstract only.
Vasmant1991[602]	No relevant outcomes.
Yener 2007 [626]	Open label study. Uncontrolled and hypertensive patients. More of a dose study.

J.3.4 ACE inhibitors vs. ARBs

Reference	Reason for exclusion
Cohn 2001 [115]	All HF patients who were treated with ACE inhibitors.
Kasanuki 2009 [310]	Control patients were treated with ACE inhibitors.
Spinar 2000 [555]	No relevant outcomes.
Peters 2008 [466]	Not relevant comparison: dose comparison.

J.3.5 Duration of clopidogrel treatment

Reference	Reason for exclusion
Akbulut2004[16]	No relevant outcomes.
Atary2010[34]	Intervention not relevant. All patients received clopidogrel. Comparing stents.
Andrade2013[27]	Systematic review.
Bartorelli[44]	Results do not allow outcomes to be extracted. Compared ticlopodine vs. clopidogrel.
Berger2009[52]	Systematic review.
Bhatt2006[64]	Population is broad. Follow-up study is more relevant to our guideline.
Bowry2008[75]	SR. Used as a reference.
Butler2009[88]	Intervention not relevant. All received clopidogrel.
Byrne2009[89]	Methods paper for a trial we did not include. ISAR_SAFE study.
Cannon2010[92]	Intervention not relevant. Ticagrelor vs. clopidogrel.
Cassesse2012[97]	Meta-analysis. Used as a reference.
Chen2009[104]	Economic review. Not needed for clinical review.
Chin2010[108]	Intervention not relevant. Prasugrel vs. clopidogrel.
Collet2009[116]	Study design does not fit protocol. Compared those who withdrew vs. those who continued.
Dean2090[141]	Intervention not relevant. All received clopidogrel.
DeLuca2009[139]	Systematic review. Used as a reference.

Reference	Reason for exclusion
Deo2013[145]	Systematic review. Used as a reference.
Dobesh2012[159]	Guideline. Used as a reference.
Eisenstein2007[173]	Observational study.
Fox2004[196]	Composite outcome from CURE trial. Follow-up data.
Geng 2012 [220]	Systematic review of cilostazol-based antiplatetelet therapy.
Gent1996[221,451]	Population not relevant. At risk of ischemic attacks.
Gibler2010[227]	Economic review. Not needed for clinical review.
Gwon2012[248]	Indirect study population.
Harrington2006[262]	Review.
Karnon2006[308]	Economic review. Not needed for clinical review.
Lengenfelder2011 [337]	Intervention not relevant. Tirofiban.
Lucioni2011[350]	Not in English.
Main2004[360]	Systematic review.
Mannacio2013 [363]	Stable CAD patients undergoing CABG. 38% had an MI in the past.
Mauri2010[373]	Methods paper.
Nikolsky 2012 [426]	Not relevant intervention (Bivalirudin).
Park2010[451]	Intervention not relevant. Not treated acutely.
Pekdemir2003[462]	Indirect population. Data not needed given that direct data was available.
Peters2003[465]	Intervention not relevant. Dose-related study on aspirin.
Pettersen 2012 [469]	Not relevant comparison. Clopidogrel vs. aspirin.
Postula2009[482]	Review.
Sabatine2005[516]	Intervention not relevant. Compared the effects of pre-PCI treatments of aspirin and clopidogrel.
Sanon2009[521]	Study design not included in protocol – retrospective observational. Included heart failure patients.
Smith 2012 [546]	Conference abstract, withdrawal study on clopidogrel.
Steg2010[558]	Intervention not relevant. Ticagrelor vs. Clopidogrel.
Squizzato2011[556]	Cochrane review, their inclusion criteria was different. They excluded any papers <30days.
Roe 2012 [506]	Not a relevant comparison. Prasugrel vs. clopidogrel.
Tada 2012 [566]	Patients mostly given ticlopidine, not clopidogrel.
Thurston2010[580]	Economic review. Not needed for clinical review.
Ussia2011[591]	Population not relevant. Aortic valve implant patients.
Valgimigli2010[592]	Methods paper for trial not included. PRODIGY.
Vavuranakis2006[603]	No relevant outcomes.
Wiisanen2010[617]	Review.
Zhang2009[639]	Economic review. Not needed for clinical review.
Zhou2012[640]	SR. Used as a reference.

J.3.6 Late initiation of antiplatelet therapy

Reference	Reason for exclusion

Reference	Reason for exclusion
Akbulut2004[16]	No relevant outcomes.
Berger2008[53]	Systematic review on patients on aspirin. Not specific to our question.
Bhatt2001[63]	Population is not correct. Subgroup analysis of patients from CAPRIE trial and patients in that trial were treated acutely.
Bhatt2005 [64]	Population is not correct. Large trial with mixed population. Subgroup analysis from this trial on patients with MI is used in this review.
Dobesh2012[159]	Guideline. Used as a reference.
Eisenstein2007[173]	Observational study.
Fox2004[196]	Composite outcome from CURE trial. Follow-up data.
Frilling2004[203]	Patients weren't treated acutely but they were not given subsequent medication.
Gent1996[221,451]	Population not relevant. At risk of ischemic attacks.
Gosselin2012[232]	Comparisons weren't correct. All patients were given ASA+Clopidogrel. They compare the effects of PCI.
Gwon2012[248]	Indirect study population.
Lengenfelder2011 [337]	Intervention not relevant. Tirofiban.
Main2004[360]	Systematic review.
Park2010[451]	Population is not correct. Patients were receiving antiplatelets at the time of enrolment.
Peters2003[465]	Intervention not relevant. Dose-related study on aspirin.
Ringleb2004[499]	Population is not correct. Subgroup analysis of patients from CAPRIE trial. Patients had MI <35 days prior to randomisation.
Smith 2012 [546]	Conference abstract, withdrawal study on clopidogrel.
Valgimigli2010[592]	Methods paper for trial not included. PRODIGY.
Vavuranakis2006[603]	No relevant outcomes.
Wiisanen2010[617]	Review.
Zhang2009[639]	Economic review. Not needed for clinical review.
Zhou2012[640]	SR. Used as a reference.

J.3.7 Antiplatelet therapy in those with an additional indication for anticoagulation

This section was updated and replaced in 2020. See www.nice.org.uk/guidance/ng185 for the 2020 evidence review.

Reference	Reason for exclusion
Akkerhuis[17]	Not relevant treatment. Lefradafiban.
Anon2006[10]	Not relevant population. AF patients with no subgroup analysis on MI population.
Anon1982[3]	Not relevant treatment. Various anticoagulants.
Buresly2005[85]	Observational study. We have RCTs that give us data for the comparison: Warfarin+ASA vs. Warfarin or ASA.
Cohen1994[113]	Not relevant treatment. Comparing different types of ASA.
Cohen1993[114]	Outcomes were categorised according to diagnosis.

Reference	Reason for exclusion
Connolly2009 RE-LY [118]	Not relevant population. AF patients with no subgroup analysis on MI population.
Connolly2010[119]	Abstract. Used data from large trial in review.
De Luca2009[140]	Not relevant treatment. Tirofiban.
Ezekowitz2007[180]	Not relevant population. AF patients with no subgroup analysis on MI population.
Freeman2011[199]	Cost effectiveness of AC for AF patients.
Galatro1998[207]	Post-hoc of ATACS study. Larger trial in used in review.
Gorin2010[231]	Not relevant population. AF patients with no subgroup analysis on MI population.
Hansen2010[257]	Not relevant population. AF patients with no subgroup.
Hohnloser2012[271]	Not relevant population. AF patients with no subgroup analysis on MI population.
Hurlen2006[279]	No relevant outcomes.
Julian1996[303]	Not relevant comparison: Aspirin vs. warfarin in MI patients
Kereiakes1998[311]	Not relevant treatment. Abciximab.
Konstantino2006[320]	For this comparison of Warfarin+dual therapy vs. dual therapy, we used patients who had an indication for anticoagulants. This is just patients who have a MI. For those patients we compared warfarin+ASA vs. ASA or Warfarin.
Kouvaras1990[322]	No relevant outcomes. Thrombus size.
Kubitza2012[326]	Phase I trial.
James2002[288]	Not relevant treatment. Heparin
James2011[289]	Abstract on APPRAISE 2. Final paper is used in review.
Lamberts2012[329]	Non RCT when RCT data is available.
Lopes2001[347]	Not clear what the results were for each group.
Mahaffey2011[358]	Abstract. Rivaroxaban vs. Warfarin
Manzano-Fernandez2008[365]	Not relevant outcome. Tested predictors of outcome
Mehilli2009 [383]	Not relevant treatment. Abciximab
Montalescot2007[395]	Not relevant treatment. Abciximab
Nguyen2007[423]	Non RCT when RCT was available.
O'Connor2001[431]	Not relevant population. Stroke patients.
Olgren2010[437]	Abstract, Phase II trial. Dabigatran vs. Warfarin. Larger trial is used in review.
Orford2004[444]	All patients on triple therapy. No control group.
Petronio2002[468]	Not relevant treatment. Abciximab
Porter2006[481]	All patients on triple therapy. No control group.
Ruiz-Nodar2011[513]	All on the same therapy. NO control group.
Schomig2005[525]	Not relevant treatment. Abciximab
Schreiber1990[526]	Registry data on warfarin vs. aspirin in post MI patients. Not relevant outcome
Schwalm2010[529]	No relevant outcomes.
Tamburino2002[567]	Not relevant treatment. Abciximab

Reference	Reason for exclusion
Udell2010[590]	No relevant outcomes. No control group
Valgimigli 2012A[594]	Short-term follow-up of 2 hours post treatment
vandenBergy2009[597]	Not relevant outcomes. Long term follow-up of patients no longer on the trial.
Veeger2010[604]	Not relevant treatment. Dipridamole vs. ASA

J.3.8 Beta-blocker vs. placebo

This section was partially updated in 2020. See www.nice.org.uk/guidance/ng185 for the 2020 evidence review.

Reference	Reason for exclusion
Anon 1981 NWSG [2]	Incorrect population, 33% HF.
Anon1984A ICSG [5]	Incorrect population, 57% HF.
Anon 1975 [1]	Beta-blocker not used in the UK: Practolol.
Atar 2006 [33]	Open label study and no relevant oucomes.
Balcon 1966 [40]	Incorrect population, 56% HF.
Bhala 2006 [62]	Not an RCT. Correspondance.
Basat 2006 [45]	Incorrect comparison, beta-blocker vs. different beta-blocker.
Cay 2011[100]	Incorrect comparison, BB vs. Ivarabine.
Chatterjee 2011 [102]	Systematic review abstract.
Darasz [134]	BB not used in UK: Xamoteol.
Dotremont 1968 [162]	Incorrect population, 67% HF.
Fasullo 2009 [181]	Incorrect comparison, beta-blocker vs. Ivarabine.
Faynyk 2010 [182]	Incorrect comparison, beta-blocker vs. different beta-blocker.
Hanada 2012 [254]	Beta-blocker not used in UK: Landiolol.
Jonsson 2007 [300]	Incorrect comparison, beta-blocker vs. different beta-blocker.
Kontopoulos 1999 [321]	No relevant outcomes.
Miller 2007A [389]	Non-RCT, outcome <24 hours.
Moiseev 2011.[392]	Incorrect comparison, beta-blocker vs. Different beta-blocker.
Mrdovic 2007 [406] .	Incorrect comparison, beta-blocker vs. different deta-blocker.
Nakagomi 2011 [411]	Incorrect comparison, beta-blocker vs Calcium channel blocker.
Nakatani 2013 [412]	Non-RCT.
Ozasa 2010 [446]	Abstract, registry data but PCI + beta-blocker.
Poulsen 2000 [483]	No relevant outcomes.
Shirotani 2000 [542]	Not an RCT, prospective cohort but PCI + beta-blocker.
Tolgi 2006 [583]	Incorrect comparison, beta-blocker vs. different beta-blocker.
Zedigh 2010 [638]	Incorrect comparison, beta-blocker vs. morphine.

J.3.9 Beta-blocker initiation

Reference	Reason for exclusion
Flu et al 2010[192]	Not patients who have had an MI (direct population) or all patients with CHD (indirect population).
Atar2006[33]	Beta-blocker vs placebo. Open label and no relevant

Reference	Reason for exclusion
	outcomes.
Barber1967[43]	Beta-blocker vs. placebo. No relevant study design.
Basat2006[45]	Beta-blocker vs. beta-blocker. Study design does not fit protocol.
Bhala2006[62]	Correspondence, not a full study.
Carter2008[95]	Beta-blocker review.
Cay2011[100]	Beta-blocker vs. placebo. No relevant study design.
Chatterjee2011[102]	Abstract only.
Edwards2011[170]	Registration data (indirect data) not needed since we have RCTs.
Fasullo2009[181]	Beta-blocker vs. beta-blocker. Study design does not fit protocol.
Faynyk2010[182]	Beta-blocker vs. beta-blocker. Study design does not fit protocol.
Fujita2010[204]	Beta-blocker. vs. placebo. No relevant study design.
Gelbrich 2012 [214]	Review on beta-blocker titration.
Hanada2012[254]	Beta-blocker vs. placebo. No relevant study design.
Jonsson2007[300]	Beta-blocker vs. beta-blocker. Study design does not fit protocol.
Kontopoulos1999[321]	No relevant outcomes.
Miller2007A[389]	Beta-blocker vs. placebo. No relevant study design.
Moiseev2011[392]	Beta-blocker vs. beta-blocker. Study design does not fit protocol.
Mrdovic2007[406]	Beta-blocker vs. beta-blocker. Study design does not fit protocol.
Nakagomi2011[411]	Beta-blocker vs Calcium channel blocker.
Pfisterer1997[474]	Compares iv vs. oral beta-blocker
Poulsen2000[483]	Beta-blocker vs. placebo. No relevant design.
Shirotani2000[542]	Beta-blocker vs. placebo. No relevant study design.
Tolg2006[583]	Beta-blocker vs. beta-blocker. Study design does not fit protocol.
Zedigh2010[638]	Beta-blocker vs. placebo. No relevant study design.

Appendix K: Excluded economic studies

K.1 Lifestyle

K.1.1 Omega-3 fatty acids

Reference	Reason for exclusion
Franzosi MG, Brunetti M, Marchioli R et al. Cost-effectiveness analysis of n-3 polyunsaturated fatty acids (PUFA) after myocardial infarction: results from Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto (GISSI)-Prevenzione Trial. Pharmacoeconomics. 2004; 19(4):411-420. Ref ID: 1834	Analysis based on the GISSI-P study which was considered not reflective of the current clinical evidence base.
Innovus Research (UK) Ltd. Cost-effectiveness Analysis of Omacor for Myocardial infarction Survivors in the UK. High Wycombe: Innovus Research (UK) Ltd, 2004. Ref ID: 3773	Analysis based on the GISSI-P study which was considered not reflective of the current clinical evidence base.
Lamotte M, Annemans L, Kawalec P et al. A multi-country health economic evaluation of highly concentrated N-3 polyunsaturated fatty acids in secondary prevention after myocardial infarction. Pharmacoeconomics. 2006; 24(8):783-795. Ref ID: 5301	Analysis based on the GISSI-P study which was considered not reflective of the current clinical evidence base.
Quilici S, Martin M, McGuire A et al. A cost-effectiveness analysis of n-3 PUFA (Omacor) treatment in post-MI patients. Int J Clin Pract. 2006; 60(8):922-932. Ref ID: QUILICI2006	Analysis based on the GISSI-P study which was considered not reflective of the current clinical evidence base.
J. K. Schmier, N. J. Rachman, and M. T. Halpern. The cost-effectiveness of omega-3 supplements for prevention of secondary coronary events. Manag.Care 43-50:-50, 2006. Ref ID: SCHMIER2006	Analysis based on the GISSI-P study which was considered not reflective of the current clinical evidence base.

K.2 Drug therapy

K.2.1 ACE inhibitor vs. placebo and optimal duration

Reference	Reason for exclusion
W. K. Redekop, E. Orlewska, P. Maciejewski, F. F. Rutten, and L. W. Niessen. Costs and effects of secondary prevention with perindopril in stable coronary heart disease in Poland: an analysis of the EUROPA study including 1251 Polish patients. Pharmacoeconomics 26(10):861-877, 2008. Ref ID: REDEKOP2008	Same analysis as the study by Briggs et al 2007 [78] but not from a UK perspective (less applicable compared to Briggs et al (2007)).
J. R. Cook, H. A. Glick, W. Gerth, B. Kinosian, and J. B. Kostis. The cost and	Less applicable compared to Briggs et al 2007 [78]. Didn't take a UK perspective.

Reference	Reason for exclusion
cardioprotective effects of enalapril in hypertensive patients with left ventricular dysfunction. Am.J.Hypertens. 11 (12):1433-1441, 1998. Ref ID: 3239	
L. Erhardt, S. Ball, F. Andersson, P. Bergentoft, and C. Martinez. Cost effectiveness in the treatment of heart failure with ramipril: a Swedish substudy of the AIRE study. Pharmacoeconomics 12 (2):256-266, 1997. Ref ID: 3241	Less applicable compared to Briggs et al 2007 [78]. Didn't take a UK perspective.
W. M. Hart, C. Rubio-Terres, F. Pajuelo, and J. R. Juanatey. Cost-effectiveness of the treatment of heart failure with ramipril: a Spanish analysis of the AIRE study. Eur J Heart Fail 4 (4):553-558, 2002. Ref ID: 3243	Less applicable compared to Briggs et al 2007 [78]. Didn't take a UK perspective.
C. LePen, H. Lilliu, T. Keller, and S. Fiessinger. The economics of TRACE:a cost-effectiveness analysis of trandolapril in postinfarction patients with left ventricular dysfunction. Pharmacoeconomics 14 (1):49-58, 1998. Ref ID: 3245	Less applicable compared to Briggs et al 2007 [78]. Didn't take a UK perspective.
L. G. Mantovani, A. Belisari, and T. D. Szucs. Captopril in the management of patients after acute myocardial infarctions:a cost effectiveness analysis in Italy. Pharmacol.Res. 37 (5):345-351, 1998. Ref ID:96	Less applicable compared to Briggs et al 2007 [78]. Didn't take a UK perspective.
B. C. Michel, M. J. Al, W. J. Remme, J. H. Kingma, J. A. Kragten, R. van Nieuwenhuizen, and A. B. van Hout. Economic aspects of treatment with captopril for patients with asymptomatic left ventricular dysfunction in The Netherlands. Eur.Heart J. 17 (5):731-740, 1996. Ref ID: 275	Less applicable compared to Briggs et al 2007 [78]. Didn't take a UK perspective.
P. K. Schadlich, E. Huppertz, and J. G. Brecht. Cost-effectiveness analysis of ramipril in heart failure after myocardial infarction:economic evaluation of the Acute Infarction Ramipril Efficacy (AIRE) Study for Germany from the perspective of statutory health insurance. Pharmacoeconomics 14 (6):653-669, 1998. Ref ID:3248	Less applicable compared to Briggs et al 2007 [78]. Didn't take a UK perspective.
J. Tsevat, D. Duke, L. Goldman, M. A. Pfeffer, G. A. Lamas, J. R. Soukup, K. M. Kuntz, and T. H. Lee. Cost-effectiveness of captopril therapy after myocardial	Less applicable compared to Briggs et al 2007 [78]. Didn't take a UK perspective.

Reference	Reason for exclusion
infarction. J.Am.Coll.Cardiol. 26 (4):914-919, 1995. Ref ID: 3250	
C. Martinez and S. G. Ball. Cost-effectiveness of ramipril therapy for patients with clinical evidence of heart failure after acute myocardial infarction. Br.J.Clin.Pract. Supplement 78:26-32, 1995. Ref ID: 102	Less applicable compared to Briggs et al 2007 [78]. The excluded study was old and used LYG as measurement of health gain.
A. Aurbach, W. Russ, E. Battegay, H. C. Bucher, J. G. Brecht, P. K. Schadlich, and P. Sendi. Cost-effectiveness of ramipril in patients at high risk for cardiovascular events: a Swiss perspective. Swiss Medical Weekly. 134 (27-28):399-405, 2004. Ref ID: 178	Less applicable and with more limitations compared to the model developed in CG48.
M. E. Backhouse, A. Richter, and L. Gaffney. Economic evaluation of ramipril in the treatment of patients at high risk for cardiovascular events. Journal of Drug Assessment 3(Part 4):253-265, 2000. Ref ID: 3237	Less applicable and with more limitations compared to the model developed in CG48.
I. Bjorholt, F. L. Andersson, T. Kahan, and J. Ostergren. The cost-effectiveness of ramipril in the treatment of patients at high risk of cardiovascular events: a Swedish sub-study to the HOPE study. J.Intern.Med. 251 (6):508-517, 2002. Ref ID: 907	Less applicable and with more limitations compared to the model developed in CG48.
I. S. Malik, V. K. Bhatia, and J. S. Kooner. Cost effectiveness of ramipril treatment for cardiovascular risk reduction. Heart (British Cardiac Society) 85 (5):539-543, 2001. Ref ID: 152	Less applicable and with more limitations compared to the model developed in CG48.
M. G. Smith, A. M. Neville, and J. C. Middleton. Clinical and economic benefits of ramipril: an Australian analysis of the HOPE study. Internal Medicine Journal. 33 (9-10):414-419, 2003. Ref ID: 194	Less applicable and with more limitations compared to the model developed in CG48.

K.2.2 ACE inhibitors vs. ARBs

Reference	Reason for exclusion
C. Boersma, J. Radeva, I, M. A. Koopmanschap, A. A. Voors, and M. J. Postma. Economic evaluation of valsartan in patients with chronic heart failure: results from Val-HeFT adapted to the Netherlands. J.Med.Econ. 9:121-131:121-131, 2006. Ref ID: BOERSMA2006	Only reports cost (non UK). The comparators are ARB vs. placebo (ACE inhibitors are not considered in this study).

K.2.3 Duration of clopidogrel treatment

Reference	Reason for exclusion
J. Berg, D. Fidan, and P. Lindgren. Cost-effectiveness of clopidogrel treatment in percutaneous coronary intervention: a European model based on a meta-analysis of the PCI-CURE, CREDO and PCI-CLARITY trials. Curr.Med.Res.Opin. 24 (7):2089-2010, 2008. Ref ID: BERG2008	Less applicable and with more limitations compared to the included studies.
J. Berg, P. Lindgren, J. Spiesser, D. Parry, and B. Jonsson. Cost-effectiveness of clopidogrel in myocardial infarction with ST-segment elevation: A European model based on the CLARITY and COMMIT trials. Clin.Ther. 29:1184-1202:1184-1202, 2007. Ref ID: BERG2007	Less applicable and with more limitations compared to the included studies.
S. Y. Chen, E. Russell, S. Banerjee, B. Hutton, A. Brown, K. Asakawa, L. McGahan, M. Clark, M. Severn, J. Cox, and M. Sharma. Clopidogrel compared with other antiplatelet agents for secondary prevention of vascular events in adults undergoing percutaneous coronary intervention: clinical and cost-effectiveness analyses. Technology report no 131. Anonymous. Anonymous. Canada:Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH). 2010. Ref ID: CHEN2010	Less applicable and with more limitations compared to the included studies.
Z. Zhang, P. Kolm, F. Mosse, J. Jackson, L. Zhao, and W. S. Weintraub. Long-term cost-effectiveness of clopidogrel in STEMI patients. Int.J.Cardiol. 135 (3):353-360, 2009. Ref ID: ZHANG2009	Less applicable and with more limitations compared to the included studies.
0 S. Banerjee, A. Brown, L. McGahan, K. Asakawa, B. Hutton, M. Clark, M. Severn, M. Sharma, and J. L. Cox. Clopidogrel versus other antiplatelet agents for secondary prevention of vascular events in adults with acute coronary syndrome or peripheral vascular disease: clinical and cost-effectiveness analyses. Technology report no. 133. Anonymous. Anonymous. Canada:Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH). 2010. Ref ID: BANERJEE2010	Less applicable and with more limitations compared to the included studies.
S. Banerjee, A. Brown, L. McGahan, K. Asakawa, B. Hutton, M. Clark, M. Severn, M. Sharma, and Jl Cox. Clopidogrel versus Other Antiplatelet Agents for Secondary Prevention of Vascular Events in Adults with Acute Coronary Syndrome or Peripheral Vascular Disease: Clinical and Cost-	Less applicable and with more limitations compared to the included studies.

Reference	Reason for exclusion
Effectiveness Analyses. CADTH Technol Overv 2 (1):e2102, 2012. Ref ID: BANERJEE2012	
G. Kourlaba, V. Fragoulakis, and N. Maniadakis. Economic evaluation of clopidogrel in acute coronary syndrome patients without ST-segment elevation in Greece: a cost-utility analysis. Applied Health Economics and Health Policy 10 (4):261-271, 2012. Ref ID: KOURLABA2012	Less applicable and with more limitations compared to the included studies.
B. Bruggenjurgen, P. Lindgren, B. Ehlken, H. J. Rupprecht, and S. N. Willich. Long-term cost-effectiveness of clopidogrel in patients with acute coronary syndrome without ST-segment elevation in Germany. European Journal of Health Economics 8 (1):51-57, 2007. Ref ID: BRUGGENJURGEN2007	Less applicable and with more limitations compared to the included studies.
K. B. Gibler, H. A. Huskamp, M. S. Sabatine, S. A. Murphy, D. J. Cohen, and C. P. Cannon. Cost-effectiveness analysis of short-term clopidogrel therapy for ST elevation myocardial infarction. Critical Pathways in Cardiology 9 (1):14-18, 2010. Ref ID: GIBLER2010	Less applicable and with more limitations compared to the included studies.
B. M. Heeg, R. J. Peters, M. Botteman, and B. A. van Hout. Long-term clopidogrel therapy in patients receiving percutaneous coronary intervention. Pharmacoeconomics 25(9):769-782, 2007. Ref ID: HEEG2007A	Less applicable and with more limitations compared to the included studies.
S. J. Thurston, B. Heeg, Charro F. de, and Hout B. van. Cost-effectiveness of clopidogrel in STEMI patients in the Netherlands: a model based on the CLARITY trial. Curr.Med.Res.Opin. 26 (3):641-651, 2010. Ref ID: THURSTON2010	Less applicable and with more limitations compared to the included studies.
J. Chen, D. L. Bhatt, E. S. Dunn, C. Shi, J. J. Caro, E. M. Mahoney, S. Gabriel, J. D. Jackson, E. J. Topol, and D. J. Cohen. Cost-effectiveness of clopidogrel plus aspirin versus aspirin alone for secondary prevention of cardiovascular events: results from the CHARISMA trial. Value.Health. 12 (6):872-879, 2009. Ref ID: CHEN2009	Less applicable and with more limitations compared to the included studies.
C. Main, S. Palmer, S. Griffin, L. Jones, V. Orton, and M. Sculpher. Clopidogrel used in combination with aspirin compared with aspirin alone in the treatment of non-ST-segment-elevation acute coronary	Less applicable and with more limitations compared to the included studies.

Reference	Reason for exclusion
syndromes: a systematic review and economic evaluation. Health Technol.Assess. 8 (40):1-156, 2004.Main 2004 Ref ID: 3719	
P. Kolm, Y. Yuan, E. Veledar, S. R. Mehta, J. A. O'Brien, and W. S. Weintraub. Cost-effectiveness of clopidogrel in acute coronary syndromes in Canada: a long-term analysis based on the CURE trial. Can.J.Cardiol. 23(13):1037-1042, 2007. Ref ID: KOLM2007	Less applicable and with more limitations compared to the included studies.

K.2.4 Late initiation of antiplatelet therapy

Reference	Reason for exclusion
Chen J, Bhatt DL, Dunn ES et al. Cost-effectiveness of clopidogrel plus aspirin versus aspirin alone for secondary prevention of cardiovascular events: results from the CHARISMA trial. Value Health. 2009; 12(6):872-879. Ref ID: CHEN2009	USA analysis based on CVD subgroup of CHARISMA trial - a more applicable analysis based the same subgroup is available.

K.2.5 Beta-blocker vs. placebo

This section was partially updated in 2020. See www.nice.org.uk/guidance/ng185 for the 2020 evidence review.

Reference	Reason for exclusion
L. Goldman, S. T. Sia, E. F. Cook, J. D. Rutherford, and M. C. Weinstein. Costs and effectiveness of routine therapy with long-term beta-adrenergic antagonists after acute myocardial infarction. N.Engl.J.Med. 319 (3):152-157, 1988. Ref ID: 3764	Less applicable and with more limitations compared to the model developed in CG48.
G. Olsson, L.-A. Levin, and N. Rehnqvist. Economic consequences of postinfarction prophylaxis with beta blockers: cost effectiveness of metoprolol. BMJ 294 (6568):339-342, 1987. Ref ID: 3768	Less applicable and with more limitations compared to the model developed in CG48.

Appendix L: Cost-effectiveness analysis of interventions to increase uptake and adherence to cardiac rehabilitation programmes

L.1 Introduction

A model comparing the costs and effects of cardiac rehabilitation (CR) with no CR was developed in the previous guideline (CG48); the same model also assessed the cost effectiveness of some interventions (letters and telephone calls plus healthcare professional visits) aimed at increasing the uptake of CR programmes. As part of the update of CG48, a new model was prioritised and developed in order to include more recent evidence on the interventions analysed in CG48 and additional interventions aimed at increasing uptake and adherence of CR. Compared to the previous model, the new model includes more interventions and also considers the adherence to the CR programme in the base case analysis as well as the uptake.

L.2 Economic question

The aim of the model was to estimate the cost effectiveness of alternative interventions to increase the uptake and aherence of CR, including the combination of early initiation of CR with further specific interventions.

L.3 Methods

L.3.1 Model overview

L.3.1.1 Comparators

The decision on which strategies to model was made, in consultation with the GDG, on the basis of the availability of data on the efficacy of interventions to increase uptake and adherence of CR. The interventions compared are:

- Usual care (UC)
- Automatic referral (AR)
- CR Liaison (CRL)
- Automatic referral with a CR liaison (ARCRL)
- Personalised goal setting (PGS)
- Calls-Letters-Home visits (CLHV)
- Letters (L)
- Phone calls (PC)
- Early initiation of CR (EI)
- EI followed by automatic referral (EI + AR)
- EI followed by CR liaison (EI + CRL)
- EI followed by automatic referral with a CR liaison (EI + ARCRL)
- EI followed by personalised goal setting (EI + PGS)
- EI followed by Calls-Letters-Home visits (EI + CLHV)
- EI followed by letters (EI + L)
- EI followed by phone calls (EI + PC)

EI was combined with the rest of the interventions because the clinical evidence showed that it was the most effective option to increase uptake and adherence of CR; assessing the cost effectiveness of a combination of EI and other interventions was considered important by the GDG.

L.3.1.2 Population

The model considered a cohort of patients who had had a recent MI. The baseline characteristics of the patients in the model are those reported for the Cardiac Rehabilitation model from CG48 (see Appendix Q).

L.3.1.3 Time horizon, perspective, discount rates used

The time horizon is defined as a lifetime using lifetime costs and outcomes from CG48 model which were discounted using 3.5% discount rates on both costs and outcomes, as per the NICE reference case.[419] Intervention costs were updated and because they occur only once and are assumed to happen during the first year, they were discounted for subsequent years. The analysis is conducted from the National Health Service and Personal Social Service perspective.

L.3.2 Approach to modelling

A decision tree was built in TreeAge 2009® to calculate cost and effectiveness of interventions aimed at increasing uptake and adherence of CR programmes.

L.3.2.1 Model structure

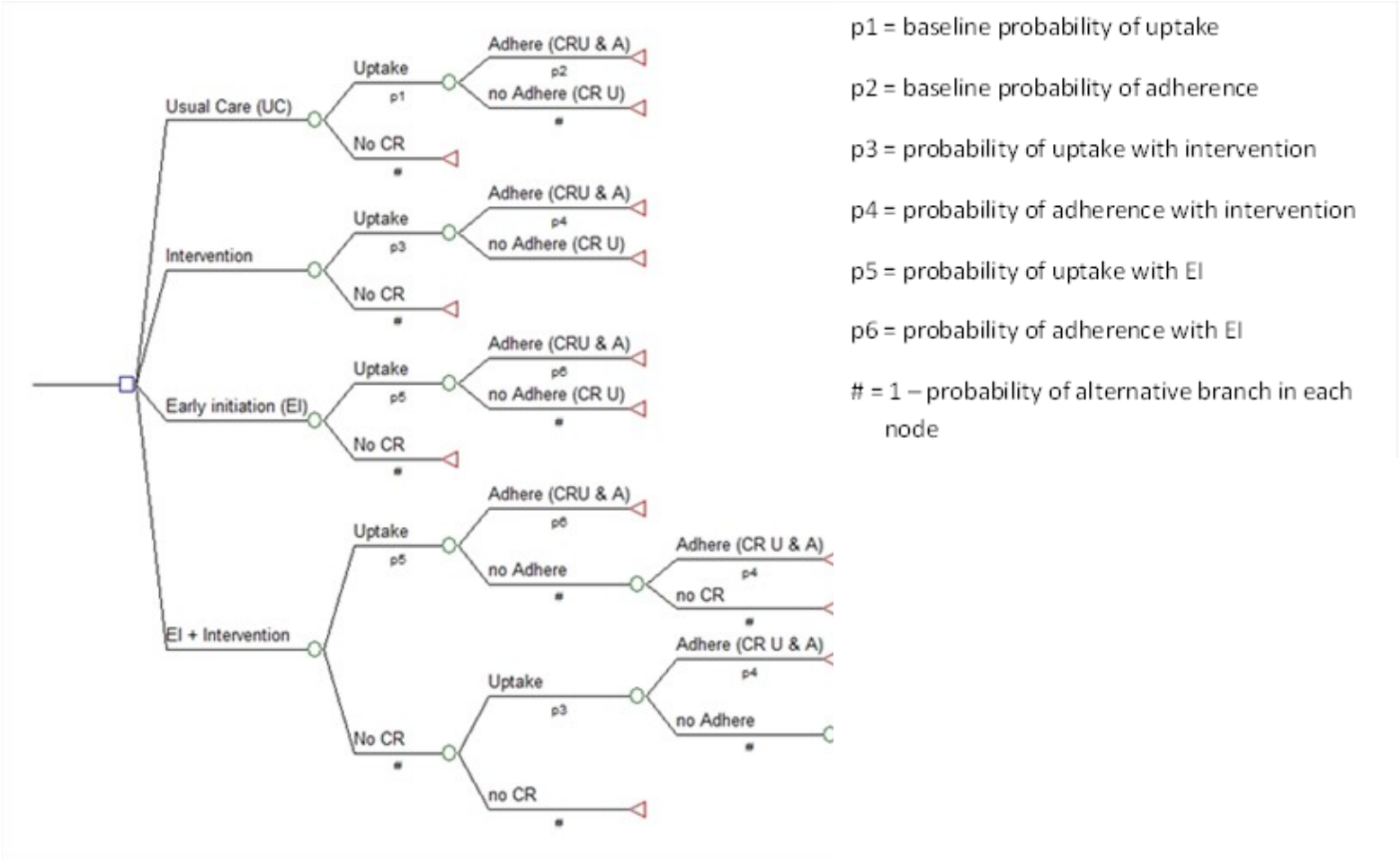
The decision tree compared different strategies as described above. A simplified structure of the decision tree is reported in Figure 282, where the branch called 'Intervention' represents any single intervention and 'EI+ Intervention' the combination of EI with one of the single interventions included in the model. Within each of the single interventions, individuals entering the model would either take up or not take up CR. Individuals who take up CR on the first place can either adhere to it or not. The probability of CR uptake and the following probability of CR adherence are determined by each strategy. In strategies where an additional intervention is added to EI, a structural assumption was made that when early initiation fails to achieve uptake or adherence, the second intervention is then implemented and it determines the second probability of either uptake or adherence.

The possible outcomes of each strategy are:

- CR uptake and adherence (CR U & A)
- No uptake of CR (no CR)
- CR uptake but no adherence (CR U)

Costs and QALYs are assigned to each one of these outcomes (see L.3.3.3 and L.3.3.4).

Figure 282: Simplified representation of the decision tree



Note: The branch named "Intervention" may refer to any of the individual interventions studied in the model (see L.3.1.1)

L.3.2.2 Uncertainty

The model was run probabilistically in order to take into account the uncertainty in the model inputs. In a probabilistic model, each parameter is assigned a distribution reflecting its uncertainty; random draws are then taken from each distribution, to calculate expected costs and QALYs. This process is repeated 10,000 times and a model result which represents an average of the simulations is computed.

One way sensitivity analyses were also conducted in order to test the robustness of model results to changes in key parameters.

Distributions were defined for all model parameters, except for the resource use and the unit costs of the interventions since there were no parameters to define the distribution for the former and the latter were deemed to be fixed. Statistical distributions were selected based on the nature of the data, so for example probabilities were given a beta distribution, which is bounded by zero and one (Table 169). Costs were assigned a gamma distribution because negative costs are not possible.

Table 169 - Types of distributions used in the model

Parameter	Type of distribution	Properties of distribution	Parameters for the distribution
Proportion and probabilities	Beta	Bounded on 0 – 1 interval. Derived from sample size, number of patients experiencing events	α = events β = sample size – α
Cost	Gamma	Bounded at 0. Derived from mean and standard error	α = (mean/SEM)2 λ = mean/SEM2
QALYs	Gamma	Bounded at 0. Derived from mean and standard error	α = (mean/SEM)2 λ = mean/SEM2
Odds Ratios (RR)	Lognormal	Bounded at 0. Derived from log (mean) and standard error.	μ = ln(OR) σ = SE(μ)

L.3.3 Model inputs

Model inputs were based on clinical evidence identified in the systematic review undertaken for the guideline, supplemented by additional data sources as required. Model inputs were validated with clinical members of the GDG.

L.3.3.1 Baseline transition probabilities

The baseline uptake rate of CR of a post MI patient following the usual care in the UK was obtained from the National Audit of Cardiac Rehabilitation.[413] The baseline adherence rates that would follow uptake were obtained from a health technology assessment about cardiac rehabilitation programmes in the UK[58] (see Table 170).

L.3.3.2 Relative effects of intervention

To obtain the relative effectiveness of the strategies included in the model, we used the studies identified by the clinical review conducted for this guideline (see Chapter 6 in the Full Guideline).

To derive probabilities of uptake that we could use for each strategy, we used both the baseline probabilities which represent the uptake and adherence probabilities for UC, and the relative risks of

each intervention vs. UC as explained below. The parameters thus calculated are reported in Table 170.

Probabilities of uptake could be calculated for each intervention 'int' as:

p_Uptake_int = p_baselineUptake_UC * RR_Uptake_Int

where

p_baselineUptake_UC is the baseline probability of taking up CR with usual care

RR_Uptake_Int is the relative risk of taking up CR with the intervention compared to usual care.

However, when running the model probabilistically, if the RR is particularly high, p_Uptake_int can take values above 1, inconsistently with the definition of probability which goes from 0 to 1.In order to keep the probabilities in the model between 0 and 1, we calculated the logarithm of the odds ratio (LogOR) and then transform it again into the natural scale by using the following approach:

1. We calculated the log odds of the control group from the study that informs the intervention effectiveness in our model:

LogOdds_control = Ln(p_control / (1 - p_control))

2. We calculated the log odds of the risk in the intervention group from the same study:

LogOdds_Int = Ln(p_Int / (1 - p_Int))

3. We calculated the log odds ratio from the parameters defined in step 1 and 2:

LogOR_Int = LogOdds_Int - LogOdds_control

4. We calculated the log odds of the baseline risk which is the probability in the usual care strategy in our model:

LogOdds_baseline_UC = Ln(p_baseline_UC / (1 - p_baseline_UC))

5. We calculated the log odds of the risk in the treatment group using the parameters defined in step 3 and 4:

LogOddsRisk_Int = LogOR_Int + LogOdds_baseline_UC

6. We transformed the risk in the treatment group from the log scale to the natural scale:

p_Int= Exp(LogOddsRisk_Int) / (1 + Exp(LogOddsRisk_Int))

We used this method to obtain probabilities of both uptake and adherence for each one of the interventions that we compare in the model.

To make the model probabilistic, we used the log normal distribution for the LogOR parameters using the mean and the SE of the LogOR. We calculated the SE of of the logOR as:

SE (log OR) = $\sqrt{\frac{1}{d1}+\frac{1}{h1}+\frac{1}{d0}+\frac{1}{h0}}$

Where

d1=number of events in the intervention group

h1 =number of no events in the intervention group

d0 = number of events in the control group

h0 = number of no events in the control group

The values obtained for these parameters are listed in Table 170.

Table 170: Probabilities and relative treatment effects of CR uptake and adherence

Parameter description	% of cases out of the total N		Relative Risk	LogOR	Distribution	Distribution parameters	Source
	Intervention	Control					
	Baseline probabilities						
Uptake	41%						National Audit of Cardiac Rehabilitation (Annual Statistical Report 2011. London: British Heart Foundation, 2011) [413]
Adherence	77%						Beswick2004 [58]
	Relative treatment effect						
	Personalised goal setting						
Uptake	45.5%	24%	1.90	1.012	Lognormal	μ = 0.97 σ = 0.28	Cossette2012 [125]
Adherence	51.5%	42.8%	1.29	0.362	Lognormal	μ = 0.35 σ = 0.15	Sniehotta2005 [549], Sniehotta2006 [548], Miller1988 [390] and Moore2006 [399]
	Automatic referral						
Uptake	49%	36.2%	1.35	0.541	Lognormal	μ = 0.52 σ = 0.18	Grace2007 [241]
Adherence	45.2%	34%	1.33	0.490	Lognormal	μ = 0.47 σ = 0.18	
	Automatic referral with a CR liaison						
Uptake	71.1%	27.9%	2.55	1.824	Lognormal	μ = 1.81 σ = 0.17	Grace2011 [240]
Adherence	81%	83%	0.98	-0.068	Lognormal	μ = -0.14 σ = 0.37	
	CR liaison						
Uptake	41.1	30.3%	1.36	0.507	Lognormal	μ = 0.48 σ = 0.21	Jolly1999 [295]
Adherence	77%						Data not available from studies. Assumed this

Parameter description	% of cases out of the total N		Relative Risk	LogOR	Distribution	Distribution parameters	Source
	Intervention	Control					
							intervention did not change adherence and applied the baseline adherence rate.
	Letters						
Uptake	86%	59.1%	1.46	1.595	Lognormal	μ = 1.45 σ = 0.54	Wyer2001 [622]
Adherence	94.6%	73.1%	1.29	2.226	Lognormal	μ = 1.86 σ = 0.85	
	Phone calls						
Uptake	24.4%	12%	2.04	1.019	Lognormal	μ = 0.86 σ = 0.56	Parry2009 [453]
Adherence	77%						Data not available from studies. Assumed this intervention did not change adherence and applied the baseline adherence rate.
	Calls-Letters-Home visits						
Uptake	76%	36.5%	2.08	1.748	Lognormal	μ = 1.71 σ = 0.28	Carroll2007 [94]
Adherence	76.6%	87.9%	0.87	-0.683	Lognormal	μ = -0.80 σ = 0.48	Pinto2011 [475]
	Early initiation of CR						
Uptake	77%	59%	1.50	0.827	Lognormal	μ = 3.92 σ = 0.39	Pack 2012[447]
Adherence	87.8%	33.5%	2.62	3.993	Lognormal	μ = 2.66 σ = 0.24	Parker2011 [452]

L.3.3.3 Health outcomes - QALYs

Health outcomes in this model were in the form of quality adjusted life years (QALYs). As already mentioned, there are three outcomes in this model:

i. The individual take up and adheres to CR (CR U & A).
ii. The individual takes up but does not adhere to CR (CR U).
iii. The individual does not take up CR (no CR).

Lifetime QALYs were taken from CG48 model on CR for the 'CR U & A' and 'no CR' outcomes; these were essentially the overall QALYs calculated in the model respectively for the CR strategy and for the no CR strategy. QALYs for the outcome 'CR U' could not be obtained from the CG48 model on CR, so an assumption was made that the QALYs associated with this outcome are an average between the QALYs of CRU & A and no CR. The rationale behind this assumption was that QALYs are highly dependent on the recurrence of cardiovascular events, and that these are driven by the attendance to CR. When running the model probabilistically, QALYs associated with uptake and adherence may take a lower value than QALYs associated with no CR. To avoid this inconsistency, we have set up these variables so that if the value sampled for QALYs of CR U & A is less than the value sampled for QALYs of no CR, then the former takes the same value of the latter (i.e. we assume they are at least equal).

In the CG48 model, individuals in the CR arm took up CR but not all of them adhered to it. Therefore the QALYs associated with the CR U & A outcome may be an underestimate.

Table 171: QALYs associated with possible outcomes of the model

	Point estimate	Probability distribution	Distribution parameters	Source
CR U & A	6.2	Gamma	Alpha = 78.45 Lambda = 12.65	CG48
CR U	5.94	NA	NA	Assumption: average between CR U & A and no CR
no CR	5.68	Gamma	Alpha = 201.64 Lambda = 35.5	CG48

L.3.3.4 Resource use and cost

Lifetime costs of patients in this model have mainly two components: the cost of the intervention implemented to increase uptake and adherence of CR (see Table 175) and the cost of CR itself. The model in CG48 assumed that a patient who takes up CR also adheres to it. The other strategy was that the patient never took up CR. We used the lifetime costs of CR and no CR respectively for the outcomes 'CR U & A' and for the outcome 'no CR'. As with the QALYs parameter, for patients who take up CR but do not adhere to it, we assumed that the costs associated with this outcome 'CR U' are an average between the costs of CRU & A and no CR (Table 172).

Table 172: Lifetime costs associated with possible outcomes of the model

	Point estimate	Probability distribution	Distribution parameters	Source
CR U & A	£9,450	Gamma	Alpha = 206.24 Lambda = 0.02	CG48
CR U	£7,405	NA	NA	Assumption: average

	Point estimate	Probability distribution	Distribution parameters	Source
				between CR U & A and no CR
no CR	£5,359	Gamma	Alpha = 325.64 Lambda = 0.06	CG48

The costs described above would include both the cost of CR and the costs of related cardiovascular events. The events considered in CG48 model were: myocardial infarctions, revascularisations including hospitalisation, and death by any cause. The six-month costs of these health states were made of different cost components: outpatient costs including monitoring and medications (£171); revascularisation (£8,676); six months subsequent to revascularisation (£500); MI (£4,448); subsequent MI (£500). It was assumed that death had no cost for the NHS.

The resources associated with each intervention to increase uptake and adherence compared in the model were obtained from the studies used to populate the effectiveness data (see Table 173). Unit costs were obtained from national published data where possible, however sometimes assumptions were required. All the unit costs involved in the interventions to increase uptake and adherence studied in the model can be found in Table 174.

Table 173: Resource use per component of interventions implemented to increase uptake and adherence to CR

Intervention components	Resources involved with each component	Units of resources
Personalised goal setting		
Individual planning session	Medical consultant; £ per contract hour	30 minutes
Booklet	Postage	1 unit
6 Diaries tailored to individual requirements	Administrative staff time	30 minutes
	Postage	1 unit
Automatic referral		
Information package	Administrative staff time	30 minutes
	Postage	1 unit
Automatic referral with a CR liaison		
Questionnaire mailing including a motivational cover letter, followed by thank you/reminder postcard	Administrative staff time	30 minutes
	Postage	1 unit
Replacement questionnaire sent to non-responding patients	Administrative staff time	30 minutes
	Postage	1 unit
Telephone contacts	National phone call by community nurse	30 minutes
	National phone call by nurse specialist (community) –– referred to as nurse practitioner in paper	15 minutes for 20% of patients [(a)]
	National phone call by nurse advanced;– referred to as nurse practitioner physiotherapist in paper	15 minutes for 10% of patients [(a)]
CR liaison		
On-going support group	Community nurse; £ per hour of patient-related work – referred to as	Two contacts of 10 minutes each for 30% of patients

Intervention components	Resources involved with each component	Units of resources
	practice nurse in paper	
Pre-discharge liaison contact	Nurse advanced; £ per hour of client contact cost – referred to as specialist cardiac liaison nurse in paper	10 minutes
	Community nurse; £ per hour of patient-related work – referred to as practice nurse in paper	10 minutes
	National phone call	10 minutes
Nurse support liaison contact	Nurse advanced; £ per hour of client contact cost – referred to as specialist cardiac liaison nurse in paper	Two contacts of 10 minutes each for 30% of patients
	Community nurse; £ per hour of patient-related work – referred to as practice nurse in paper	Two contacts of 10 minutes each for 30% of patients
	National phone call	10 minutes for 30% of patients
Letters		
Motivational Letters	Administrative staff time	30 minutes
	Postage	1 unit
Phone calls		
Training of peer volunteers	4 hours of training	1 peer volunteer was assumed to see 5 patients
Peer volunteer – patient contact	National phone call	360 minutes
Calls-Letters-Home visits		
Home visit	Nurse advanced; £ per hour of client contact cost – referred to as advanced practice nurse in paper	45 minutes
Phone calls nurse – patient	Nurse advanced; £ per hour of client contact cost – referred to as advanced practice nurse in paper	3 calls per patient of 15 minutes each
	National phone call	45 minutes
14 Tip sheets on exercise	Administrative time	30 minutes
14 Tip sheets on cardiovascular health	Administrative time	30 minutes
5 Feedback letters	Administrative time	30 minutes
Postage of sheets and letters	Postage	33 units
Early initiation of CR		
Consultation to give the patient education about CAD and CR orientation	Nurse advanced; £ per hour of client contact cost – referred to as cardiac rehabilitation specialist nurse in paper	30 minutes
	Medical consultant; £ per contract hour – Cardiologist	30 minutes
	Community physiotherapist; £ per hour	30 minutes for 20% of patients

Intervention components	Resources involved with each component	Units of resources
	Clinical psychologist; £ per hour of client contact	30 minutes for 20% of patients
	NHS community occupational therapist; £ per hour	15 minutes for 10% of patients
	Dietician; £ per hour	30 minutes for 20% of patients
	Administrative staff time	30 minutes
Nurse – patient telephone contact	Nurse advanced; £ per hour of client contact cost – referred to as cardiac rehabilitation specialist nurse in paper	15 minutes
	National phone call	15 minutes

(a) Based on GDG expert opinion.

Abbreviations: CAD = Coronary artery disease; CR = Cardiac rehabilitation.

Table 174: Unit costs for per component of interventions implemented to increase uptake and adherence to CR

Cost component	Unit cost	Source
Cost per hour of client contact – advanced nurse	£91	PSSRU2011[129]
Cost per contract hour – medical consultant	£162	PSSRU2011[129]
Cost per hour – community physiotherapist	£34	PSSRU2011[129]
Cost per hour of client contact – clinical psychologist	£135	PSSRU2011[129]
Cost per hour – occupational therapist	£34	PSSRU2011[129]
Cost per hour - dietician	£35	PSSRU2011[129]
Cost per hour – administrative staff	£28	Assumption that this unit cost is the same as in CG48
Cost of training of peer volunteers – per peer	£60	Assumed by the GDG
Expert patients programme	£289	PSSRU2011[129]
Postage costs	£0.40	Assumption that this unit cost is the same as in CG48
Cost per minute of national phone call	£0.04	Assumption that this unit cost is the same as in CG48

Based on the resource use estimates and the unit costs, we calculated the initial cost of the interventions per patient (Table 175).

Table 175: Cost per patient of interventions to increase uptake and adherence to CR

Name of intervention	Cost (£)
Usual care (UC)	-
Personalised goal setting (PGS)	£96
Automatic referral (AR)	£14
Automatic referral with a CR liaison (ARCRL)	£51
CR liaison (CRL)	£43
Letters (L)	£28
Phone calls (PC)	£26

Name of intervention	Cost (£)
Calls-Letters-Home visits (CLHV)	£194
Early initiation of CR (EI)	£185

L.3.4 Computations

The mean cost and effectiveness and the incremental monetary benefit of the compared strategies were calculated by developing a decision tree in TreeAge®2009.

To estimate deterministic results of the model, the point estimates of transition probabilities, lifetime costs and effects would be used in the computations. To obtain the probabilistic results, the distributions would be used instead to take 10,000 random samples and then calculate the mean and incremental results for the whole cohort.

L.3.4.1 Calculating QALYs

QALYs associated with each strategy depend on the strategy-specific proportions of patients that take up and adhere to CR and on the overall lifetime QALYs of each outcome (see Table 171).

Overall QALYs for a strategy i are calculated as:

$$\boldsymbol{QALYs_i = QALY\_CRU\&A_i + QALY\_noCR_i + QALY\_CRU_i}$$

where

QALY_CRU&Ai, QALY_noCRi, and QALY_CRUi represent the QALYs of each outcome of the model weighted by the proportion of patients in each outcome based on the effectiveness of strategy i.

L.3.4.2 Calculating costs

Costs in the model are a combination of lifetime costs of outcomes plus cost of each strategy.

Costs associated with each strategy depend on the strategy-specific proportions of patients that uptake and adhere to CR.

Overall costs for a strategy i are calculated as:

$$\boldsymbol{Cost_i = InitialCost_i + Cost\_CRU\&A_i + Cost\_noCR_i + Cost\_CRU_i}$$

where

$InitialCost_i$ is the cost of implementing strategy i, and Cost_CRU&Ai, Cost_noCRi, and Cost_CRUi represent the lifetime costs of each outcome of the model weighted by the proportion of patients in each outcome based on the effectiveness of strategy i.

In strategies that are a combination of EI plus an additional intervention, as explained in section L.3.2.1, the second intervention would only be implemented after a patient failed to uptake or adhere with EI only. Therefore, for those patients who do not fail to take up and adhere to CR, the cost of the strategy would always be only that of EI, and in patient that do not uptake or that uptake but do not adhere, it would be the cost of both interventions in strategies that are a combination of two interventions.

L.3.4.3 Calculating cost-effectiveness

The cost-effectiveness of a strategy is typically shown as a ratio of the incremental QALYs and incremental costs between two alternatives. However, often the ratio can be hard to interpret

because the costs and QALYs are in different units of measurement. Therefore it is common to convert QALYs into a monetary value to allow an estimate of cost effectiveness, known as net monetary benefit (NMB). This is calculated by multiplying the average QALYs for a comparator by the threshold cost per QALY value (£20,000 per QALY in our case)[420] and then subtracting the average costs. Cost-effectiveness results can also be expressed as incremental net monetary benefits of a comparator vs. baseline comparator. It would be calculated the same way but using incremental costs and QALYs of the comparator vs. the baseline instead of the average costs and QALYs of the comparator (see equation below). The decision rule then applied is that the comparator with the highest NMB is the most cost-effective option at the specified threshold. That is the option that provides the highest number of QALYs at an acceptable cost. For ease of computation the NMB is used to identify the optimal strategy in the probabilistic analysis simulations.

For a given strategy **i**

$$\boldsymbol{INMB_i = incQALYS_i \times \lambda - incCOST_i}$$

Where:

$incQALYS_i$ = total incremental QALYs of strategy i vs baseline comparator

λ = cost-effectiveness threshold

$incCOST_i$ = incremental cost of strategy i vs baseline comparator

The probabilistic analysis was run for 10,000 simulations. For each simulation, the NMB of each strategy was calculated and the most cost-effective option identified (that is, the one with the highest NMB), at a threshold of £20,000 per QALY gained.

The results of the probabilistic analysis were summarised in terms of mean discounted costs and QALYs with rank-probability plots, where cost effectiveness rankings were calculated for each strategy and the probability of a given treatment attaining a certain rank determined by the number of times the treatment achieved that rank in all the simulations, divided by the number of simulations. For example, suppose treatment 2 achieved rank 1, that is, it had the highest net benefit in 200 simulations, the probability of treatment 2 being ranked 1st is $\frac{200}{10000} = 2\%$

L.3.5 Sensitivity analyses

A one way sensitivity analysis varying costs and health benefits of CR uptake with no adherence was conducted.

The impact on the results of the following four different scenarios regarding QALYs gained from CR uptake with no adherence was assessed:

- QALY gain from CR U equal to that of no CR (5.68)
- QALY gain from CR U = 5.853
- QALY gain from CR U = 6.027
- QALY gain from CR U equal to that of CR U&A (6.2).

The impact on the results of the following four different scenarios regarding cost of CR uptake with no adherence was assessed:

- Cost of CR U equal to that of no CR (£5,359)
- Cost of CR U = £6,723

- Cost of CR U = £8,086
- Cost of CR U equal to that of CR U&A (£9,450).

Finally, a threshold analysis on the cost and QALYs of CR U was conducted. In this type of one-way sensitivity analysis, we vary the value of one variable at a time (the cost of CR U first, then the QALYs of CR U in this case) between a lower and upper limit until two strategies are equally cost-effective.

L.3.6 Model validation

The model was developed in consultation with the GDG; model structure, inputs and results were presented to and discussed with the GDG for clinical validation and interpretation.

The model was systematically checked by the health economist undertaking the analysis; this included inputting null and extreme values and checking that results were plausible given inputs. The model was peer reviewed by an external expert from the University of Sheffield; this included systematic checking of all the model calculations.

L.3.7 Interpreting results

This model will aid the GDG in making decisions on which intervention to recommend on the basis of cost-effectiveness.

L.4 Results

L.4.1 Base case

In the base case analysis, early initiation of CR followed by letters (EI+L) is the most cost effective strategy to increase uptake and adherence of CR. The results of the probabilistic analysis are reported in Table 176.

Table 176: Base case results – probabilistic analysis

Strategy	Costs (£)	QALYs	Net Monetary Benefit (£)	Incremental Net Monetary Benefit vs usual care (£)	Ranking (by NMB)
Usual Care (UC)	£6,842	5.915	£111,458	-	16
CR Liaison (CRL)	£7,337	5.983	£112,323	£865	15
Automatic referral (AR)	£7,404	6.001	£112,616	£1,158	14
Phone calls (PC)	£7,602	6.032	£113,038	£1,580	13
Personalised goal setting (PGS)	£7,857	6.062	£113,383	£1,925	12
Early initiation of CR (EI)	£7,994	6.071	£113,426	£1,968	11
Calls-Letters-Home visits (CLHV)	£8,126	6.088	£113,634	£2,176	10
Automatic referral with a CR liaison (ARCRL)	£8,288	6.134	£114,393	£2,935	8
Letters (L)	£8,315	6.142	£114,525	£3,067	7
EI + Phone calls (EI+PC)	£8,370	6.129	£114,210	£2,752	9
EI + CR liaison (EI+CRL)	£8,787	6.192	£115,053	£3,595	6

Strategy	Costs (£)	QALYs	Net Monetary Benefit (£)	Incremental Net Monetary Benefit vs usual care (£)	Ranking (by NMB)
EI + Automatic referral (EI+AR)	£8,792	6.195	£115,108	£3,650	5
EI + Personalised goal setting (EI+PGS)	£8,992	6.223	£115,468	£4,010	4
EI + Calls-Letters-Home visits (EI+CLHV)	£9,092	6.232	£115,548	£4,090	3
EI + Automatic referral with a CR liaison (EI+ARCRL)	£9,157	6.251	£115,863	£4,406	2
EI + Letters (EI+L)	£9,172	6.255	£115,928	£4,470	1

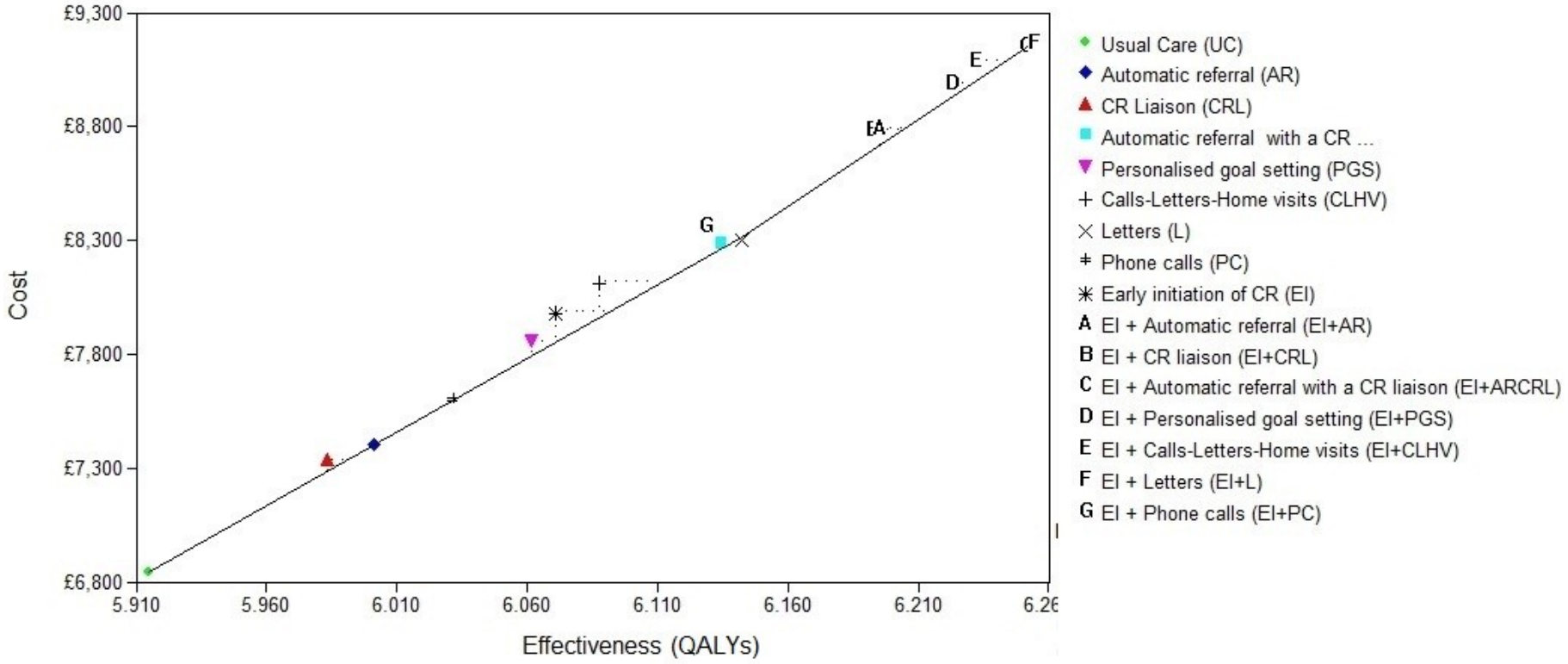
The strategies in Table 176 are sorted from lowest to highest cost. UC generates the least benefits and the least costs. EI +L is the strategy that generates the highest costs and the highest number of QALYs. Some interventions (EI+PC) are dominated as another intervention (Letters) is less costly and yields more QALYs.

The principle of extended dominance is applied in the incremental cost-effectiveness analysis to eliminate from consideration strategies that are less effective and more costly than a linear combination of two other strategies with which it is mutually exclusive. To establish which of the treatments with positive INMB is the most cost-effective, we can look at the graph in Figure 283.Here some interventions are above the line connecting all the interventions that are cost-effective. Although some interventions were not subject to simple dominance (i.e. more costly and less effective), the line representing their ICER is steeper than the line representing the ICER of the other interventions lying on the line. This shows that most of them are extendedly dominated with the exception of UC (the baseline), Letters, and EI + Letters (see Table 177).

Table 177: Results table without dominated options (simple or extended)

Strategy	Costs (£)	QALYs	ICER in full incremental analysis (£/QALY)
Usual Care (UC)	6,842	5.915	
Letters (L)	8,315	6.142	6,479
EI + Letters (EI+L)	9,172	6.255	7,624

Figure 283: Cost-effectiveness graph



The deterministic analysis revealed very similar results to the probabilistic results. Dominance and extended dominance were present for the same strategies. There were only relatively small variations in mean costs, effects, and net benefits. There is a reasonable linear relationship in the model and so the expected PSA results are very similar to the deterministic results.

L.4.2 Sensitivity analyses

One way sensitivity analyses were conducted on the cost of CR U (Table 178) and on the health benefits of CR U (Table 179); similarly a two-way sensitivity analysis was conducted varying both parameters simultaneously (Figure 284). The sensitivity analysis shows that results are stable with respect to the cost and QALY assumptions of the CR U outcome of the model within the possible range. When the QALYs of CR U are closer to the QALYs of CR U&A than to the QALYs of no CR, then EI+ARCRL becomes the most cost-effective strategy.

Table 178: One way sensitivity analysis - QALYs gained from CR U (without dominated options)

QALYs CR U	Strategy	Cost (£)	QALYs strategy	ICER (£/QALY)
5.680	Usual Care (UC)	6,843	5.844	-
	Letters (L)	8,376	6.051	7,400
	EI + Letters (EI+L)	9,202	6.143	9,015
5.853	Usual Care (UC)	6,843	5.860	-
	Letters (L)	8,376	6.060	7,799
	EI + Letters (EI+L)	9,202	6.150	9,367
6.027	Usual Care (UC)	6,843	5.880	-
	Automatic referral with a CR liaison (ARCRL)	8,322	6.070	7,734
	EI + Automatic referral with a CR liaison (EI+ARCRL)	9,176	6.150	10,545
6.200	Usual Care (UC)	6,843	5.890	-
	Calls-Letters-Home visits (CLHV)	8,149	6.090	6,555
	EI + Calls-Letters-Home visits (EI+CLHV)	9,108	6.160	14,415
	EI + Automatic referral with a CR liaison (EI+ARCRL)	9,176	6.160	15,219

When the costs of CR U are closer to the costs of no CR than to the costs of CR U&A, then EI+ARCRL becomes the most cost-effective strategy.

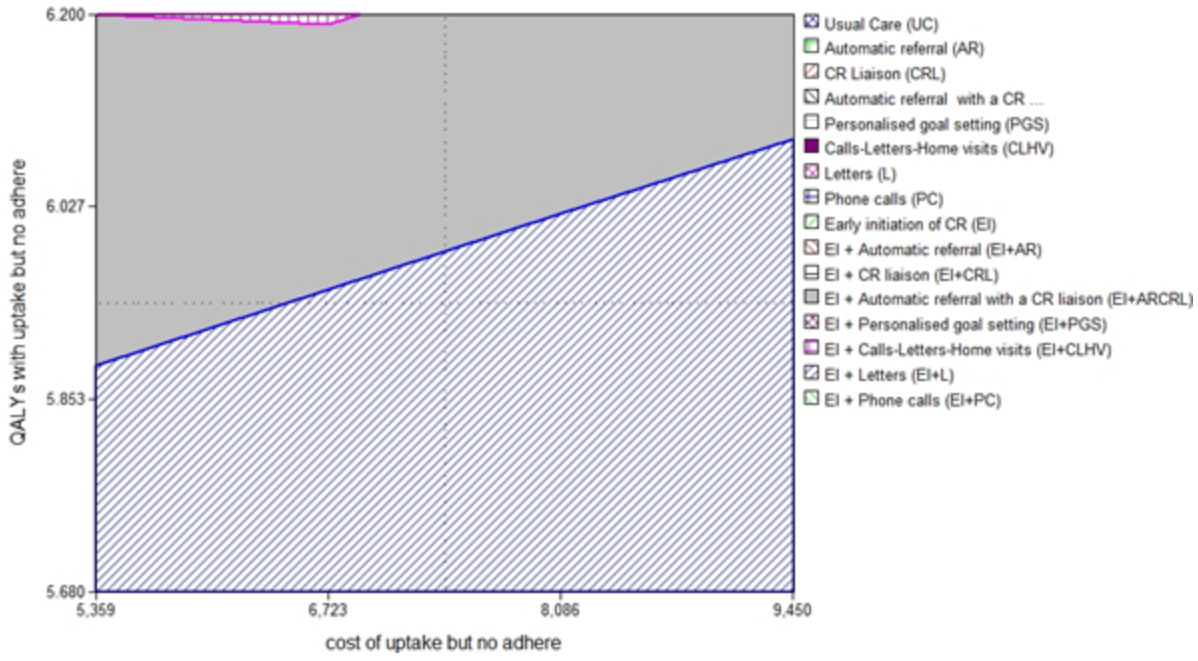
Table 179: One way sensitivity analysis - cost of CR U (without dominated options)

Cost of CR U	Strategy	Cost strategy (£)	QALYs	ICER (£/QALY)
£5,359	Usual Care (UC)	6651	5.870	
	Calls-Letters-Home visits (CLHV)	7502	6.010	6,020
	Automatic referral with a CR liaison (ARCRL)	7897	6.050	9,901
	EI + Automatic referral with a CR liaison (EI+ARCRL)	9007	6.140	12,087
	EI + Letters (EI+L)	9175	6.150	37,504
£6,723	Usual Care (UC)	6,779	5.870	
	Automatic referral with a CR liaison	8,180	6.050	7,727

Cost of CR U	Strategy	Cost strategy (£)	QALYs	ICER (£/QALY)
	(ARCRL)			
	EI + Automatic referral with a CR liaison (EI+ARCRL)	9,120	6.140	10,228
	EI + Letters (EI+L)	9,193	6.150	16,358
£8,086	Usual Care (UC)	6,908	5.870	
	Letters (L)	8,399	6.060	7,798
	EI + Letters (EI+L)	9,211	6.150	9,397
£9,450	Usual Care (UC)	7,036	5.870	
	Letters (L)	8,444	6.060	7,361
	EI + Letters (EI+L)	9,229	6.150	9,083

Figure 284**Error! Reference source not found.** shows that at a willingness to pay of £20,000 per QALY gained and accounting for the selected range of possible variations in costs and health benefits of CR U, the strategy that is in most cases cost effective is EI+L, followed by EI+ARCRL and in few instances, letters.

Figure 284: Two way sensitivity analysis of costs and QALYs of CRU



Two-way sensitivity analysis of costs and QALYs of uptake but no adherence. The grey and blue areas of the graph represent respectively the combinations of the two parameters where EI+ARCRL or EI+L is cost-effective. The pink area at the top of the graph is where Letters is the cost-effective intervention based on the combination of the two parameters.

The results of the threshold analysis on the cost and QALYs of CR U, assuming a willingness to pay of £20,000 per QALY gained (NICE2008A[419]), was:

- For cost of CR U:

    - Between £5359 and £6,488, the option with the highest net benefit is "EI + Automatic referral with a CR liaison (EI+ARCRL)".
    - Between £6,488 and £9450, the option with the highest net benefit is "EI + Letters (EI+L)".
- For QALYs of CR U:
    - Between 5.68 and 5.99 the option with the highest net benefit is "EI + Letters (EI+L)".
    - Between 5.99 and 6.20 the option with the highest net benefit is "EI + Automatic referral with a CR liaison (EI+ARCRL)".

L.5 Discussion

L.5.1 Summary of results

In the base case, EI+L is likely to be the most cost effective strategy to increase uptake and adherence to CR; however other strategies involving EI could possibly be cost-effective as well. In the base case incremental analysis, other interventions were either dominated or extendedly dominated by combinations of EI+L and letters. However, when looking at the ranking by NMB, dominated strategies such as EI+CLHV or EI+ARCRL could be cost-effective if EI+L is not an option. Generally, strategies involving EI ranked higher than strategies where EI is not contemplated.

In this model, interventions to increase uptake and adherence to CR are more costly the more effective they are. The reason is that by increasing uptake and adherence to CR, the cost of CR is added to the total costs of the strategy. The positive linear correlation between costs and effectiveness (the higher the QALYs the higher the costs) is evident from the cost-effectiveness graph in Figure 283: all the interventions between UC (baseline) and the most effective strategy (EI+L) lie on a straight line, which indicates this positive linear correlation. This also means that the cost of the intervention itself does not have a substantial impact on the overall cost-effectiveness but the main drivers of the model are the probabilities of uptake and adherence.

L.5.2 Limitations and interpretation

The results of the model need to be treated with caution due to some limitations and assumptions. QALYs for the outcome ‘CR U’ could not be obtained from the CG48 model, so an assumption was made that the QALYs associated with this outcome are an average between the QALYs of CRU & A and no CR. As with the QALYs parameter, for patients who take up CR but do not adhere to it, we assumed that the costs associated with this outcome ‘CR U’ are an average between the costs of CRU & A and no CR. Nevertheless, the sensitivity analyses conducted on these parameters should account for that source of uncertainty and allow for a valid interpretation of the results of this model.

We also assumed that the effectiveness of interventions to increase uptake and adherence to CR observed in independent studies could be combined in sequences of interventions without affecting the effectiveness of the second intervention (e.g. in the sequence EI + L, the effectiveness of letters at increasing uptake and/or adherence to CR in patients that did not attend in the same place, is assumed to be the same as in letters alone). This assumption could be an overestimation of the effectiveness of the strategies that are a sequence of two interventions to increase uptake and adherence to CR.

Another limitation of our model is that interventions are compared in a non-randomised setting and therefore the populations on which the clinical data are based on are likely to have some differences.

L.5.3 Generalisability to other populations/settings

The trial evidence that the model is based on included relatively few older (>65) or black patients, so the results may not be reliable for these groups.

L.5.4 Comparisons with published studies

There is no comparative cost effectiveness data on interventions to increase uptake and adherence of cardiac rehabilitation. This is the first economic evaluation to assess the cost effectiveness of different interventions, and sequences of interventions, to increase uptake and adherence of CR.

L.5.5 Conclusion/evidence statement

One original cost-effectiveness analysis suggested that early initiation followed by letters may be the most cost-effective intervention for increasing uptake and adherence of cardiac rehabilitation following MI. Early initiation increases both costs and QALYs compared, however this is within the £20,000/QALY threshold. This evidence is directly applicable with potentially serious limitations.

L.5.6 Implications for future research

Studies that addressed the effectiveness of different sequences of interventions at increasing uptake and subsequent adherence to CR would be of great value to reduce one of the main sources of uncertainty of this model.

Appendix M: Unit costs

Table 180: Unit costs for ACE inhibitors

Drug	Prep.	Mg/unit	Units /pack	Cost/ pack (p)	Cost/ unit (£)	Cost/mg (£)	Units /day	Cost/ day	Cost/year	Costing notes	Cat.	Brand	Source
Captopril	Tablets	50	56	159	£0.03	£0.0006	3	£0.09	£31.09	Secondary prevention dose (there are also tablets of 12.5 and 25 mg)	M (a)		Drug tariff June 2012
Cilazapril	Tablets	1	30	607	£0.20	£0.2023	1	£0.20	£73.85	Heart failure (adjunct) - 1 or 2.5 mg; 5 mg max	C (b)	Vascace	Drug tariff June 2012
	Tablets	2.5	28	720	£0.26	£0.1029	1	£0.26	£93.86	Heart failure (adjunct) - 1 or 2.5 mg; 5 mg max	C(b)	Vascace	
	Tablets	5	28	1251	£0.45	£0.0894	1	£0.45	£163.08	Heart failure (adjunct) - 1 or 2.5 mg; 5 mg max	C(b)	Vascace	
Enalapril	Tablets	10	28	99	£0.04	£0.0035	2	£0.07	£25.81	Heart failure (adjunct)	M(a)		Drug tariff June 2012
	Tablets	20	28	112	£0.04	£0.0020	2	£0.08	£29.20	Heart failure (adjunct)	M(a)		
Fosinopril sodium	Tablets	20	28	349	£0.12	£0.0062	2	£0.25	£90.99	Heart failure (adjunct)	M(a)		
Imidapril hydrochloride	Tablets	10	28	722	£0.26	£0.0258	1	£0.26	£94.12	Essential hypertension	C(b)	Tanatril	Drug tariff June 2012

Drug	Prep.	Mg/unit	Units /pack	Cost/ pack (p)	Cost/ unit (£)	Cost/mg (£)	Units /day	Cost/ day	Cost/year	Costing notes	Cat.	Brand	Source
	Tablets	20	28	867	£0.31	£0.0155	1	£0.31	£113.02	Essential hypertension	C(b)	Tanatril	
Lisinopril	Tablets	5	28	93	£0.03	£0.0066	1	£0.03	£12.12	Secondary prevention dose	M(a)		Drug tariff June 2012
	Tablets	10	28	99	£0.04	£0.0035	1	£0.04	£12.91	Secondary prevention dose	M(a)		
Moexipril Hydrochloride	Tablets	7.5	28	604	£0.22	£0.0288	1	£0.22	£78.74	Essential hypertension (max dose of 30 mg per day)	-	Perdix	Not in drug tariff. BNF 63 (Mar 2012)
		15	28	696	£0.25	£0.0166	1	£0.25	£90.73	Essential hypertension (max dose of 30 mg per day)	-	Perdix	
Perindopril erbumine	Tablets	2	30	166	£0.06	£0.0277	1	£0.06	£20.20	Secondary prevention dose	M(a)		Drug tariff June 2012
	Tablets	4	30	176	£0.06	£0.0147	1	£0.06	£21.41	Secondary prevention dose	M(a)		
	Tablets	8	30	192	£0.06	£0.0080	1	£0.06	£23.36	Secondary prevention dose	M(a)		
Perindopril arginine	Tablets	2.5	30	443	£0.15	£0.0591	1	£0.15	£53.90	Secondary prevention dose	C(b)	Coversyl arginine	Drug tariff June 2012
	Tablets	5	30	628	£0.21	£0.0419	1	£0.21	£76.41	Secondary prevention dose	C(b)	Coversyl arginine	
	Tablets	10	30	1065	£0.36	£0.0355	1	£0.36	£129.58	Secondary prevention dose	C(b)	Coversyl arginine	
Quinapril	Tablets	5	28	284	£0.10	£0.0203	1	£0.10	£37.02	Heart failure (adjunct)	A (c)		Drug tariff June 2012
	Tablets	10	28	221	£0.08	£0.0079	1	£0.08	£28.81	Heart failure	A(c)		

Drug	Prep.	Mg/unit	Units /pack	Cost/ pack (p)	Cost/ unit (£)	Cost/mg (£)	Units /day	Cost/ day	Cost/year	Costing notes	Cat.	Brand	Source
										(adjunct)			
	Tablets	20	28	221	£0.08	£0.0039	1	£0.08	£28.81	Heart failure (adjunct)	M(a)		
	Tablets	40	28	270	£0.10	£0.0024	1	£0.10	£35.20	Heart failure (adjunct)	M(a)		
Ramipril	Tablets	2.5	28	123	£0.04	£0.0176	2	£0.09	£32.07	Secondary prevention dose	M(a)		Drug tariff June 2012
	Tablets	5	28	139	£0.05	£0.0099	2	£0.10	£36.24	Secondary prevention dose	M(a)		
	Capsules	2.5	28	114	£0.04	£0.0163	2	£0.08	£29.72	Secondary prevention dose	M(a)		
	Capsules	5	28	122	£0.04	£0.0087	2	£0.09	£31.81	Secondary prevention dose	M(a)		
Ramipril with felodipine	Tablets	5.00	28	1613	£0.58	£0.1152	1	£0.58	£210.27	Hypertension in patients stabilised on the individual components in the same proportions	C(b)	Triapin	Drug tariff June 2012
Trandolapril	Capsules	0.5	14	149	£0.11	£0.2129	1	£0.11	£38.85	Secondary prevention dose	A(c)		Drug tariff June 2012
	Capsules	1	28	679	£0.24	£0.2425	1	£0.24	£88.51	Secondary prevention dose	A(c)		
	Capsules	2	28	246	£0.09	£0.0439	1	£0.09	£32.07	Secondary prevention dose	M(a)		
	Capsules	4	28	1169	£0.42	£0.1044	1	£0.42	£152.39	Secondary prevention dose	A(c)		

Source: Drug Tariff June 2012 (except for Moexipril Hydrochloride)

Maintenance doses are used.

(a) Category M - Drugs which are readily available. Broken Bulk may be claimed for those products whose smallest pack size has a price greater than or equal to £50, if necessary. The Secretary of State determines the price based on information submitted by manufacturers. The following pack sizes are considered when calculating Category M prices:

· for tablets and capsules, all prescription only medicine pack sizes up to and including 120 unit doses;

· for liquids and some creams (including special containers) up to and including 500ml/500g.

Where a pack size for a product listed in this Part exceeds the quantities stated above, the listed pack size is the only pack size considered when calculating the price.

(b) Category C - Drugs which are not readily available as a generic, where the price is based on a particular proprietary product, manufacturer or as the case may be supplier. Endorsement of pack size is required if more than one pack is listed. Broken Bulk may be claimed, if necessary. Where the price of the product is based upon a non-proprietary product the price listed in this Part of the Drug Tariff is indicative of the price determined and in this case the Secretary of State determines the price to be the price listed by the manufacturer or as the case may be supplier on or before the 8th of the month being reimbursed.

(c) Category A - Drugs which are readily available. Broken Bulk may be claimed for those products whose smallest pack size has a price greater than or equal to £50, if necessary. The prices listed in this Part of the Drug Tariff are indicative of the prices determined by the Secretary of State for Health. The following pack sizes are considered when calculating Category A prices:

· for tablets and capsules, all prescription only medicine pack sizes up to and including 120 unit doses.

· for liquids and some creams (including special containers) up to and including 500ml/500g.

Where a pack size for a product listed in this Part exceeds the quantities stated above, the listed pack size is the only pack size considered when calculating the price. The Secretary of State determines the prices for Category A drugs to be the average of the price calculated for the pack size listed in the Drug Tariff weighted by the following four manufacturers and suppliers; AAH, Alliance Healthcare (Distribution) Ltd, Teva UK and Actavis on or before the 8th of the month being reimbursed. In the weighted formula, AAH and Alliance Healthcare (Distribution) Ltd prices have a weighting of 2, the prices from the other suppliers have a weighting of one.

Table 181: Unit costs for ARBs

Drug	Prep.	Mg/unit	Units /pack	Cost/ pack (p)	Cost/ unit (£)	Cost/mg (£)	Units /day	Cost/ day	Cost/year	Costing notes	Cat.	Brand	Source
Candesartan cilexetil	Tablets	4	7	388	£0.55	£0.1386	1	£0.55	£202.31	Heart failure	C(b)	Amias	Drug tariff June 2012
	Tablets	4	28	978	£0.35	£0.0873	1	£0.35	£127.49	Heart failure	C(b)	Amias	
	Tablets	8	28	989	£0.35	£0.0442	1	£0.35	£128.92	Heart failure	C(b)	Amias	
	Tablets	16	28	1272	£0.45	£0.0284	1	£0.45	£165.81	Heart failure	C(b)	Amias	
	Tablets	32	28	1613	£0.58	£0.0180	1	£0.58	£210.27	Heart failure	C(b)	Amias	
Eprosartan	Tablets	300	28	731	£0.26	£0.0009	1	£0.26	£95.29	Hypertension	C(b)	Teveten	Drug tariff June 2012
	Tablets	400	56	1577	£0.28	£0.0007	2	£0.56	£205.57	Hypertension	C(b)	Teveten	
	Tablets	600	28	1431	£0.51	£0.0009	1	£0.51	£186.54	Hypertension	C(b)	Teveten	
Irbesartan	Tablets	75	28	969	£0.35	£0.0046	1	£0.35	£126.32	Hypertension	C(b)	Aprovel	Drug tariff

Drug	Prep.	Mg/unit	Units /pack	Cost/ pack (p)	Cost/ unit (£)	Cost/mg (£)	Units /day	Cost/ day	Cost/year	Costing notes	Cat.	Brand	Source
	Tablets	150	28	1184	£0.42	£0.0028	1	£0.42	£154.34	Hypertension	C(b)	Aprovel	June 2012
	Tablets	300	28	1593	£0.57	£0.0019	1	£0.57	£207.66	Hypertension	C(b)	Aprovel	
Losartan potassium	Tablets	12.5	28	623	£0.22	£0.0178	1	£0.22	£81.21	Hypertension (including reduction of stroke risk in hypertension with left ventricular hypertrophy); chronic heart failure when ACE inhibitors are unsuitable or contra-indicated	A(c)**Error! Reference source not found.**		Drug tariff June 2012
	Tablets	25	28	109	£0.04	£0.0016	1	£0.04	£14.21	Hypertension (including reduction of stroke risk in hypertension with left ventricular hypertrophy); chronic heart failure when ACE inhibitors are unsuitable or contra-indicated	M(a)		
	Tablets	50	28	122	£0.04	£0.0009	1	£0.04	£15.90	Hypertension	M(a)		

Drug	Prep.	Mg/unit	Units /pack	Cost/ pack (p)	Cost/ unit (£)	Cost/mg (£)	Units /day	Cost/ day	Cost/year	Costing notes	Cat.	Brand	Source
										(including reduction of stroke risk in hypertension with left ventricular hypertrophy); chronic heart failure when ACE inhibitors are unsuitable or contra-indicated			
Olmesartan medoxomil	Tablets	10	28	1095	£0.39	£0.0391	1	£0.39	£142.74	Hypertension	C(b)	Olmetec	Drug tariff June 2012
	Tablets	20	28	1295	£0.46	£0.0231	1	£0.46	£168.81	Hypertension	C(b)	Olmetec	
	Tablets	40	28	1750	£0.63	£0.0156	1	£0.63	£228.13	Hypertension	C(b)	Olmetec	
Telmisartan	Tablets	80	28	1700	£0.61	£0.0076	1	£0.61	£221.61	Secondary prevention dose	C(b)	Micardis	Drug tariff June 2012
Valsartan	Tablets	40	7	295	£0.42	£0.0105	1	£0.42	£153.82	Myocardial infarction with left ventricular failure or left ventricular systolic dysfunction (adjunct); heart failure when ACE inhibitors cannot be used, or in conjunction	A(c)		Drug tariff June 2012

Drug	Prep.	Mg/unit	Units /pack	Cost/ pack (p)	Cost/ unit (£)	Cost/mg (£)	Units /day	Cost/ day	Cost/year	Costing notes	Cat.	Brand	Source
										with an ACE inhibitor when a beta-blocker cannot be used			
	Capsules	40	28	408	£0.15	£0.0036	2	£0.29	£106.37	Myocardial infarction with left ventricular failure or left ventricular systolic dysfunction (adjunct); heart failure when ACE inhibitors cannot be used, or in conjunction with an ACE inhibitor when a beta-blocker cannot be used	M(a)		
	Tablets	160	28	1841	£0.66	£0.0041	2	£1.32	£479.98	Myocardial infarction with left ventricular failure or left ventricular systolic dysfunction (adjunct); heart failure when ACE inhibitors cannot be used,	C(b)	Aspire Pharma Ltd	

Drug	Prep.	Mg/unit	Units /pack	Cost/ pack (p)	Cost/ unit (£)	Cost/mg (£)	Units /day	Cost/ day	Cost/year	Costing notes	Cat.	Brand	Source
										or in conjunction with an ACE inhibitor when a beta-blocker cannot be used			
	Capsules	160	28	527	£0.19	£0.0012	2	£0.38	£137.40	Myocardial infarction with left ventricular failure or left ventricular systolic dysfunction (adjunct); heart failure when ACE inhibitors cannot be used, or in conjunction with an ACE inhibitor when a beta-blocker cannot be used	M(a)		

Source: Drug Tariff June 2012

Maintenance doses are used.

(a) Category M - Drugs which are readily available. Broken Bulk may be claimed for those products whose smallest pack size has a price greater than or equal to £50, if necessary. The Secretary of State determines the price based on information submitted by manufacturers. The following pack sizes are considered when calculating Category M prices:
· for tablets and capsules, all prescription only medicine pack sizes up to and including 120 unit doses;
· for liquids and some creams (including special containers) up to and including 500ml/500g.
Where a pack size for a product listed in this Part exceeds the quantities stated above, the listed pack size is the only pack size considered when calculating the price.

(b) Category C - Drugs which are not readily available as a generic, where the price is based on a particular proprietary product, manufacturer or as the case may be supplier. Endorsement of pack size is required if more than one pack is listed. Broken Bulk may be claimed, if necessary. Where the price of the product is based upon a non-proprietary product the price listed in

this Part of the Drug Tariff is indicative of the price determined and in this case the Secretary of State determines the price to be the price listed by the manufacturer or as the case may be supplier on or before the 8th of the month being reimbursed.

(c) Category A - Drugs which are readily available. Broken Bulk may be claimed for those products whose smallest pack size has a price greater than or equal to £50, if necessary. The prices listed in this Part of the Drug Tariff are indicative of the prices determined by the Secretary of State for Health. The following pack sizes are considered when calculating Category A prices:
· for tablets and capsules, all prescription only medicine pack sizes up to and including 120 unit doses.
· for liquids and some creams (including special containers) up to and including 500ml/500g.

Where a pack size for a product listed in this Part exceeds the quantities stated above, the listed pack size is the only pack size considered when calculating the price. The Secretary of State determines the prices for Category A drugs to be the average of the price calculated for the pack size listed in the Drug Tariff weighted by the following four manufacturers and suppliers; AAH, Alliance Healthcare (Distribution) Ltd, Teva UK and Actavis on or before the 8th of the month being reimbursed. In the weighted formula, AAH and Alliance Healthcare (Distribution) Ltd prices have a weighting of 2, the prices from the other suppliers have a weighting of one.

Table 182: Antiplatelet and anticoagulant drug costs

Drug	Preparation	Mg/ unit	Units / pack	Cost/ pack (p)	Cost/ unit (£)	Units/ day	Cost/ day	Cost/year	Costing notes	Cat.	Brand
Aspirin	Dispersible tablets	75	28	78	£0.03	1	£0.03	£10.17	SP dose	M(a)	
	Dispersible tablets	75	100	96	£0.01	1	£0.01	£3.50	SP dose	M(a)	
	Gastro-resistant tablets	75	28	96	£0.03	1	£0.03	£12.51	SP dose	M(a)	
	Gastro-resistant tablets	75	56	110	£0.02	1	£0.02	£7.17	SP dose	M(a)	
	Tablets	75	28	82	£0.03	1	£0.03	£10.69	SP dose	C(b)	Alissa Healthcare Research Ltd
	Powder	250	1	774	£7.74	0.3	£2.32	£847.53	SP dose	C(b)	J M Loveridge Ltd
Clopidogrel	Tablets	75	30	218	£0.07	1	£0.07	£26.52	SP dose	M(a)	
Prasugrel	Tablets	10	28	4756	£1.70	1	£1.70	£619.98	>60kg SP dose	C(b)	Efient

Drug	Preparation	Mg/ unit	Units / pack	Cost/ pack (p)	Cost/ unit (£)	Units/ day	Cost/ day	Cost/year	Costing notes	Cat.	Brand
	Tablets	5	28	4756	£1.70	1	£1.70	£619.98	<60kg or >75 SP dose	C(b)	Efient
Ticagrelor	Tablets	90	56	5460	£0.98	2	£1.95	£711.75	SP dose	C(b)	Brilique
Warfarin	Tablets	1	28	84	£0.03	1	£0.03	£10.95	1mg/day (typical dose 3-9mg)	M(a)	
	Tablets	3	28	88	£0.03	1	£0.03	£11.47	3mg/day (typical dose 3-9mg)	M(a)	
	Tablets	0.5	28	170	£0.06	1	£0.06	£22.16	0.5mg/day (typical dose 3-9mg)	M(a)	
	Tablets	5	28	91	£0.03	1	£0.03	£11.86	5mg/day (typical dose 3-9mg)	M(a)	
Dabigatran	Capsules	75	10	1260	£1.26	1	£1.26	£459.90	75mg/day	-	
	Capsules	75	60	7560	£1.26	1	£1.26	£459.90	75mg/day	-	
	Capsules	110	10	1260	£1.26	2	£2.52	£919.80	Standard VTE dose; AF dose for >80y, high risk of bleeding, mild renal impairment or receiving conc. verapamil,	-	
	Capsules	110	60	7560	£1.26	2	£2.52	£919.80	Standard VTE dose	-	
	Capsules	150	60	7560	£1.26	1	£1.26	£459.90	VTE dose <75y or conc. amiodarone or verapamil	-	
	Capsules	150	60	7560	£1.26	2	£2.52	£919.80	Standard AF dose	-	
Rivaroxaban	Tablets	10	30	6300	£2.10	1	£2.10	£766.50	VTE dose	C(b)	Xarelto
	Tablets	15	28	5880	£2.10	1	£2.10	£766.50	15mg/day	C(b)	Xarelto
	Tablets	20	28	5880	£2.10	1	£2.10	£766.50	20mg/day	C(b)	Xarelto
Apixaban	Tablets	2.5	10	1715	£1.72	2	£3.43	£1,251.95	VTE dose	-	Eliquis
	Tablets	2.5	20	3430	£1.72	2	£3.43	£1,251.95	VTE dose	-	Eliquis
	Tablets	2.5	60	10290	£1.72	2	£3.43	£1,251.95	VTE dose	-	Eliquis

Source: Drug Tariff June 2012; where not listed (dabigatran and apixaban) BNF 63.

(a) Maintenance doses are used.

Table 183: Unit costs for beta-blockers

Drug (b)	Preparation	Mg/ unit	Units /pack	Cost/ pack (£)	Cost/unit (£)	Units/ day	Cost/ day	Cost/year	Costing notes	Cat.
Propranolol	Tablets	40	28	0.89	£0.03	4	£0.13	£46	Secondary prevention dose	M(c)
	Tablets	80	28	1.18	£0.04	2	£0.08	£31	Secondary prevention dose	M(c)
Acebutolol	Tablets	200	56	19.18	£0.34	2	£0.69	£250	Hypertension	C (d)
	Tablets	400	28	19.59	£0.70	1	£0.70	£255	Hypertension	A(e)
Atenolol	Tablets	100	28	0.88	£0.03	1	£0.03	£12	Secondary prevention dose	M(c)
Bisoprolol	Tablets	10	28	1.27	0.05	1	0.05	£17	Secondary prevention dose	M(c)
Carvedilol	Tablets	12.5	28	1.67	£0.06	1	£0.06	£22	Hypertension	M(c)
	Tablets	25	28	1.87	£0.07	1	£0.07	£24	Hypertension	M(c)
	Tablets	25	28	1.87	£0.07	2	£0.13	£49	Hypertension	M(c)
Celiprolol	Tablets	200	28	4.85	£0.17	1	£0.17	£63	Hypertension	M(c)
	Tablets	400	28	17.41	£0.62	1	£0.62	£227	Hypertension	M(c)
Co-tenidone	Tablets	50	28	1.46	£0.05	1	£0.05	£19	Hypertension	M(c)
	Tablets	100	28	1.60	£0.06	1	£0.06	£21	Hypertension	M(c)
Esmolol (a)	-	-	-	-	-	-	-	-	-	-
Labetalol Hydrochloride	Tablets	100	56	8.76	£0.16	2	£0.31	£114	Hypertension	M(c)
	Tablets	200	56	11.99	£0.21	2	£0.43	£156	Hypertension	M(c)
	Tablets	400	56	19.64	£0.35	2	£0.70	£256	Hypertension	A (f)
Metoprolol	Tablets	100	28	1.42	£0.05	1	£0.05	£19	Hypertension	M(c)

Drug (b)	Preparation	Mg/ unit	Units /pack	Cost/ pack (£)	Cost/u nit (£)	Units/ day	Cost/ day	Cost/year	Costing notes	Cat.
Tartrate	Tablets	100	28	1.42	£0.05	2	£0.10	£37	Hypertension	M(c)
	Tablets	100	28	1.42	£0.05	4	£0.20	£74	Hypertension	M(c)
Nadolol	Tablets	80	28	5.00	£0.18	1	£0.18	£65	Hypertension	C(d)
	Tablets	80	28	5.00	£0.18	2	£0.36	£130	Hypertension	C(d)
	Tablets	80	28	5.00	£0.18	3	£0.54	£196	Hypertension	C(d)
	Tablets	80	28	5.00	£0.18	4	£0.71	£261	Hypertension	C(d)
Nebivolol	Tablets	5	28	2.32	£0.08	0.5	£0.04	£15	Hypertension	M(c)
	Tablets	5	28	2.32	£0.08	1	£0.08	£30	Hypertension	M(c)
Oxprenolol	Tablets	40	56	3.73	£0.07	2	£0.13	£49	Hypertension	A(f)
	Tablets	80	56	6.20	£0.11	2	£0.22	£81	Hypertension	C(d)
Pindolol	Tablets	5	100	10.45	£0.10	3	£0.31	£114	Hypertension	C(d)
	Tablets	5	100	10.45	£0.10	6	£0.63	£229	Hypertension	C(d)
Sotalol	Tablets	80	56	1.91	£0.03	2	£0.07	£25	Arrhythmias	C(d)
	Tablets	160	28	3.54	£0.13	2	£0.25	£92	Arrhythmias	A(f)
Timolol	Tablets	10	30	2.08	£0.07	1	£0.07	£25	Secondary prevention dose	C(d)
	Tablets	10	30	2.08	£0.07	2	£0.14	£51	Secondary prevention dose	C(d)

Source: Drug tariff July 2012 [424]

(a) Cost not reported in the drug tariff and could not be calculated from BNF

(b) Maintenance doses are used.

(c) Category M - Drugs which are readily available. Broken Bulk may be claimed for those products whose smallest pack size has a price greater than or equal to £50, if necessary. The Secretary of State determines the price based on information submitted by manufacturers. The following pack sizes are considered when calculating Category M prices:

- *for tablets and capsules, all prescription only medicine pack sizes up to and including 120 unit doses;*
- *for liquids and some creams (including special containers) up to and including 500ml/500g.*

Where a pack size for a product listed in this Part exceeds the quantities stated above, the listed pack size is the only pack size considered when calculating the price.

(d) Category C - Drugs which are not readily available as a generic, where the price is based on a particular proprietary product, manufacturer or as the case may be supplier. Endorsement of pack size is required if more than one pack is listed. Broken Bulk may be claimed, if necessary. Where the price of the product is based upon a non-proprietary product the

price listed in this Part of the Drug Tariff is indicative of the price determined and in this case the Secretary of State determines the price to be the price listed by the manufacturer or as the case may be supplier on or before the 8th of the month being reimbursed.

(e) Category A - Drugs which are readily available. Broken Bulk may be claimed for those products whose smallest pack size has a price greater than or equal to £50, if necessary. The prices listed in this Part of the Drug Tariff are indicative of the prices determined by the Secretary of State for Health. The following pack sizes are considered when calculating Category A prices:

- *for tablets and capsules, all prescription only medicine pack sizes up to and including 120 unit doses.*
- *for liquids and some creams (including special containers) up to and including 500ml/500g.*

Where a pack size for a product listed in this Part exceeds the quantities stated above, the listed pack size is the only pack size considered when calculating the price. The Secretary of State determines the prices for Category A drugs to be the average of the price calculated for the pack size listed in the Drug Tariff weighted by the following four manufacturers and suppliers; AAH, Alliance Healthcare (Distribution) Ltd, Teva UK and Actavis on or before the 8th of the month being reimbursed. In the weighted formula, AAH and Alliance Healthcare (Distribution) Ltd prices have a weighting of 2, the prices from the other suppliers have a weighting of one.

Appendix N: Research recommendations

N.1 Cardiac rehabilitation

Research question: What characteristics are associated with uptake and adherence to cardiac rehabilitation after an acute MI when rehabilitation is started early?

Why this is important:

There is wide variation across the UK in style, staffing and resources of cardiac rehabilitation (CR). Participation in CR following acute myocardial infarction significantly reduces mortality and improves quality of life. However the latest national audit highlights only 44% of all patients following an acute myocardial infarction take part. This falls far short of the National Service Framework for Coronary Heart Disease (2000) target of more than 85% of people discharged from hospital after acute myocardial infarction. The current national audit data also highlights patients following an acute myocardial infarction are waiting on average 53 days to commence the Phase III component. Early CR (defined as attendance at a CR orientation appointment within 10 days) significantly improves attendance and is also cost-saving through reduced incidence of unplanned cardiac readmissions.

Importance to patients or the population	An analysis of more than 48 randomised trials (Taylor et al, 2004) suggested that participation in cardiac rehabilitation (CR) results in a 26% relative reduction in cardiac mortality over five years. Cardiac rehabilitation has also been demonstrated to show a reduction in cardiac-related morbidity and an improvement in functional capacity. Moreover, participation in CR is associated with a reduction in anxiety and depression, an increase in physical activity and participation in smoking cessation programmes; all of which would impact upon a patient's quality of life. In addition, evidence suggests that CR programmes provide support for patients to return to work and fosters the development of self-management skills as well as having a positive impact on overall health and well-being. Providing early CR is associated with improved attendance and health outcomes. Identifying additional factors that positively impact upon uptake and adherence to CR and subsequently tailoring services to consider these factors may ensure that those who have had an MI benefit from these improved outcomes.
Relevance to NICE guidance	Identifying factors which improve uptake and adherence would improve the strength of recommendations relating to CR, which may have an impact upon other cardiac guidelines. Additionally, the results may be extrapolated to other behaviour change interventions and programmes managing long term conditions. The NICE cardiac rehabilitation services commissioning guide may also benefit from the research.
Relevance to the NHS	Over and above the well-documented, positive effects of rehabilitation on mortality, morbidity and quality of life, increasing the uptake of 'gold standard' CR has the potential to reduce cardiac-related readmissions and deliver significant financial savings.
National priorities	Uptake and adherence to cardiac rehabilitation is reflected in the Department of Health Cardiovascular Disease Outcomes Strategy.
Current evidence base	A wealth of evidence has been identified to highlight potential barriers to uptake and adherence of cardiac rehabilitation, as well as studies focusing on interventions to increase this. This evidence is generally from a non-UK perspective and of variable quality, often focusing on a non-MI population. Furthermore, there are methodological flaws with the majority of studies and

	adherence is not consistently defined across papers. Finally, barriers identified and interventions to improve uptake have not been investigated in programmes that include early programme commencement as standard. Recent evidence demonstrates arranging for attendance to CR orientation within 10 days of hospital discharge significantly increases uptake. There is no data in the UK on the inherent characteristics of programmes already delivering early cardiac rehabilitation that are associated with the greatest uptake and adherence.
Equality	There are a number of groups which are less likely to uptake and adhere to cardiac rehabilitation and limited evidence is available to focus on these populations. These groups include people from South Asian communities, people with physical and mental health conditions, those who live in rural areas and women. The proposed study design would allow for aspects of cardiac rehabilitation likely to improve uptake and adherence for these specific groups to be identified. Secondly, the national audit for cardiac rehabilitation highlights there is significant inequality in service provision of cardiac rehabilitation services across England, Wales and Northern Ireland. Identifying the attributes of a cardiac rehabilitation that promotes uptake and adherence may help to standardise the provision of services.
Study design	The study would take the form of survey based methodology measuring programme characteristics (including but not limited to demographics, staffing, staffing mix, timing of sessions etc) across England, Wales and Northern Ireland. Characteristics identified will be correlated with rates of uptake and adherence to the cardiac rehabilitation programme.
Feasibility	No feasibility issues.
Other comments	None.
Importance	High: the research is essential to inform future updates of key recommendations in the guideline.

N.2 Clopidogrel

Research question: In patients who have had a STEMI who undergo PPCI with a bare metal stent, and 4 weeks of aspirin and clopidogrel is there an additional benefit to continuing clopidogrel for a further 11 months?

Why this is important:

There are no randomised trials to demonstrate the benefit of long term treatment with clopidogrel in addition to aspirin versus aspirin alone in patients with STEMI. This applies to all patients with STEMI, whether treated with PPCI or medical therapy alone. Two large trials have provided data on short term efficacy in medically treated STEMI patients (Commit/CCS-2, and Clarity – TIMI 28). Because it is counter-intuitive to treat STEMI and NSTEMI patients differently with regard to secondary prevention with antiplatelet drugs, in widespread clinical practice physicians extrapolate the data from patients with NSTEMI, in whom this problem has been studied in both medically and invasively managed patients and who receive clopidogrel for up to 12 months (CURE, PCI-CURE, CREDO). These trials have suggested a reduction in composite endpoints including mortality, but have also demonstrated an increased risk of bleeding. Whereas the risk of bleeding is always increased throughout the period of administration of dual antiplatelet therapy (aspirin with clopidogrel), it may be that the majority of benefit occurs in the short term reduction of fatal and non-fatal reinfarction, and a reduced risk of stent thrombosis in patients treated with PCI. There is a large and increasing body of evidence which

shows that bleeding complications following MI are associated with significantly higher rates of morbidity and mortality. At the time of PPCI for STEMI about 60% of patients receive a drug eluting stent (DES) and would routinely receive up to 1 year of clopidogrel (or other P2Y12 blocker) in addition to aspirin. The 40% of patients who receive a bare metal stent (BMS) would receive clopidogrel for between 1 and 12 months.

Importance to patients or the population	Combination treatment with aspirin and clopidogrel is associated with an increased risk of major and minor bleeding, therefore reducing the duration of therapy could reduce this risk in people who have had a STEMI and who have undergone primary PCI. However, there is also the possibility that the combination could be associated with benefit from reduced reinfarction or stent thrombosis over a prolonged administration. The results of this study would inform recommendations on the duration of clopidogrel therapy in those who have had a STEMI and received a bare metal stent. A decreased duration of clopidogrel treatment may reduce treatment burden, morbidity and mortality for patients and would be cost saving for the NHS because of reduced emergency admissions to hospital, as well as assessments in primary care for minor bleeding. However, a prolonged duration of clopidogrel may be justified by a reduction in fatal and non-fatal ischaemic events, and this also would be associated with decreased cost of emergency admissions.
Relevance to NICE guidance	Future updates of the guideline would be able to produce a stronger recommendation in this area.
Relevance to the NHS	A reduction in the duration of clopidogrel therapy for people who have had an MI and who have had bare metal stents implanted may be cost saving to the NHS. The cost reduction may come from a reduction in the duration of therapy and the treatment of harms relating from long term clopidogrel use (for example, hospitalisation from major or minor bleeding). However, there is also the possibility of the opposite finding if the reduced incidence of bleeding complications is exceeded by a greater number of ischaemia related complications. At present there is widespread variation in practice because of this uncertainty.
National priorities	No relevant national priorities.
Current evidence base	The evidence review identified only one study which directly considered the duration of clopidogrel therapy in a population who had stents implanted following a STEMI. However, the study compared clopidogrel and aspirin for 1 month, followed by aspirin alone for 5 months vs. dual antiplatelet therapy for 6 months. The study does not therefore consider long term clopidogrel therapy up to and past 12 months. Additionally, only a proportion of the population had bare metal stents implanted.
Equality	No equality issues.
Study design	The study should be a randomised, placebo-controlled, double blinded study.
Feasibility	No known feasibility issues.
Other comments	None.
Importance	High: the research is essential to inform future updates of key recommendations in the guideline

N.3 Dual antiplatelet therapy

Research question: In people who have not undergone revascularisation after an MI, does clopidogrel and placebo have a better outcome than clopidogrel and aspirin?

Why this is important:

Following the publication of the CURE study, standard antiplatelet therapy after an acute coronary syndrome has consisted of dual therapy (DAPT) with aspirin and clopidogrel, the combination producing better clinical outcomes than aspirin alone. Recent research has demonstrated that new P2Y12 inhibitors improve on the outcomes with clopidogrel, when combined with aspirin. However bleeding is increased, and this increases overall risk substantially in people with acute coronary syndromes.

Few studies have used P2Y12 inhibitors without aspirin. There are theoretical reasons why aspirin may detract from the vascular benefits of strong P2Y12 inhibitors in particular. In addition, as clopidogrel alone produces at least the benefit of aspirin alone, it is possible that the supposed benefit of the combination of clopidogrel and aspirin over aspirin is due solely to the action of clopidogrel. The limited data regarding the use of clopidogrel alone in people with a range of vascular diseases suggest at least the possibility that the addition of aspirin to clopidogrel adds little or no reduction in vascular event rate, at the cost of a definite, well established increased risk of bleeding. This is supported by in vitro studies which suggest that aspirin may add little or nothing to the antiplatelet effects of clopidogrel alone. A study of clopidogrel alone compared with clopidogrel and aspirin in people after MI would be valuable because of the potential to preserved benefit and reduced risk of bleeding. This might lead to new strong P2Y12 inhibitors being assessed without concomitant aspirin.

It may be that aspirin is important in people undergoing revascularisation using PCI with stents, treated with clopidogrel, due to variation in clopidogrel responsiveness. However there are limited data regarding the importance of aspirin in the presence of clopidogrel in patients not undergoing revascularisation, for either STEMI or NSTEMI.

Importance to patients or the population	Antithrombotic treatment is a cornerstone of the treatment of MI. Optimising this treatment to reduce bleeding risk without reducing antithrombotic effect would improve outcomes, reduce costs, and reduce treatment burden in this important population. Specifically people who do not undergo revascularisation after MI would benefit from knowing that clopidogrel alone was sufficient to reduce thrombotic events, with less increase in bleeding than with DAPT. Importantly. Such a result would pave the way for trials of the new strong P2Y12 inhibitors without aspirin, which may optimise their safe use with a considerable increase in the population benefitting.
Relevance to NICE guidance	Dual antiplatelet therapy is a cornerstone of the treatment of acute coronary syndromes. Hence it is described and recommended in current NICE guidelines. A demonstration of a reduction in the adverse bleeding events associated with this treatment would importantly improve the advice given.
Relevance to the NHS	Although aspirin is available generically and therefore, at a low cost, there is still potential for cost saving, given the proportion of the population affected. More important financially would be the reduction in aspirin associated bleeding complications which are often costly, being associated with long in patient stays and further acute ischaemic complications consequent on the mandated withdrawal of antithrombotic therapy in the context of such bleeding events.
National priorities	No.

Current evidence base	No evidence was identified in the current evidence review that directly compared dual antiplatelet therapy against treatment with clopidogrel and placebo in this population
Equality	No equality issues are identified however, the GDG noted that people who do not undergo revascularisation are likely to be older people, or those with significant comorbidities. These people are also more likely to suffer bleeding complications of DAPT, so would be likely to benefit from a change in the treatment recommendations.
Study design	The study should be a randomised, placebo-controlled, double-blinded study comparing clopidogrel alone with clopidogrel and aspirin in people not undergoing revascularisation after MI. The study should have a sequential design, given its exploratory nature. The primary outcome should be total mortality. Other outcomes could include: acute ischaemic events, including recurrent infarction, bleeding events, revascularisation, hospitalisation, and resource use Prespecified stratification should include bleeding risk score.
Feasibility	As up to 43% of the MI population do not undergo revascularisation, recruitment should be feasible. The NHS has performed many successful studies in this population.
Other comments	None.
Importance	High: the research is essential to inform future updates of key recommendations in the guideline.

N.4 Antiplatelet therapy in those with an additional indication for anticoagulation

****This research recommendation has been removed from the 2020 update.****

Research question: In patients who have had an MI, who otherwise have an indication for oral anticoagulation and who are treated either: medically, by primary percutaneous intervention or by coronary artery bypass surgery, is treatment with an oral anticoagulant, aspirin and clopidogrel preferable to treatment with an oral anticoagulant and clopidogrel?

Why this is important:

Many patients who have had an MI have indications for long term treatment with both oral anticoagulants and combination antiplatelet drugs. Those with atrial fibrillation, mechanical heart valves or a history of pulmonary emboli are at high risk of stroke or thromboembolism and therefore require anticoagulation for the prevention of these events. It is well recognised that patients receiving a combination of antiplatelet therapy and oral anticoagulation are at high risk of bleeding events both minor, major and fatal. These outcomes are often recurrent and associated with hospitalisation, blood transfusion and interventional procedures. The evidence review failed to identify high quality evidence to identify whether, in this population, treatment with triple therapy (an oral anticoagulant, plus dual antiplatelet therapy) or dual therapy (an oral anticoagulant plus clopidogrel) is more effective. The GDG recognise that this question is increasingly important in an increasingly elderly population, who are more likely to have comorbidities and who are at a higher risk of bleeding.

Importance to patients or the population	The need to provide combined antiplatelet therapy in combination with oral anticoagulation affects a significant proportion of people who have had an MI. Identifying whether dual or triple therapy is more effective may result in a reduction in bleeding events which can affect the majority of patients receiving combined treatment. It is likely that there will also be an effect other major outcomes including hospitalisation, mortality and fatal events. From a patient perspective, it could potentially reduce treatment burden.

Relevance to NICE guidance	These findings would be relevant to a large population of patients with vascular disease and an indication for oral anticoagulation as covered in guidance on atrial fibrillation, stable angina and peripheral vascular disease. The results could therefore inform guidelines on a range of conditions.
Relevance to the NHS	This would be highly relevant to the NHS as it may result in reduced use of both primary and secondary care including the need for hospitalisation, blood transfusion and interventional procedures
National priorities	No relevant national priorities.
Current evidence base	Limited evidence was found to help inform this research question. No evidence was identified on a population of people who have had an MI. One study was identifying in a population with ischaemic heart disease and this included some people who have had an MI and who have undergone PCI. No high quality evidence in a direct or indirect population was identified in people who have had an MI who are medically treated or who have undergone CABG.
Equality	Research should consider people of all ages, including older people who have an increased likelihood of requiring antiplatelet therapy for an MI where there is a pre-existing indication for anticoagulation. This population are also at an increased risk of bleeding. The research will include a large number of women as other studies of acute coronary syndromes have shown that many older women with a lower body weight are at a higher risk of bleeding.
Study design	The study should be a randomised, placebo-controlled, double-blinded study. The study should include a broad range of patients, including the older population. Current evidence suggests that novel oral anticoagulants should not be used in combination with dual antiplatelet therapy, therefore the study will look at warfarin.
Feasibility	No known feasibility issues.
Other comments	This research would benefit from being publically funded, rather than funded by industry.
Importance	High: the research is essential to inform future updates of key recommendations in the guideline. The population it covers is one of the highest risk groups following an MI.

N.5 Beta-blockers

Research question: Does continuing beta-blocker treatment beyond one year after an MI improve outcomes for people with normal LV function?

Why this is important:

Recent cohort studies have suggested that continuing treatment with a beta-blocker beyond a year after an acute myocardial infarction may not confer any benefit to the person in terms of reduced morbidity or mortality. This is particularly relevant given recent changes in acute management strategies. Whilst beta-blockers are valuable in reducing mortality and morbidity for up to a year following an MI, they have side effects and represent an additional treatment burden to people who are already taking many other medications. However, there is also some suggestion that there are risks associated with withdrawal of beta-blockers in this population. The balance of risks and

benefits of long term beta blockade, has not been clearly determined, particularly in the context of modern acute treatment of MI.

The rationale for this research recommendation was updated in 2020. See www.nice.org.uk/guidance/ng185 for the 2020 evidence review.

Appendix O: Proposed changes to the original recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng185

Appendix P: Removed text from CG48

Preface

The immediate care of heart attack in England and Wales has improved substantially over the last few years. These improvements have resulted from a number of major drivers coming together including modernisation and redesign of services, clinical enthusiasm, a national audit with publication of data and the implementation of the National Service Framework for Coronary Heart Disease.

Every extra life saved because of better care is welcome while at the same time presenting an additional challenge to the National Health Service. This challenge is to ensure that every individual surviving a heart attack is offered the best chance of a long and healthy life free, as far as possible, of further events.

One of the mantras of the National Service Framework was to make sure that simple things were done right all the time. In many ways the clinical community has responded to this need so that record numbers of patients leaving hospital are now being prescribed the drugs that are effective in reducing risk after heart attack. Drugs such as aspirin, beta-blockers and statins are being provided for almost all eligible patients as they leave hospital.

Some of the actions that improve outcomes after heart attack are less simple to provide and are clearly outlined in this guideline. These measures include ensuring that the best guidance is given to every individual on the lifestyle that will improve life expectancy and help to ensure freedom from further events. Patients not only need to understand these benefits but also need to help to attain these goals. Here, exercise programmes in the form of cardiac rehabilitation schemes and other programmes have a vital role in helping the 1.2 million people who suffer a heart attack year in the United Kingdom each of whom warrants the very best of care as they recover.

This guideline is very welcome as it clearly emphasises the importance of exercise, smoking habit, diet and cardiac rehabilitation as the pillars that support full recovery. It also clarifies the role of the various treatments available including the best drugs and defines which patients might benefit from interventions such as angioplasty and coronary bypass surgery.

Professor Roger Boyle CBE FRCP FRCPE

National Director for Heart Disease and Stroke

Department of Health, London

Methods

2.6 Responsibility and support for guideline development

2.6.1 The National Collaborating Centre for Primary Care (NCC-PC)

The NCC-PC is a partnership of primary care professional associations and academic units, formed as collaborating centre to develop guidelines under contract to the NICE. It is entirely funded by NICE. The NCC-PC is contracted to develop five guidelines at any one time, although there is some overlap at start and finish. Unlike many of the other centres which focus on a particular clinical area, the NCC-PC has a broad range of topics relevant to primary care. However, it does not develop guidelines

exclusively for primary care. Each guideline may, depending on the scope, provide guidance to other health sectors in addition to primary care.

The Royal College of General Practitioners (RCGP) acts as a host organisation. The Royal Pharmaceutical Society and the Community Practitioners and Health Visitors' Association are partner members with representation of other professional and lay bodies on the Board. The RCGP holds the contract with the Institute for the NCC-PC. The work is carried out on two sites in London, where the work on this particular guideline was based, and in Leicester under contract to the University of Leicester.

2.6.2 The Development Team

The Development Team had the responsibility for this guideline throughout its development. It is responsible for preparing information for the Guideline Development Group (GDG), for drafting the guideline and for responding to consultation comments. The development team working on this guideline consisted of the:

- Guideline Lead who is a senior member of the NCC-PC team who has overall responsibility for the guideline
- Information Scientist, who searched the bibliographic databases for evidence to answer the questions posed by the GDG
- Reviewer (Senior Health Services Research Fellow), with knowledge of the field, who appraised the literature and abstracted and distilled the relevant evidence for the GDG
- Health Economist who reviewed the economic evidence, constructed economic models in selected areas and assisted the GDG in considering cost effectiveness
- Project Manager, who was responsible for organising and planning the development, for meetings and minutes and for liaising the Institute and external bodies
- Clinical Advisor, with an academic understanding of the research in the area and its practical implications to the service, who advised the Development Team on searches and the interpretation of the literature.

With the exception of the Clinical Advisor, all of the Development Team was based at the NCC-PC in London. Applications were invited for the post of Clinical Advisor, who was recruited to work on average a half a day a week on the guideline. The members of the Development Team attended the GDG meetings and participated in them.

The Development Team met regularly with the Chairman of the GDG during the development of the guideline to review progress and plan work.

2.6.3 The Guideline Development Group (GDG)

A Chairman was chosen for the group for his understanding of the field. His primary role was to facilitate the work at GDG meetings.

Guideline Development Groups (GDGs) are working groups with the aim to get the range of experience and expertise needed to address the scope of the guideline. Nominations for GDG members were invited from the relevant stakeholder organisations which were sent the draft scope of the guideline and some guidance on the expertise needed. From the nominations, two patient representatives and the healthcare professionals joined the GDG.

Nominees who were not selected for the GDG were invited to act as Expert Peer Reviewers and were sent drafts of the guideline by the Institute during the consultation periods and invited to submit comments by the same process as stakeholders.

Each member of the GDG served as an individual expert in their own right and not as a representative of their nominating organisation, although they were encouraged to keep the nominating organisation informed of progress.

In accordance with guidance from NICE, all GDG members' interests were recorded on a standard declaration form that covered consultancies, fee-paid work, share-holdings, fellowships, and support from the healthcare industry.

The names of GDG members appear list below.

Professor Gene Feder (Chairman)

Professor of Primary Care Research and Development, Barts and the London Queen Mary's School of Medicine and Dentistry, London

Dr Jane Skinner (Clinical Advisor)

Consultant Community Cardiologist, the Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne

Dr Keith MacDermott

General Practitioner, York

Dr Rubin Minhas

General Practitioner, Primary Care CHD Lead, Kent

Dr Chris Packham

Director of Public Health, Nottingham City Primary Care Trust, Nottingham

Mrs Helen Squires (until April 2006)

Superintendent Physiotherapist, Luton & Dunstable Hospital NHS Trust, Bedfordshire

Mr David Thomson

Patient, Buckinghamshire

Professor Adam Timmis

Professor of Clinical Cardiology, Barts, London and the London Queen Mary's School of Medicine and Dentistry

Mr John Walsh

Patient, Swindon

Ms Helen Williams

Pharmacy Team Leader for Cardiac Services & London Region CHD Advisor for Clinical Pharmacy. King's College Hospital, London

Ms Anne White

British Heart Foundation Cardiac Specialist Nurse, Cambridgeshire PCT and Addenbrooke's NHS Trust

Members of the GDG from the NCC-PC were:

Ms Nancy Turnbull

Guideline Lead and Chief Executive, National Collaborating Centre for Primary Care

Dr Angela Cooper

Senior Health Services Research Fellow, National Collaborating Centre for Primary Care

Ms Gabrielle Shaw (until Dec 2005) and Dr Meeta Kathoria (from May 2006)

Project Manager, National Collaborating Centre for Primary Care

Mr Leo Nherera

Health Economist, National Collaborating Centre for Primary Care

Observers

Ms Colette Marshall

Commissioning Manager, National Institute for Health and Clinical Excellence

2.6.4 Guideline Development Group Meetings

The GDG met at 4 to 5 weekly intervals for 18 months to review the evidence identified by the Development Team, to comment on its quality and relevance and to develop recommendations for clinical practice based on the available evidence. The final recommendations were agreed by the full GDG which met following the consultation to review and agree any changes to the guideline resulting from stakeholder comments

2.7 Care pathway

Two clinical care pathways have been designed to indicate the essential components in the secondary prevention of patients after an MI, one for patients with a recent MI, and one for patients with a proven MI in past. Each pathway has three main sections. These are; secondary prevention drug treatment, specialist cardiological assessment, and lifestyle and cardiac rehabilitation. Recommendations for key secondary prevention measures in each section are indicated.

Algorithms

The current visual summaries can be found at www.nice.org.uk/guidance/ng185

Chapter 4 – Lifestyle

4.1.1. Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng185

4.2 Evidence statements

4.2.1.4 In patients after an MI, advice to increase consumption of oily fish reduced all-cause mortality (1+).

4.2.1.5 The only large trial of supplementation with 1g of omega 3 polyunsaturated fatty acids has shown a reduction in mortality and cardiovascular morbidity, although there was a low uptake to statins and other secondary prevention drugs at baseline in this trial (1++).

4.2.4 Fish diet

Advice to eat oily fish has been examined in a randomised trial in men under the age of 70 years following a recent MI (DART1). [86] There were 1015 patients recruited to the oily fish advice group and 1018 patients recruited to the no diet advice group. The mean age at recruitment was 57 years, and the recruitment mean interval after the incident MI was 41 days. Patients were advised to eat at least two weekly portions (220 to 400 g) of oily fish (mackerel, herring, kipper, pilchard, sardine, salmon or trout). Advice to eat oily fish was compared with no dietary advice and two further dietary advice regimes; fat advice (to reduce fat intake to 30% of total energy and to increase the polyunsaturated fat / saturated fat ratio to 1.0) and fibre advice (to eat more cereal fibre). Patients in the oily fish advice group who could not tolerate oily fish were given omega-3- acid ethyl esters capsules; 3 x 0.5 g per day supplying 2.5 g of eicosapentaenoic acid per week as well as docosahexaenoic acid. Study duration was 2 years and at 6 months 14% of patients were taking omega-3- acid ethyl esters capsules, while at 2 years 22% of patients were taking omega-3- acid ethyl esters capsules as a partial or total substitute for oily fish. Percentages of plasma eicosapentaenoic acid in total plasma fatty acid were measured in a subset of the dietary advice group and the no diet advice group. The differences were consistent with the reported dietary changes, in that oily fish intake was approximately 35 g per day in the oily fish advice group and 9 g per day in those receiving no diet advice.

Advice to eat oily fish was associated with a reduction in all-cause mortality compared with no dietary advice after adjustment for confounders (RR 0.71, 95%CI 0.54 to 0.92). There was no reduction in ischaemic heart disease events (ischaemic heart disease death and non-fatal MI) in the oily fish advice group compared with the group given no advice (RR 0.84, 95% CI 0.67 to 1.07). Patients given oily fish advice had a lower mortality than patients within other dietary groups (percentage difference in all-cause mortality for oily fish advice minus no fish advice in the following groups; fat advice, fibre advice, fat and fibre advice, and no dietary advice was -4.3%, -2.1%, -5.5% and -2.1%, respectively). [86]

A follow up study of DART was conducted ten years after the end of the original trial. [422] In the oily fish group, 447 of 1015 patients had survived and in the diet advice group 432 of 1018 survived. Oily fish intake (g/day) in the fish advice group was 21 g compared with 13 g in the no fish advice group ($P < 0.01$). Prescription fish oil supplementation was higher in the fish advice group (10%) compared with the no fish advice group (2%) ($P = 0.02$). Fish oil supplementation of unknown source (not

reported) was also higher in the fish advice group (26.9%) compared with the no fish advice group (19.3%) (P < 0.01). At 10 year follow up, oily fish advice was not associated with a reduction in all-cause mortality (HR 0.95, 95% CI 0.85 to 1.07), coronary heart disease mortality (HR 0.92, 95% CI 0.80 to 1.07) or stroke (HR 1.23, 95% CI 0.71 to 2.14). This study may suggest that advice to eat oily fish does not have a sustained effect on mortality, or that the original findings were a chance effect. There are a number of limitations to the follow up study. Data was only available for oily fish intake at the end of the study, and it is possible that the diets of those who survived were different from those who did not. The results may also be confounded by the fact that compliance in the oily fish advice group was 56% at the end of the 10 year trial follow up period (patients reported a much lower intake of oily fish compared with intake during the trial, 21 g/day versus 35 g/day), while in the no diet advice group compliance was 37% (patients reported an increase oily fish consumption from 9 g/day during the trial to 13 g/day, and increased their supplement intake). [422]

4.2.5 Omega-3- acid ethyl esters treatment

A randomised trial of 11 324 patients with a prior MI within 3 months of recruitment compared the effectiveness of omega-3- acid ethyl esters with no supplementation. [228].There was no upper age limit and the mean age ± standard deviation was 59±10 years. Fourteen percent had impaired LV function (ejection fraction < 40%) and more than 70% of patients reported eating fish at least once a week at the start of the randomised controlled trial in both the treatment and control groups, with no difference between the groups. At 42 months, this had risen to 82% in both groups. The type of fish was not stipulated. At the start of the trial, the percentage of patients prescribed cholesterol lowering drug therapy in the treatment and control groups was 4.4% and 5.1%, respectively. At 42 months the percentage rose in the treatment and the control groups to 46.0% and 44.4%, respectively. Patients in the treatment group were given a 1 g capsule to be taken daily containing 850 to 882 mg of eicosapenteanoic acid and docosahexaenic acid in a ratio of 1.2:1. This supplied approximately 3.3 g of eicosapentaenoic acid per week.

Compared with control, omega-3- acid ethyl esters treatment was associated with a lower risk of the two primary endpoints; the combination of death, non-fatal MI, or non-fatal stroke (RR 0.85, 95% CI 0.74 to 0.98) and the combination of cardiovascular death, non-fatal MI, or non-fatal stroke (RR 0.80, 95% CI 0.68 to 0.95). There was also a lower risk of the following secondary endpoints: all fatal events (RR 0.80, 95% CI 0.67 to 0.95), cardiovascular deaths (RR 0.70, 95% CI 0.56 to 0.87), cardiac deaths (RR 0.65, 95% CI 0.51 to 0.82), coronary death (RR 0.65, 95% CI 0.51 to 0.84) and sudden death (RR 0.55, 95% CI 0.40 to 0.76). [228]

In contrast, a much smaller randomised controlled trial [427] of 300 patients found that compared to corn oil, treatment with omega-3- acid ethyl esters was not associated with a reduced risk of; cardiac death, resuscitation, recurrent MI, unstable angina pectoris, revascularisation, total mortality. The median follow up was 1.5 years. The study was powered to measure the effects of omega-3- acids ethyl esters only on serum lipids. Total cholesterol concentrations decreased in both the omega-3-acid ethyl esters and corn oil groups. HDL-cholesterol levels increased in the omega-3- acids ethyl esters group compared with corn oil group. Triacylglycerol concentrations decreased in the omega-3-acid ethyl esters group, whereas they increased in the corn oil group.

The guideline development group recognised that there was only one major trial of omega-3- acid ethyl esters supplementation in patients within 3 months of an MI which reported a favourable impact on clinical outcome. It was noted that a high proportion of participants in this trial reported eating fish at least once per week throughout the trial in both the treatment and control groups. The low cholesterol lowering drug therapy at the start of the trial and its subsequent increase in both groups was also recognised. The consensus of the guideline development group was that the results of the trial should not be dismissed and that treatment with omega-3-acid ethyl esters should be considered in patients within 3 months of an MI, although the results could not be extrapolated to recommending initiation of supplementation beyond 3 months after the acute event. A study in

angina patients of which 50% had a prior MI found that advice to each oily fish or take omega-3- acid ethyl esters supplements was not associated with clinical benefits compared with no advice or no supplementation. [87] This may suggest that the clinical benefit of omega-3- acid ethyl esters treatment is restricted to commencing therapy within 3 months of an MI.

Health economics of omega-3-acid ethyl esters treatment

Three studies were identified which examined the economic consequences of omega-3- acid ethyl esters supplements compared to no supplements in improving outcomes in patients after MI from the National Health Service (NHS) perspective. All three analyses used effectiveness data from a single trial [228] of post MI patients with no age restriction.

An Italian study [198,330] reported omega-3- acid ethyl esters supplements compared to no supplements resulted in 0.0332 life years gained. The incremental cost effectiveness was 24 603 Euros/LYG in the base case model. It is unclear whether this estimate would lie below the NICE threshold of £20-30 000 per QALY. Results were sensitive to the cost of omega-3- acid ethyl esters supplements and a worst case scenario.

A report by Innovus Research on behalf of Solvay Pharmaceutical submitted to NICE was a cost utility analysis, [284] extrapolating data for lifetime treatment from the NHS perspective. The authors considered a short term model (until the end of the trial) and a longer term model (lifetime). Omega-3- acid ethyl esters supplements were found to be cost effective as long as the NHS was willing to pay £15 189/QALY over 4 years or £3717/QALY over a lifetime. Although the authors did some sensitivity analysis on some parameters which was robust. The authors stated that the parametric form assumed for fitting the survival curves to the trial data, and their method for extrapolating survival benefits beyond the trial period. However they did not provide any evidence for the fit of this curve, or do any sensitivity analysis over the assumptions. They also did not do any sensitivity analysis around their estimates of effectiveness which weakened their study.

A third study [330] assessed the cost effectiveness of adding omega-3- acid ethyl esters supplements to the current secondary prevention treatment versus standard prevention alone after acute MI in five countries: Australia, Belgium, Canada, Germany and Poland from the healthcare payers perspective using a decision model. Treatment with highly concentrated omega-3- acid ethyl esters supplements yielded between 0.261 (Poland) and 0.284 (Australia) LYG, at an additional cost of 787 Euros (Canada) to 1439 Euros (Belgium). The ICER varied between 2788 Euros (Canada) and 5097 Euros (Belgium) per LYG. Sensitivity analyses on effectiveness, cost of complications and discounting suggested the robustness of the results. A second-order Monte Carlo simulation based on the 95% confidence intervals obtained from GISSI-P trial [228] suggests that highly concentrated omega-3- acid ethyl esters supplements are cost effective in 93% of simulations in Poland and in > 98% of simulations in the other countries, using the country-specific societal willingness-to-pay threshold. The authors rightly acknowledge that a Markov model could have been more appropriate than the decision model as it can take account of more than one event over time.

We developed a model to estimate the cost effectiveness of omega-3- acid ethyl esters supplements for patients after a recent MI who cannot comply with recommendations for the dietary intake of fatty fish (see appendix B). The model was subjected to extensive sensitivity analysis to test the robustness of the results to changes in the input data and assumptions. The findings were broadly consistent with those of the submitted company model and two published cost effectiveness analyses (Lamotte M et al, 2006 5301). [198] (Company submission to NICE from Innovus Research on behalf of Solvay Pharmaceutical).

The guideline model found omega-3- acid ethyl esters supplements to be cost effective when compared with no supplements in patients after a recent MI, with estimated ICERs of about £12 500. This result is sensitive to uncertainty over the size of treatment effects and supplements do not appear to be cost effective at the upper confidence limit for the relative risk of mortality. These

results depend on the assumption that treatment effects do not persist beyond the longest trial period, 3.5 years for the GISSI-P trial ,[228] and that supplements are not continued after this time. DART1 was of shorter duration (2 years), and clinical benefits may not be sustained beyond this period (Ness et al 2002). If treatment effects do not persist beyond two years, supplements are of borderline cost effectiveness (£23 400 per QALY). From an NHS perspective, it will clearly be more cost effective for patients to obtain omega 3 fatty acids from dietary sources. But if a patient is unable to do this, provision of supplements does appear to be a cost effective use of NHS resources. The model assumed use of the cheapest available supplement with the correct quantities of eicosapentaenoic acid and docosahexaenoic acid (Maxepa). The use of a second supplement (Omacor) also appears to be cost effective compared with no supplementation; however, it will not be cost effective when compared with the cheaper alternative (assuming clinical equivalence between these products). Other supplements are available for patients to purchase over-the-counter. However, the clinical efficacy and safety of these alternatives has not been considered in randomised controlled trials in a post MI population. It is important to note that the validity of the cost effectiveness analysis depends on the premise that the benefits of omega 3 fatty acids are confined to people with a recent MI, as clinical effectiveness data was used from two randomised controlled trials recruiting patients within 3 months of an MI. Omega-3- acid ethyl esters supplements would not be clinically or cost effective if the evidence base was broadened to include a randomised controlled trial in patients with angina (DART2).

In conclusion omega-3- acid ethyl esters treatment compared to no treatment in patients after MI appears to be cost effective not withstanding the caveats mentioned above.

Chapter 5 - Cardiac rehabilitation

5.1.2 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng185

5.3.1 Patient engagement evidence statements

5.3.1.1 In unselected patients after MI, uptake of cardiac rehabilitation programmes can be improved by motivational communication such as written letters, or pamphlets, or conversation with a healthcare professional (1++).

5.3.1.2 Regular support and practical help from lay volunteers may improve uptake in unselected patients after MI (1++).

5.3.1.3 Effective co-ordination between hospital and primary care to encourage patients to see the practice nurse after discharge improves uptake of cardiac rehabilitation programmes in unselected patients after MI (1++).

5.3.1.4 There was little evidence found on interventions to improve adherence to cardiac rehabilitation and it was of poor quality.

5.3.1.5 The use of letters or telephone calls plus a visit from a healthcare professional to improve uptake of cardiac rehabilitation was found to be cost effective, but the result was sensitive to efficacy of the interventions.

5.3.1.6 There was no evidence found of interventions to improve either uptake or adherence to cardiac rehabilitation in ethnic minority groups, patients living in socially deprived areas, deprived areas, elderly patients, women, or patients in rural areas.

5.3.2 Clinical effectiveness of patient engagement

5.3.2.1 Introduction

A Health Technology Assessment entitled 'Provision, uptake and cost of cardiac rehabilitation programmes: improving services to under-represented groups' [58] examined hospital discharge statistics for 2000. In England, Wales and Northern Ireland there were nearly 146 000 patients discharged from hospital with primary diagnosis of acute MI, unstable angina or following revascularisation that were potentially eligible for cardiac rehabilitation. In England, 45 to 67% of these patients were referred, with 27 to 41% attendance rates, of those eligible for cardiac rehabilitation. Surveys in the UK of patients after MI attendance at cardiac rehabilitation centres have cited participation rates ranging from 14 to 43%. The review [58] found that response rates in patients referred to, joining and completing programmes from under-represented groups was much poorer. The Health Technology Assessment [58] conducted an audit of cardiac rehabilitation in the south-west of England and areas of high ethnic minority populations in London and the Midlands. From January to July 2002, audit data was obtained from 24 centres (42% of centres contacted). The proportion of discharged patients attending rehabilitation was 35%, and of those referred attendance was 55%. Of those attending a programme, 77% subsequently completed it. In five centres providing a service to a high proportion of ethnic minorities, the percentage of discharged patients referred was significantly lower than in three centres from other areas (29% compared with 45%).

The National Service Framework on Coronary Heart Disease [147] states that every hospital should ensure that 85% of people discharged from hospital with a primary diagnosis of acute MI, or after coronary revascularisation, are offered cardiac rehabilitation.

The Health Technology Assessment [58] presented information from an NHS-funded, multicentre randomised controlled trial that was deemed to represent a more optimal protocol-led level of care than that given in cardiac rehabilitation centres. [614] Healthcare professionals identified 73-81% of

patients with acute MI as eligible for cardiac rehabilitation. Excluded patients tended to have a previous MI, pre-existing angina, MI with left ventricular failure, or MI with cardiac shock. They also tended to be older. The experiences of the recruited patients identified a number of areas which could be addressed to improve uptake;

- motivation and relevance of rehabilitation to future well-being
- comorbidities
- site and time of programme
- transport
- care for dependents

The Health Technology Assessment [58] also summarised the literature on barriers to uptake and adherence to cardiac rehabilitation as follows:

Patient factors

- lack of interest
- reluctance to change lifestyle
- depression
- dislike of classes / hospitals
- work or domestic commitments
- lack of family support
- rural residence / distance and transport problems
- misconceptions about cardiac problems

Service Factors

- cost and reimbursement
- ECG monitoring requirement
- location and accessibility
- car parking
- lack of flexibility

Professional factors

- knowledge and attitudes
- referral
- prejudice (age, race and gender)

5.3.2.2 Patient engagement to improve uptake to comprehensive cardiac rehabilitation

The Health Technology Assessment [58] conducted a systematic review of studies to improve uptake to comprehensive cardiac rehabilitation. Eight studies were identified that reported an evaluation of an intervention relating to uptake by an appropriate patient group, and with a relevant outcome. [622] [295] [445] [402] [283] [530] [270] [323]

Six of these studies reported interventions designed to increase uptake of outpatient cardiac rehabilitation. [622] [295] [445] [402] [283] [530] The other 2 studies described interventions designed to improve uptake of community or voluntary services (cardiac or heart clubs) following discharge from inpatient cardiac rehabilitation. [270] [323] All studies recruited post MI patients. One study also included patients with angina [295] and another included post cardiac surgery patients. [283]

Three of the eight studies were randomised controlled trials. [622 270 295] Five studies reported non-randomised studies. One study compared a district providing the intervention with another not giving any intervention. [445] The two districts had patient populations with comparable demographics, and they were served by the same general hospital. The other four studies compared uptake of cardiac rehabilitation before and after implementation of an intervention. [402 283 530 323] All studies evaluated generic interventions that were applicable to general patients after MI, rather than interventions specifically for underrepresented patient groups. The Health Technology Assessment [58] grouped the interventions into four themes:

1. healthcare led professional interventions at the patient level
2. trained lay volunteers
3. coordination of referral post-discharge care at the service level
4. written or aural motivational communications

The authors stated that the evidence for benefits from motivational communications was reasonably good. There were improvements in uptake of outpatient cardiac rehabilitation and heart groups demonstrated in two randomised controlled trials [622 270] and in one before and after study. [323] Methods of communication used were written letters, [622] or pamphlets [323] or conversation with a healthcare professional. [270]

There was limited information reported in the one study assessing the effectiveness of an intensive home-based nurse-led approach. [283] The Health Technology Assessment [58] stated that no conclusions could be drawn.

A multifaceted approach to the coordination of transfer of care from hospital to general practice was effective in improving cardiac rehabilitation in a randomised control trial [295]. It was noted that the two non-randomised studies on the multifaceted approach had problems in study design and therefore were of limited value. [402 530] Regular support and practical help from lay volunteers were effective in improving uptake in a non-randomised study conducted in two separate districts. [445]

All studies reported that there was benefit from intervention to improve uptake. The authors of the Health Technology Assessment [58] noted that there might be publication bias.

5.3.2.3 Patient engagement to improve adherence to comprehensive cardiac rehabilitation

The Health Technology Assessment [58] conducted a systematic review of studies to improve adherence to comprehensive cardiac rehabilitation. A broad definition of adherence was applied, and studies were included on interventions reporting attempts to improve overall adherence and also studies on compliance with aspects of cardiac rehabilitation. Fourteen studies were identified that reported an evaluation of an intervention relating to adherence in an appropriate patient group, and with a relevant outcome. [440 132 368 15 31 164,272 340 390 391 328 368 276 377 177]

Seven of the fourteen studies identified were randomised controlled trials. [440 132 368 15 31 272 164] The other seven studies were non-randomised studies. [340 390 391, 328 276 377 177] One randomised [368] and one non-randomised study [377] reported two distinct interventions. In two studies the group allocation was not clearly described. [276 377]

Three studies were of post MI patients. [15 390 391 377] Eight studies included post MI patients in the recruitment group, and three studies had no post MI patients in their recruits. [368 164 368]

The outcome of eight studies was attendance at exercise sessions. [440 440 368 31 340 328 276 377 177] The outcome of the other six studies was questionnaire assessment of diet or exercise behaviours to ascertain compliance with lifestyle changes. [390 391 368 15 272 164]

All studies found were generic interventions that were applicable to general patients, rather than interventions for under-represented patient groups. The Health Technology Assessment [58] grouped the interventions into five themes:

1. formal patients, commitment
2. spouse or family involvement
3. strategies to aid self-management
4. education
5. psychological interventions

There were four studies that utilised a formal agreement strategy between patient and healthcare professionals. [440] [132] [340] [276] The findings of these studies do not support the use of formal commitment in promoting adherence to cardiac rehabilitation. One study used a written contract, but this showed no effect using a non-randomised study design. [340] A randomised controlled trial of a self-management programme incorporating a signed agreement to participate as an adjunct to an exercise program showed no effect.[440] Similarly, a package of persuasive telephone conversations, with spouse counselling, and oral commitment, did not improve attendance. [132]

The evidence for the benefits of spouse or family member involvement enhancing adherence is limited by the design of the studies. A spouse support study did not provide information on baseline characteristics or group allocation. [177] A randomised study utilising telephone counselling for spouses and intensive patient counselling had no effect on adherence. [132] The study on family involvement in adherence-promoting behaviour provided little information on design or methodology. [276]

There is some evidence for the benefits of self-management to improve adherence to cardiac rehabilitation. One randomised controlled study showed improvement in dietary habits, [15] and a small randomised controlled study showed benefit in reduced sodium intake. [164] Another randomised control study of self-evaluation and information feedback on exercise and risk factors demonstrated a non-significant improvement in attendance at rehabilitation. [440] However, one randomised controlled study [31] and a study with non-random assignment to groups [390] [391] showed no benefit for assessment and goal setting for improving health behaviours or exercise adherence. In the discussions of these studies, it was noted that control patients received regular self-evaluation questionnaires and nurse visits, which may have affected outcomes.

There was little evidence that educational interventions improve adherence. Two randomised controlled studies showed no benefit of education and counselling (telephone intervention) on attendance at an exercise programme. [132] [272] A videotaped educational intervention given pre-discharge was effective in increasing diet and exercise compliance. [368] It was noted that this approach might help initially, but may be of limited value in the promotion of adherence to a cardiac rehabilitation programme. A non-randomised study using a before-and-after structured teaching approach was effective in increasing diet and exercise. [368]

Only one partially randomised study used a psychological approach to improve adherence. [328] No significant improvement was found in self-reported exercise, but the patients in the psychological intervention group did attend more cardiac rehabilitation classes.

Two other studies described alternative approaches to adherence: the inclusion of recreational sports in cardiac rehabilitation [276] and the use of outpatient rehabilitation designed specifically for women. [377] Insufficient information on the patients and methodology of these studies prevented any analysis of the studies.

In summary, the authors of the Health Technology Assessment [58] stated that they found few studies of sufficient quality to make specific recommendations on methods to improve adherence to cardiac

rehabilitation. Their opinion was that the most promising approach was the use of self-management techniques based around individualised assessment, problem-solving, goal-setting and follow up.

Professional compliance with cardiac rehabilitation

The Health Technology Assessment systematic review [58] searched the literature up to the end of 2001, with the aim to identify interventions that encourage healthcare professionals to comply with guidelines or good practice regarding invitation and support of patients' cardiac rehabilitation. Six studies were identified that reported an evaluation of an intervention to improve professional compliance with cardiac rehabilitation. [560 295 402 530 305 99]

Two of the studies identified were randomised controlled trials. One randomised on an individual basis [560] and the second randomised patients by general practice. [295] This study described methods of randomisation, blind outcome assessment and baseline characteristics of the group, and the loss to follow up in this study was small. None of the other studies reported loss to follow up. Four of the studies described outcomes in periods before and after implementation. [402 530 305 99]

The outcome for three studies was attendance. [402 295 530] Referral was the outcome in two studies [305] and another study had an outcome of patient commitment to attend cardiac rehabilitation. [560] There were four studies that recruited post MI patients. [402 530 305 560] One study included both post MI and angina patients [295] and another study recruited only post-revascularisation patients. [99]

Three themes were identified from the systematic review:

1. improvement of the referral process
2. coordination of transfer of care
3. physician endorsement

There were four studies that evaluated methods to improve the referral process. [402 530 305 99] One study compared patient referral before and after the introduction of an electronic referral pathway. [305] The intervention was initiated with a referral section on the patient record of patients discharged with a diagnosis of MI. There was a significant increase in patient referral to rehabilitation. Another study compared participation before and after the introduction of a prompt for cardiac rehabilitation in a discharge critical care pathway. [402] The improvement in participation was not statistically significant. Two studies reported an educational intervention for healthcare providers, which included information on the comprehensive nature and benefits of cardiac rehabilitation. [99] Information on health outcomes and cost effectiveness was given to members of the clinical cardiology council. After the intervention, there was significantly increased referral from both the hospital and the physician office. [530] These were before, during and after dissemination of clinical guidelines and feedback of clinical indicators to healthcare professionals. During the implementation period, the cardiac rehabilitation programme was operational and this served as a baseline period for evaluation. There was a steady increase in participation in the rehabilitation program and this was attributed to the intervention. However, no comparisons of the patients' characteristics were made in the three time periods.

A cluster randomised controlled study of coordination of care of MI and angina patients between hospital and general practice by specialist cardiac liaison nurses found there was a significant increase in attendance at one or more cardiac rehabilitation sessions for the intervention patients. [295] The intervention involved three components: liaison nurse support for practice nurses, liaison nurse encouragement for patients to see the practice nurse, and prompts and guidance for patients by means of a personal record card.

A randomised controlled trial comparing attending physician cardiac rehabilitation endorsement with a generic endorsement found that the intervention was associated with a non-significant increase in patient-reported intention to participate in a cardiac rehabilitation program. [560]

In summary, the authors of the Health Technology Assessment [58] stated that none of the four studies reporting interventions to improve the referral process included adequate methodological information. A randomised controlled study utilising a multifaceted approach to the coordination of transfer of care from hospital to general practice was effective in improving cardiac rehabilitation uptake. [295] In contrast, the value of physician endorsement in encouraging patient participation in cardiac rehabilitation is not confirmed. It was noted that uptake of cardiac rehabilitation is influenced by the knowledge and enthusiasm of the healthcare providers in the referral process. Therefore, education of healthcare providers on the benefits of cardiac rehabilitation may help to improve uptake and referral.

5.3.2.5 Further interventions that may improve compliance of cardiac rehabilitation

The Health Technology Assessment [58] identified a number of suggested interventions for improving professional compliance with cardiac rehabilitation. The interventions were not evaluated and were as follows:

- appointment of a cardiac rehabilitation programme director to lead, audit and commission appropriate resources
- programme run in accordance with national guidelines
- physicians and insurers educated on benefits for patient groups
- education for cardiac rehabilitation coordinators and staff
- explicit criteria for cardiac rehabilitation eligibility
- streamlining of referral
- centralised cardiac rehabilitation attendance and contact records
- clinical pathway and clinical quality improvement tool
- early social services involvement to improve social support and hence uptake of cardiac rehabilitation
- cardiac rehabilitation commenced earlier
- removal of time restriction for start of programme

One further small intervention study was found that examined adherence in a total of 31 cardiac patients (20 with a prior MI and 11 post CABG) following successful completion of a phase III exercise programme at a district hospital in Scotland. [277] Participants were randomised to an intervention group receiving an exercise consultation plus a standard exercise leaflet or to a control group receiving the exercise leaflet alone. The exercise consultation was a 30-minute individualised counselling session between a trained researcher and the patient. The following were discussed: patient's past and present perceived physical activity behaviour, a discussion of the patterns of unsatisfactory activity and ways to overcome these, encouraging social support, setting realistic short-term goals, and relapse prevention. The participants were informed of current activity guidelines to perform 30 minutes of accumulated moderate intensity activity on most days of the week. At four week follow up, leisure physical activity of the intervention group increased by 29.5%,, while there was a non-significant decline in the physical activity of the control groups by 12%. [277]

5.3.2.6 Groups requiring specific consideration

Ethnic minorities

No studies were found of randomised controlled trials to improve uptake or adherence to cardiac rehabilitation in this under-represented group. The Health Technology Assessment [58] identified one abstract with potential suggestions to improve compliance in South Asian patients. [171] The authors describe the following strategies to improve the cardiac rehabilitation programme based at Coventry that have been implemented: translating current material into Asian languages, utilising Asian language videos, providing post-cardiac surgery tapes, increasing the numbers of home visits for Asian patients, and trialling the Heart Manual audio cassette tapes which have recently been translated.

An audit was conducted of cardiac patients of south Asian origin who were admitted to a large teaching hospital in Sheffield. [581] From the audit, the patient's suggested improvements for information giving are shown in the Table 184

Table 184: Suggested improvements for information giving (n=76)

Tasks	Number of patients
The availability of interpreters should be increased	26 (34%)
An interpreter should be available during ward rounds	7 (9%)
The proportion of staff of all grades who speak South Asian languages should be increased	7 (9%)
Medication instructions should be available in a range of South Asian languages	7 (9%)
Link-workers or interpreters should actively pursue South Asian patients on a regular, daily basis	1 (1%)
Female patients should be able to choose to be seen by a female doctor	1 (1%)
More leaflets should be available in South Asian languages	1 (1%)
More verbal communication should be provided for patients who cannot read any language	1 (1%)

Source/Note: *Adapted from [581]*

The authors raised the following problems that were identified from the audit to improve access for this patient group; [581]

- poor access and use of interpreting services by patients and staff
- untrained interpreters and whether friends, family or staff have been shown to alter or omit information putting the patient at a disadvantage
- there was negligible access to interpreting services after discharge
- written information may have a limited impact because of the number of patients who could not read
- the low uptake of the cardiac rehabilitation

The authors recommended the following to improve access to cardiac rehabilitation programs for South Asian cardiac patients; [581]

- at all points in the care pathway patients should be offered the use of a trained interpreter
- there is a need for more responsive and ward-based interpreters
- reliance on written literature should be avoided when large numbers of the patient population cannot read
- information on health, treatments and services can be recorded on tape for patients and their families

A qualitative research approach to explore the needs and experiences of Gujarati-speaking Hindu patients and their partners in the first month after an MI has been conducted. [612] There were 35 patients in total, 25 men and 10 women. The average age was 65 years. The quantitative analysis of the data revealed eight major categories

1. lack of information and advice about their diagnosis and its implications
2. poor performance of activity
3. little lifestyle adjustment
4. poor expectations of recovery
5. lack of future plans
6. strong family support
7. dissatisfaction with the family doctor
8. significant belief in fate

The authors concluded that the patient's lack of knowledge is likely to lead to poor adherence to conventional cardiac rehabilitation programmes and secondary prevention strategies. [612]

Patients living in socially deprived areas

No studies were found of randomised controlled trials to improve uptake or adherence to cardiac rehabilitation in this under-represented group. The Health Technology Assessment [58] identified one study that conducted a survey with the aim to determine factors associated with patients failing to attend cardiac rehabilitation. [463] The study reported measuring social deprivation using the Carstairs deprivation score, but this information was not utilised in the analysis for reasons of non-attendance. The authors suggested in the discussion that socially deprived patients with a prior MI may prefer a community-based cardiac rehabilitation program. The Health Technology Assessment [58] identified a second study that used a retrospective analysis to identify factors associated with the uptake of cardiac rehabilitation following an MI. [385] A multivariate logistic regression model approach was used to identify these factors from cohorts of patients admitted with MI in 1992 and 1996. Social deprivation was the only factor independently and significantly associated with poor uptake of cardiac rehabilitation in both years using the Townsend score. In 1992, being admitted to hospital and older age were also independently associated with a reduced likelihood of attendance Receiving thrombolysis increased the likelihood of attendance In 1996, a previous MI or revascularisation and not receiving an outpatient appointment were associated with reduced likelihood of attendance. [385]

Patients living in rural areas

No studies were found on improving uptake or adherence to cardiac rehabilitation in patients in rural areas.

Women

We found no randomised controlled trials of interventions to improve uptake or adherence to cardiac rehabilitation in women following an MI.

The Health Technology Assessment [58] cited four studies which gave suggestions to improve women's access to cardiac rehabilitation. A survey of 60 men and 40 women 6 months after MI found that in men, 15% did not attend cardiac rehabilitation. [489] Reasons given by men were almost exclusively related to their medical condition. Of the women that did not attend (42%) the majority that stated that they were not given the opportunity. The authors recommended in their discussion that cardiac

rehabilitation for women should encompass a one-off education session. This may help to address gender-sensitive issues such as returning to sexual relations and housework. Focus-group interviews conducted on 10 women having completed phase II of cardiac rehabilitation (4 with a prior MI) found that women wanted more women-specific support. [397] This was defined as improvements in social support, better exercise variety and choice, and social opportunities during the programme. A comparative semi-structured interview and questionnaire study to identify gender differences in psychosocial profile at entry into cardiac rehabilitation found that women had higher scores of social inhibition compared with men. [77] The authors concluded that women may benefit from women-specific counselling and women-only smaller exercise classes. [77] A small randomised controlled trial compared a 7-day retreat designed to begin lifestyle changes for postmenopausal women with coronary heart disease (including exercise training, yoga, diet, and smoking cessation) with usual care (defined as no intervention beyond the usual care of their physician). [585] There were 10 women in the intervention (9 post MI or CABG, 1 primary PCI) and 9 (8 post MI or CABG, 1 primary PCI) in the control group. At 4 and 12 months follow up, there were significant behavioural improvements in adherence to diet, physical activity and stress management for the intervention group. The authors concluded that a women's retreat may be effective in improving emotional social support and relationships with cardiac rehabilitation staff. [585]

In summary, suggested interventions to improve uptake in women patients include women-only education sessions, appropriate exercise choices, specific counselling, strategies to improve social support, and a women's retreat.

Older patients

We found no controlled trials of interventions to improve uptake or adherence to cardiac rehabilitation in elderly patients following an MI. The Health Technology Assessment [58] noted that older patients may not receive the same amount of advice from physicians on cardiac risk reduction as younger patients. Invitation to cardiac rehabilitation is often lower in older patients. [187] A US survey has found that older patients prefer home-based programmes while younger patients have a preference for comprehensive clinic-based rehabilitation. [631]

Overall, the literature on access to cardiac rehabilitation programmes for specific patients groups (elderly, women, socially deprived, ethnic minority groups, patients from rural areas) is scarce. The majority of interventions that have been suggested have not been evaluated. An important aspect in enhancing participation is the need to create 'user friendly' rehabilitation that minimises barriers and is adaptable to individual patient needs. There is a need for trials of interventions applicable to all patients, particularly targeting under-represented groups.

A set of audit criteria developed by GDG members for under-represented groups is at the end of this chapter.

Health economics for methods of inceasing uptake of cardiac rehabilitation

There were no studies found examining the cost effectiveness of methods used to increase uptake of cardiac rehabilitation. The GDG asked for an economic analysis to be done. Using effectiveness data from [58] and output data from the cardiac rehabilitation versus no cardiac rehabilitation economic model described in the appendix, a simple model was constructed comparing three different strategies used to increase the uptake of cardiac rehabilitation, usual care, the use of motivational letters and the use of telephone calls plus a visit from a healthcare professional.

The base case model showed that the cost effectiveness of the strategy of sending letters compared to usual care to increase uptake of cardiac rehabilitation is about £ 8000/QALY gained. The strategy of using a telephone call and a home visit by a healthcare professional compared to sending letters is about £ 8400/QALY gained, both of which are below the level usually considered to be affordable in

the NHS. These results are sensitive to assumptions about efficacy of letters and the use of phones plus healthcare professionals

In conclusion, the use of letters or telephone calls plus a visit from a healthcare professional to improve uptake of cardiac rehabilitation is cost effective, but the result is sensitive to efficacy of the interventions.

5.4 Education and information provision

5.1.3.5 After an MI without complications, patients can usually travel by air within 2 –3 weeks. Patients who have had a complicated MI need expert individual advice (GPP).

5.4.2.5 Travel/flying

The Aerospace Medical Association, Medical Guidelines Task Force (2003, Alexandria, Virginia) recommends that patients with recent uncomplicated MI should not fly until at least 2 to 3 weeks have passed, and they are back to usual daily activities. It is noted that some airlines allow travel earlier. The Taskforce on Practice Guidelines of the American College of Cardiology / American Heart Association recommend that post MI patients should undergo a symptom-limited treadmill test at 10-14 days for prognosis and functional capacity. The data obtained by stress testing prior to flight is invaluable in estimating the patient's ability to tolerate air travel. The absence of residual ischaemia or symptoms on maximal testing is reassuring and probably more helpful than arbitrary time restrictions. [14] Patients with complicated MIs or with limited ambulation should wait longer, or at least until they are medically stable on their treatment regimen. Patients with an MI in the past should not have a problem with air travel, unless there is significant angina or left ventricular dysfunction when individual assessment may be required. [14]

Chapter 6 - Drug therapy

The current recommendations can be found at www.nice.org.uk/guidance/ng185

6.1.2 ACE inhibitors

6.1.2.1 Short term treatment with an ACE inhibitor in unselected patients immediately after an MI was associated with a small reduction in mortality (1++).

6.1.2.2 Long term treatment with an ACE inhibitor in patients with signs of heart failure and or left ventricular systolic dysfunction who have recently experienced an MI was associated with substantial reduction in all-cause mortality, recurrent MI and readmission for heart failure (1++).

6.1.2.3 In patients with chronic heart failure and left ventricular systolic dysfunction, including patients who had had an MI in the past, treatment with ACE inhibitors improved life expectancy and reduced the risk of hospitalisation for heart failure (1++).

6.1.2.4 In stable patients with coronary artery disease without heart failure or known left ventricular systolic dysfunction, long term treatment with an ACE inhibitor was associated with a modest reduction in total and cardiovascular mortality, non-fatal MI and coronary revascularisation (1++).

6.1.2.5 Long term treatment with an ACE inhibitor in patients after MI with heart failure or left ventricular systolic dysfunction, with or without heart failure is cost effective when compared to placebo.

6.1.2.6 In stable patients with coronary artery disease without heart failure or known left ventricular systolic dysfunction, long term treatment with an ACE inhibitor was cost effective.

6.1.2.7 No trials were found which looked at the effectiveness of an ARB compared with placebo in patients after acute MI.

6.1.2.8 In one small trial of patients with stable coronary artery disease, without heart failure or left ventricular systolic dysfunction, treatment with an ARB compared to placebo was associated with a reduction in the composite end point of revascularisation, non-fatal MI and cardiovascular death (1-).

6.1.2.9 In one study, although not in a second, there were fewer cardiovascular deaths in patients treated with an ACE inhibitor compared to in those treated with an ARB (1++)

6.1.2.10 There were no trials found comparing treatment with an ACE inhibitor and an ARB which included patients early after MI without heart failure or left ventricular systolic dysfunction.

6.1.2.11 There was no difference in total mortality or cardiovascular mortality and morbidity in patients with heart failure and or left ventricular systolic dysfunction treated within 10 days of acute MI with the combination of an ACE inhibitor and ARB compared to those treated with either agent alone (1++).

6.1.2.12 In patients with chronic heart failure and left ventricular systolic dysfunction, including patients who had had an MI in the past, treatment with an ARB did not improve life expectancy compared to treatment with an ACE inhibitor (1++).

6.1.2.13 A post hoc analysis showed a reduction in investigator reported hospitalisation for MI or heart failure in patients with heart failure and or LV systolic dysfunction treated within 10 days of acute MI with the combination of an ACE inhibitor and ARB compared to those treated with either agent alone (1++).

6.2.2 Clinical effectiveness of ACE inhibitors

6.2.2.1 Unselected patients

A meta analysis of 18 randomised controlled trials in unselected patients immediately following an acute MI found that ACE inhibitor treatment improved survival compared with placebo (OR 7%, 95% CI 2% to 11% by a fixed effects model, OR 7%, 95% CI -1% to 14% by a random effects model). [416] Trial follow up ranged from 3 days to 19 months. However, the majority of patients were randomised in two large trials [285] [246] in which recruitment was within the first 24 hours of MI and the follow up duration was five and six weeks respectively.

6.2.2.2 Patients with left ventricular systolic dysfunction

A meta analysis of six randomised controlled trials of patients who had experienced an acute MI and who had heart failure and or left ventricular systolic dysfunction found that ACE inhibitor treatment increased survival compared with placebo (OR 26%, 95% CI 17% to 34% by a fixed effects model, OR 26%, 95% CI 14% to 38% by a random effects model). [416] The duration of follow up in the trials ranged from 2 weeks to 42 months, and all but one had at least six months follow up.

In a study of patients with anterior MI and systolic blood pressure ≥ 100 mmHg early (day 1) initiation of the ACE inhibitor ramipril compared with delayed initiation (day 14) was associated with attenuation of left ventricular remodelling and a more rapid recovery of left ventricular ejection. [471]

6.2.3 Clinical Effectiveness of long term ACE inhibitor therapy

Patients with preserved left ventricular function

A meta analysis of six randomised controlled trials in patients with stable coronary artery disease (CAD) and preserved left ventricular function found that treatment with an ACE inhibitor compared to placebo was associated with a reduction in cardiovascular mortality (RR 0.83, 95% CI 0.72 to 0.96), non-fatal MI (RR 0.84, 95% CI 0.75 to 0.94), all-cause mortality (RR 0.87, 95% CI 0.81 to 0.94), and coronary revascularisation rates (RR 0.93, 95% CI 0.85 to 1.00). [19] Mean duration of follow up was 4.4 years, range 2 to 4.8 years. The majority of patients were recruited to three large trials [29] [76,195] in which 53%, 65% and 55% respectively had had a prior MI, at least one month earlier in one trial [29] and at least three months in the other two trials. [76,195]

Patients with left ventricular systolic dysfunction

A systematic review of long term trials of patients after MI with left ventricular systolic dysfunction identified 3 large trials which each recruited more than 1000 patients with a minimum follow up of one year. Assignment to treatment with an ACE inhibitor, initiated between 3 and 16 days after an acute MI, was associated with a reduction in mortality (OR 0.74, 95% CI 0.66 to 0.83), readmission for heart failure (OR 0.73, 95% CI 0.63 to 0.85) and recurrent MI (OR 0.80, 95% CI 0.69 to 0.94) compared with placebo, over a median follow up of 31 months. [191] With the inclusion in the meta analysis of two randomised control trials of patients with reduced left ventricular systolic function, with [553] or without [554] symptoms of heart failure, the findings were similar. Seventy five percent of patients in these other two trials had a previous history of MI.

A 12 year follow up study of the SOLVD trials, in which 75% of participants had a previous MI [553] [554] found a reduction in all-cause mortality (OR 0.90, 95% CI 0.84 to 0.95) and cardiac deaths in those assigned for the duration of the trial to ACE inhibitor treatment compared to those assigned to placebo [299]. This result was consistent in both the prevention trial which recruited asymptomatic patients, and the treatment trial which recruited patients with symptomatic CHF. A follow up study of a randomised controlled trial which recruited patients with left ventricular systolic dysfunction 3

to 7 days after acute MI [470] found that at 12 years, patients who had been assigned to ACE inhibitor treatment during the original trial period for 2 to 4 years had a reduced risk of all-cause mortality (RR 0.89, 95% CI 0.80 to 0.99), all-cause hospitalisation (RR 0.92, 95% CI 0.88 to 0.96), and cardiovascular hospitalisations (RR 0.95, 95% CI 0.91 to 1.00). [83] Randomised controlled trials of the effectiveness of ACE inhibitor treatment in patients with chronic heart failure and left ventricular systolic dysfunction, which included patients with an MI in the past, is examined in The NICE guideline Chronic Heart Failure: national clinical guideline for diagnosis and management in primary and secondary care, 2003. [415] These guidelines state that systematic reviews of randomised controlled trials comparing ACE inhibitor to placebo have found that ACE inhibitor therapy in patients with heart failure due to left ventricular systolic dysfunction increases life expectancy compared to placebo. The effect is more marked in patients with more severe LV systolic impairment, or more severe symptoms, although there is benefit for all New York Heart Association functional classes (NYHA). Compared with placebo, ACE inhibitor therapy also reduces the risk of hospitalisation for heart failure in such patients, and also for patients with asymptomatic left ventricular systolic dysfunction.

6.2.4 Clinical effectiveness of ARBs

Only one trial comparing an ARB with placebo in patients after MI without chronic heart failure was found. This was a small un-blinded study which randomised 406 patients with CAD, of which 69% had a previous MI, to treatment with candesartan or placebo. Treatment with candesartan was associated with a reduction in the primary endpoint which was the combination of revascularisation, non-fatal MI and cardiovascular mortality ($P < 0.03$). [318] There were no studies found which specifically examined the efficacy of treatment with an ARB in asymptomatic patients with left ventricular dysfunction.

6.2.5 Clinical Effectiveness of ACE inhibitors versus ARBs

No randomised controlled trials were identified that evaluated treatment with an ARB compared to treatment with an ACE inhibitor in patients with acute MI and preserved left ventricular function.

Two randomised controlled trials compared treatment with an ACE inhibitor to an ARB in patients with acute MI complicated by left ventricular systolic dysfunction and found no significant difference in all-cause mortality between the two groups. [157 473] One randomised controlled trial showed a non significant difference in all-cause mortality (RR 1.13, 95% CI 0.99 to 1.28) and a significant reduction in cardiovascular mortality in favour of the ACE inhibitor captopril compared with the ARB losartan (RR 1.17, 95% CI 1.01 to 1.34), [157] although in the second study there was no significant difference in mortality between treatment with the ACE inhibitor captopril and the ARB valsartan (HR 1.00, 95% CI 0.90 to 1.11). [473] Treatment with the ARB losartan was better tolerated than with the ACE inhibitor captopril in one trial. [157]

Randomised controlled trials of the effectiveness of ARB treatment in patients with chronic heart failure and left ventricular systolic dysfunction, including those with an MI in the past, were reviewed in the NICE guideline Chronic Heart Failure: national clinical guideline for diagnosis and management in primary and secondary care, 2003. [415] This guideline recognised that the evidence for ARB treatment in patients with chronic heart failure was still emerging and at the time of publication none of the ARBs were licensed for use in heart failure in the UK. Several large randomised trials were ongoing, but at the time that the NICE guideline for chronic heart failure were published, ARBs had not been shown to increase life expectancy compared to ACE inhibitor therapy for patients with heart failure due to left ventricular systolic dysfunction in several randomised controlled trials. However, the 2003 NICE guideline for the management of chronic heart failure states; ‘ARBs may provide an alternative to ACE inhibitors for patients intolerant of ACE inhibitors (for example, because of cough)’

Adverse effects of ACE inhibitors were reported for three trials included in the systematic review of treatment with an ACE inhibitor in patients with left ventricular systolic dysfunction. [191] Hypotension and renal dysfunction occurred more frequently in the ACE inhibitor treated group.

A randomised controlled trial conducted in patients with symptomatic heart failure and left ventricular systolic dysfunction, who were not receiving ACE inhibitors due to previous intolerance, found that patients were more likely to stop treatment with the ARB candesartan than placebo due to renal dysfunction (6.1% versus 2.7% in all patients, respectively), hyperkalaemia (1.9% versus 0.3% in all patients, respectively) and hypotension (3.7% versus 0.9% in all patients, respectively) [243]. Patients were more likely to stop treatment with candesartan for a particular reason if they had previously been intolerant to treatment with an ACE inhibitor for the same reason.

Based on the available evidence the guideline development group came to the decision that treatment with an ARB should be considered as a second line alternative to an ACE inhibitor for those individuals with a documented history of ACE inhibitor intolerance.

6.2.6 Clinical effectiveness of ACE inhibitors plus ARBs versus ARBs or ACE inhibitors

A randomised controlled trial of patients within 0.5 to 10 days of an acute MI complicated by left ventricular systolic dysfunction compared treatment with the combination of an ARB plus an ACE inhibitor with an ACE inhibitor alone, or an ARB alone. During a median follow up of 24.7 months, treatment with the combination of the ARB valsartan and the ACE inhibitor captopril had no effect on all-cause mortality (HR 0.98, 95% CI 0.90 to 1.09), cardiovascular mortality (RR 1.00, 95% CI 0.89 to 1.11), non-fatal MI or hospitalisation for heart failure compared either with captopril alone or valsartan alone. [473] Combination therapy was associated with an increased rate of adverse events compared with either captopril alone or valsartan alone.

Randomised controlled trials of the effectiveness of ACE inhibitor and ARB treatment combined in patients with chronic heart failure and left ventricular systolic dysfunction, which included patients with an MI in the past, is examined in The NICE guideline Chronic Heart Failure: national clinical guideline for diagnosis and management in primary and secondary care, 2003. [415] This guideline states that one systematic review of 17 randomised controlled trials demonstrated that the combination of ARBs and ACE inhibitors did not reduce risk of mortality as compared to ACE inhibitors on their own. However, significantly fewer patients required hospitalisation with the dual therapy. A large randomised controlled trial reported similar effects on mortality and hospitalisation with worsening heart failure. It was recognized that at the time of publication other trials were in progress which would further inform the use of the combination of ACE inhibitors and ARBs in patients with chronic heart failure. [415]

6.2.8 Health economics of ACE inhibitors in patients after MI with LV systolic dysfunction, or with heart failure

Ten studies were found which compared the use of ACE inhibitors in selected patients after MI with left ventricular systolic dysfunction with and without heart failure, or with heart failure. Nine studies used effectiveness data from studies of patients early after MI; five from the AIRE study [524 370 26 174 263] three from the SAVE study [364 387 587] and one from the TRACE study. [339] The tenth study [120] used effectiveness data from the SOLVD trial in which 66% patients in the treatment study and 80% in the prevention study had a previous history of MI.

The NICE guidelines for the diagnosis and management of chronic heart failure in primary and secondary care also makes recommendation for treatment with ACE inhibitors in patients with heart failure due to left ventricular systolic dysfunction, including patients with chronic heart failure and a history of an MI in the past. This guideline states that 'Treatment of heart failure with ACE inhibitors is cost effective, largely due to the costs saved from the reduced risk of hospitalisation. Treatment

can be cost saving and has very favorable cost effectiveness ratios even when conservative assumptions are employed.'

The AIRE Study [12] recruited patients with clinical heart failure early after acute MI, and examined the effectiveness of treatment with ramipril compared with placebo. Five studies examined cost effectiveness based on the AIRE study [12] in different healthcare systems.

A Spanish study [263] found that compared with placebo, the incremental cost per life year gained with ramipril ranged between Euro 4784 in year 1 to Euro 1550 in the fourth year. The sensitivity analyses showed that the estimated cost per LYG was robust to wide variations in the baseline values.

A South African study [26] assessed the cost effectiveness of ramipril compared to placebo. The results were stratified according to age. The use of ramipril results in an incremental cost/life year gained, which ranges between R67 907 (approximately £6200) in the first year to R16 808/LYG (approximately £1500) in the fourth year. When the quality of life of the patients was taken into account, the cost-utility analysis shows an incremental cost/QALY of R21 382 (approximately £1900) for those younger than 65 years of age and R18 029 (approximately £1600) for those older than 65 years of age. The results were robust in sensitivity analyses.

A German study [524] reported an estimated ICER for ramipril compared to placebo of DM 2456/life year gained after 3.8 years (approximately £1100) and DM 8271/LYG (approximately £3650) for the first year. Monte-Carlo simulation results showed that ramipril was cost effective, dominating the alternative in 5% of the cases. In 99% of the cases the ICER ranged between DM 2500 to DM 8500 suggesting that ramipril is highly cost effective.

A Swedish study [174] reported incremental cost effectiveness ratios of treatment with ramipril compared with placebo over 3 treatment periods: 1, 2, and 3.8 years. The ICERs ranged from SEK 33 033 for the 1-year treatment to (approximately £2800) SEK 14 148 (approximately £1200) for the 3.8-year treatment period. Two way-sensitivity analyses indicated that the study results were robust although hospital costs had an impact on the ICERs.

Finally, a UK based study, [370] reported cost/life years gained from treatment with ramipril compared to placebo ranging between £425 for the first year to £286 in the fourth year. These results were not sensitive to the timeframe of the model, but were sensitive to changes in hospitalisation costs.

The SAVE study recruited patients early after acute MI without symptoms of heart failure and a left ventricular ejection fraction of equal to, or less than, 40%, and examined the effectiveness of treatment with captopril compared to placebo. Three studies examined cost effectiveness in different healthcare systems.

An Italian study [364] reported an incremental cost per death avoided with captopril treatment of 33, 229 million lira (approximately £13 800). The cost/life year gained was 14, 708 million lira (approximately £6100). The model was sensitive to changes in values of the prices of captopril, cost of revascularisation procedures, the number of cardiovascular deaths prevented, and the number of years of life saved.

A Dutch study [387] estimated the costs and effects of treatment. The cost per life year gained with captopril treatments was DF122 887 (approximately £2350) at 4 years. Costs per life-year gained for 20 years of treatment was estimated at DF115 729 (approximately £1600), with 95% of all estimates between DF10 and DF150 000 for the 20 year treatment. The results were sensitive to the cost of captopril and the occurrence and prevention of clinical heart failure, although the authors did not report by how much the result would change.

An American study [587] developed a Markov model from a US third payer's perspective to assess the cost effectiveness of captopril compared to placebo. The model used two scenarios based on assumptions about death rates with captopril versus placebo beyond 4 years. The first scenario

included equal mortality rates, whilst the second extrapolated a difference in mortality for the remaining time in the model. In the first scenario, the ICER of captopril ranged from $3600/QALY (approximately £2000) for 80-year old patients to $60 800/QALY (approximately £34 500) for 50-year old patients. In the second scenario, ICERs ranged from $3700 to $10 400/QALY, depending on age. The model was robust to changes in estimates of variables when they were varied individually over wide ranges for patients aged over 60 years, but for those aged 50 years it was only sensitive to the cost of captopril and changes in utilities.

The TRACE study [316] recruited patients early after acute MI with left ventricular systolic dysfunction (corresponding to a left ventricular ejection fraction ≤ 35%) and examined the effectiveness of treatment with trandolapril compared with placebo.

A French study [339] evaluated the cost effectiveness of trandolapril. The cost/life year saved was 6950 French francs (approximately £900). Probabilistic sensitivity analyses showed that in 7.4% of the cases trandolapril use was cost saving (trandolapril dominated placebo) and in 92.6% of the cases the ICER was positive, and still within the acceptable ranges of cost/LYS, lying between FF 8410 (95%CI 7990 to 8840) according to the bootstrap method (approximately £1050).

The SOLVD trials recruited patients with left ventricular systolic dysfunction (ejection fraction ≤ 35%) with [553] and without [554] symptoms of heart failure and examined the effectiveness of treatment with enalapril compared to placebo. At baseline, 66% and 80% of patients respectively had a history of MI. One study was found examining cost effectiveness of ACE inhibitors using SOLVD data from the prevention arm.

One study [120] based on US costs modelled the long-term economic and clinical impact of using enalapril versus usual therapy for hypertensive patients with left ventricular dysfunction. Enalapril dominated the alternative (more effective and less costly) in the base-case. These results were robust in sensitivity analysis. The cost effectiveness acceptability curve showed that there was a less than 10% probability that enalapril treatment would increase the costs in comparison with placebo, and less than 3% probability that the cost per life-year gained would exceed $3,000 (approximately £1800) in the trial observation period analysis. In the lifetime projection analysis, the probability that enalapril dominated placebo was 94%.

In summary treatment with ACE inhibitors compared to placebo is cost effective in patients early after MI with left ventricular systolic dysfunction, with and without heart failure. Treatment with ACE inhibitors in patients with heart failure and left ventricular systolic dysfunction, which includes those with an MI in the past, has previously been reported as cost effective in the NICE guideline for the diagnosis and management of chronic heart failure in primary and secondary care.

6.2.9 Health economics of ACE inhibitors in patients after MI with preserved LV function

Five studies were found which addressed this question. [361] [36] [544] [38] [66] The use of ACE inhibitors was compared with placebo in MI patients without left ventricular systolic dysfunction but at high risk of cardiovascular events. All five studies used data from the HOPE study which examined the effectiveness of treatment with ramipril compared to placebo, and in which 53% had a history of a previous MI at least 1 month earlier. Two were UK studies. [38] [361]

The first UK study [38] constructed a decision analytical model to estimate long-term benefits and costs of treatment with ramipril compared to placebo from the NHS perspective. The base-case analysis showed a discounted ICER of £5544 per LYG. The ICERs did not vary substantially with age. For example the ICER reduces to £2814 for those aged 52 year while increasing to £10 291 in for those aged 80 years due to differences in life expectancy.

The second UK study [361] assessed treatment with ramipril compared to placebo in patients with different risks of cardiovascular death classified as low, medium and high. The cost effectiveness of

ramipril for the base case analysis was £14 700 (5 years) and £2800 (lifetime treatment). These results were sensitive to drug costs as well as pre-treatment risk. The costs of ACE inhibitors have fallen since this study was done.

Three studies have examined the cost effectiveness of treatment with ramipril compared to placebo in three other healthcare systems.

The first study [544] assessed the clinical and economic impacts of treatment with ramipril in an Australian high-risk population. The incremental cost effectiveness analysis showed the estimated cost per life-year saved to be A$17 214, 95% CI (A$8 338 to 39 536), approximately (£6600/LYG) The results were sensitive to risk of cardiovascular death, cost and risk of revascularisation.

The second study [36] modelled the cost effectiveness of ramipril in patients with an increased risk of cardiovascular events, including a subgroup of patients with diabetes, in a Swiss context. The incremental cost effectiveness ratio of ramipril versus placebo was CHF 6 005 per life-year gained in the base case analysis (approximately £2500/LYG). The diabetic population had a much more favourable ICER of CHF 3790/LYG (approximately £1600).The results remained robust in sensitivity analysis and showed that ramipril was cost effective in more than 90% of the cases, if society was willing to pay up to CHF10000/LYG (approximately £4100) per additional LYG.

The third study [66] evaluated the long-term treatment with ramipril in patients at high risk of cardiovascular events in a Swedish context. The estimated ICERs were SEK 16 600/LYG (approximately £1200) when direct medical costs for cardiovascular reasons only were considered and SEK 45 400/LYG (approximately £3400) when direct medical costs for all diseases were considered. Using quality of life weights from the literature they found that the cost/QALY to be SEK 26 600 (approximately £2000). The results were sensitive to reduction in life expectancy at the end of the trial period.

An additional analysis was undertaken to examine the cost effectiveness of treatment with ACE inhibitors compared to placebo in patients with preserved left ventricular dysfunction. The analysis used effectiveness data from a meta analysis [19] which meta analysed data from six trials. [76 428 195 29 353 478] A Markov model was developed to evaluate the incremental costs and effects of lifetime treatment with ACE inhibitors from a UK NHS perspective. The results suggested treatment with ACE inhibitors was cost effective with an estimated ICER of about £3400/QALY gained for men and about £3700 for women compared with placebo; well below the level considered affordable in the NHS (about £20 000 to £30 000 per QALY). This was robust in sensitivity analysis.

In conclusion treatment with ACE inhibitors in patients with an MI at least 1 month earlier and preserved left ventricular function is cost effective. See Appendix C for the full model.

6.4 Beta blockers

The current recommendations can be found at www.nice.org.uk/guidance/ng185

6.4.1 Evidence statements

6.4.1.1 In unselected patients after acute MI, long-term treatment, (greater than 6 months and up to 4 years) with beta blockers resulted in 1.2% annual risk reduction and 23% reduced odds of death compared with placebo (1++).

6.4.1.2 In one randomised controlled trial of patients after acute MI with LV systolic dysfunction, treatment with carvedilol, in addition to ACE inhibitor therapy, reduced all-cause mortality, cardiovascular-cause mortality, non-fatal MI, and the combination of all-cause mortality or non-fatal MI (1++).

6.4.1.3 Carvedilol compared to placebo is cost effective in patients with LV dysfunction.

6.4.1.4 In patients after acute MI with asymptomatic left ventricular systolic dysfunction, beta blocker treatment reduced cardiovascular mortality and the risk of developing CHF (2+).

6.4.1.5 There is inconclusive evidence about the optimum time to initiate beta -blocker treatment in patients after an MI.

6.4.1.6 There is no evidence that unselected patients after acute MI treated with a beta blocker should routinely stop treatment.

6.4.1.7 No trials were found which examined the effectiveness of initiating beta blocker treatment in patients with a proven MI in the past and preserved left ventricular function.

6.4.1.8 In randomised controlled trials, initiation of beta blocker treatment in patients with chronic heart failure, of whom some had had a previous MI, reduced mortality and the need for hospitalisation. (NICE Chronic Heart Failure guideline) (1++).

6.4.2 Clinical effectiveness of beta blockers

6.4.2.1 In unselected patients

A meta analysis of 51 short term randomised controlled trials (up to 6 weeks) of treatment with beta blockers in patients after acute MI, found a non significant reduction in the odds of death compared with placebo. [200] In a more recent short term randomised controlled trial in patients recruited within 24 hours of a suspected acute MI and with a mean follow up of 16 days after MI, intravenous beta blocker treatment followed by oral therapy did not reduce total mortality in hospital. [107] Beta blocker therapy reduced the risk of reinfarction (OR 0.82, 95% CI 0.72 to 0.89) and ventricular fibrillation (OR 0.83, 95% CI 0.75 to 0.93), although there was an increase in the risk of cardiogenic shock (OR 1.30, 95% CI 1.19 to 1.41). The excess of cardiogenic shock was mainly during days 0 to 1, whereas the reduction in risk of ventricular fibrillation and reinfarction emerged more gradually.

An observational study of post MI patients aged 65 years or older found that the rate of in-hospital mortality was lower in patients treated with beta blockers compared with untreated patients (mortality rate: 5.1% and 8.1% respectively, P ≤ 0.001), even after adjustment for baseline differences in demographic, clinical, and treatment characteristics between the two groups (OR 0.81, 95% CI 0.75 to 0.87). [325]

A meta analysis of 31 long term randomised controlled trials (6 weeks to 48 months) found that treatment with beta blockers in patients after acute MI reduced the odds of death by 23% compared with placebo (pooled random effects, OR 0.77, 95% CI 0.69 to 0.85). [200] The number needed to treat for one year to avoid one death was 84. Individually, four out of nine beta blockers were found to significantly reduce the odds of death, namely propranolol (OR 0.71, 95% CI 0.59 to 0.85), timolol (OR 0.59, 95% CI 0.46 to 0.77), metoprolol (OR 0.80, 95% CI 0.66 to 0.96), and acebutolol (OR 0.49, 95% CI 0.25 to 0.93). The randomised controlled trials that included propranolol, timolol and metoprol made up 63% of the available evidence in the meta analysis. The evidence for acebutolol was supported by a single moderately sized study which is open to considerable measurement error.

No randomised controlled trials were found comparing different times for initiating beta blocker therapy after acute MI. However, a separate analysis of the meta analysis of long term randomised controlled trials showed that an initial intravenous dose of beta blocker had no additional benefit on mortality, although there was no reason to delay treatment. [200]

No randomised trials were found which compared the effectiveness of different available beta blockers. However, the Cooperative Cardiovascular Project [234] examined the two year survival of patients after MI, and reported outcomes in patients prescribed different beta blockers. This survey was based on the entire population of acute care hospital claims for acute MI to the Health Care Financing Administration for Medicare for an 8 month period, with data staggered so that most discharges fell between February 1994 and July 1995. 69 338 patients after MI were prescribed a beta blocker on discharge (metoprolol 65%, atenolol 25%, propranolol 6%, other 4%). Overall, patients treated with any beta blocker on discharge had a 40% reduction in mortality compared with those not treated with a beta blocker. Those prescribed metoprolol and atenolol had very similar survival rates after 1 and 2 years of follow up, while patients discharged on propranolol had a lower survival rate. [233]

Literature searching did not identify any randomised controlled trials of initiating beta blocker treatment in unselected patients with a proven MI in the past (greater than 1 years).

No randomised controlled trials were identified which examined the effectiveness of continued beta blocker treatment in patients treated after an acute MI. A follow up study after a 3 year randomised trial examined the effect of the withdrawal of the beta blocker metoprolol during a mean of 51 months. After beta blocker withdrawal the number of deaths, reinfarctions or cerebrovascular events in patients previously assigned to a beta blocker was not significantly different to the number of events in patients assigned to placebo. [443] However, patients who had had a further MI within the last year before withdrawal were not included, and a third of patients who stopped beta blocker treatment restarted treatment, for clinical indications. A further follow up study was conducted after a 3 year randomised controlled trial comparing beta blocker therapy with timolol versus placebo in patients after acute MI. In patients who survived the entire period, beta blocker prescription increased gradually to 28.7% in the previously allocated placebo group, and decreased to 59.5% in the previously allocated beta blocker group, whereas in those who died beta blocker therapy was prescribed less frequently 18.6% and 44.3%, respectively. [460] During follow up, the mortality curves of the two groups identified by the original randomisation to timolol treatment or placebo continued to rise in parallel, demonstrating a consistent effect on mortality over the period of the observation period. The mortality curves for patients divided by age (less than 65 years, or 65 years and older) showed the same pattern.

A systematic review examined the incidence of fatigue, sexual dysfunction and depression in randomised placebo controlled trials of beta blocker therapy. Fatigue occurred more frequently, and was more likely to lead to withdrawal from treatment in patients assigned to beta blockers compared to in those assigned to placebo. The occurrence of sexual dysfunction was similar in the two groups, although more patients in the beta blocker group withdrew from treatment due to sexual dysfunction. There was no difference in the incidence of depressive symptoms. [315]

6.4.2.2 Patients with left ventricular systolic dysfunction and or heart failure

A meta regression analysis assessed the extent to which inclusion of patients with heart failure or evidence of major cardiac dysfunction influenced the outcome of randomised controlled trials of beta blocker therapy in patients with a history of MI. Treatment may have begun at any stage after MI, and may have commenced intravenously. [274] There was a non significant interaction between treatment with beta blockers and the presence of heart failure, and the authors concluded that there is a lack of evidence to show that the relative benefits of beta blockers after MI are different in patients with or without heart failure, but that the absolute benefit may be greater in the former because of a higher baseline risk of heart failure and death.

A more recent randomised placebo controlled trial examined the effectiveness of beta blocker treatment with carvedilol in addition to other standard current therapy in patients after acute MI with reduced left ventricular function (ejection fraction ≤ 40%). Patients were recruited within 3 to 21 days of an acute MI, 46% had had thrombolysis or primary angioplasty and 97% were treated with an ACE inhibitor. Trial follow up was for a mean of 1.3 years and a minimum of 3 months, and all-cause mortality (HR 0.77, 95% CI 0.60 to 0.98), cardiovascular mortality (HR 0.75, 95% CI 0.58 to 0.96), non-fatal MI (HR 0.59, 95% CI 0.39 to 0.90), and the combination of all-cause mortality or non-fatal MI (HR 0.71, 95% CI 0.57 to 0.89) was lower in those treated with carvediolol compared with placebo. [135]

Randomised controlled trials of the effectiveness of beta blocker treatment in patients with chronic heart failure and left ventricular systolic dysfunction, which included patients with an MI in the past is examined in The NICE guideline Chronic Heart Failure: national clinical guideline for diagnosis and management in primary and secondary care, 2003. [415] This guideline states that many large clinical trials reviewed in four meta-analyses, and one subsequent randomised controlled trial, have shown that several beta blockers increase life expectancy in patients with heart failure due to LV systolic dysfunction compared with placebo. The best evidence exists for bisoprolol, carvediol and modified-release metoprolol, while there is little evidence for other beta blockers. There are no randomised controlled trials of atenolol, or some other commonly used beta blockers, in patients with heart failure.

6.4.2.3 Patients with asymptomatic left ventricular dysfunction

No randomised controlled trials were identified that assessed beta blocker therapy only in patients with asymptomatic LV dysfunction.

A post hoc analysis of a randomised controlled trial examining the effectiveness of ACE inhibitor therapy versus placebo in early post MI patients with left ventricular dysfunction without overt heart failure [470] found that beta blocker usage was associated with a reduction in the risk of cardiovascular death and the development of CHF. [600]

Two studies examined the impact of beta blocker treatment in patients with a previous MI. A post hoc analysis of a randomised controlled trial of ACE inhibitor therapy versus placebo in asymptomatic patients with left ventricular dysfunction, in which 75% had a history of MI, [554] found that beta blocker usage was associated with a lower mortality rate compared with placebo (P = 0.01). [179]

An observational study in elderly patients with prior MI and asymptomatic left ventricular systolic dysfunction examined four patient treatment groups: treatment with beta blockers alone, treatment with ACE inhibitors alone, treatment with the combination of beta blockers and ACE inhibitors, and no treatment. Follow up ranged from a mean of 19 to 34 months. Compared with no treatment, there was a reduction in new coronary events of 25% by treatment with beta blockers alone (P = 0.001), of 17% by treatment with ACE inhibitors alone (P = 0.001), and of 37% by treatment with the combination of beta blockers and ACE inhibitors (P = 0.001). Compared with no treatment, the development of CHF was reduced by 41% with beta blocker treatment alone (P = 0.001), by 32% with ACE inhibitors alone (P = 0.001), and by 60% with the combination of beta blockers and ACE inhibitors (P = 0.001). [30]

6.4.3 Economic evidence

Two studies from outside the UK comparing beta blockers and placebo were appraised. A Swedish study [442] was a cost consequence study which compared metoprolol with placebo enumerating arrays of health outcome measures alongside costs. Effectiveness data were drawn from the Stockholm Metoprolol study which included 66% post MI patients. The use of beta blockers resulted in a reduction of cardiovascular events and the cost per patient for metoprolol treated participants was Kr 118610 (approximately £11 981) compared to Kr 137220 (approximately £13 861) for participants in the control arm. However there was no difference in mortality.

An American cost effectiveness analysis [230] used effectiveness data from a pooled meta analysis of beta blocker trials conducted by the authors. Results were stratified by age and risk groups. Risk was defined as low, medium and high risk of mortality observed in a 15 year prognostic study The age groups were 45, 55 or 65 years. The authors explored two possibilities in their analysis. One was a conservative assumption that observed treatment gains will cease immediately once the treatment is stopped, and another that the gains will gradually disappear. The cost/LYG ranged between $23 457 for a low risk 45 year old man to $3609/LYG for a high risk 65 year old man using a conservative assumption. When a best guess assumption is used the cost/LYG ranged between $12 855 for a low risk 45 year old man to $2427/LYG for a high risk 65 year old man.

Mortality risk was the major cost effectiveness driver and age did not affect the cost effectiveness ratios (ICERs), The ICERs for the low risk groups were over 5 fold the ICERs for the high risk groups for all age groups.

An additional analysis was undertaken to inform the decisions of the guideline group. This examined the cost effectiveness of treatment with the beta blocker, carvedilol, in patients with left ventricular systolic dysfunction who met the inclusion criteria of the CAPRICORN trial. [135] A Markov model was developed to evaluate the incremental costs and effects of lifetime treatment from a UK NHS perspective, and the base case results were presented for 65-year-old men and women early after MI with left ventricular dysfunction. The results suggested that treatment with carvedilol is highly cost effective for this population with an ICER of about £1100/QALY gained, compared with placebo which is well below the level usually considered to be affordable in the NHS (about £20 000 to £30 000 per QALY).

In conclusion treatment with beta blockers compared to placebo in patients early after MI is cost effective. This conclusion for unselected patients is based on two non-UK studies. However, given the substantial clinical effectiveness of beta blockers and their cost, it is highly unlikely that any new cost effectiveness study will conclude differently. The findings in patients with left ventricular systolic dysfunction are robust and the use of beta blockers in these patients is cost effective.

6.3 Antiplatelet therapy

The current recommendations can be found at www.nice.org.uk/guidance/ng185

6.5 Vitamin K antagonists

Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng185

6.5.1 Evidence statements

6.5.1.1 In patients after acute MI high-intensity warfarin compared to placebo is associated with reduction in cardiovascular events and mortality (Grade 1+).

6.5.1.2 There is inconsistent evidence that high-intensity warfarin is more effective than aspirin in reduction of mortality or reinfarction and stroke (Grade 1+).

6.5.1.3 High-intensity warfarin is associated with a higher incidence of major bleeding compared to aspirin (1+).

6.5.1.4 Treatment with aspirin is likely to be more cost effective when compared with with warfarin in patients with CAD.

6.5.1.5 In patients after acute MI, the combination of low intensity warfarin and aspirin did not consistently reduce the incidence of major cardiovascular events compared to aspirin on its own, and was associated with an increased risk of haemorrhagic complications (1+).

6.5.1.6 In patients after an acute MI, the combination of moderate intensity warfarin (target INR 2 to 2.5) and aspirin compared to aspirin on its own resulted in a reduction in the composite end point of death, non-fatal MI or stroke (1+).

6.5.1.7 In patients after an acute MI, the combination of moderate intensity warfarin (target INR 2 to 2.5) and aspirin compared to aspirin on its own was associated with an increased risk of bleeding (Grade 1+).

6.5.1.8 In patients after acute MI, the combination of moderate intensity warfarin (target INR 2 to 2.5) and aspirin did not reduce the incidence of major cardiovascular events compared to high intensity warfarin (target INR 2.8 to 4.2) on its own, and was associated with a similar risk of bleeding (Grade 1+).

6.5.2.1 Introduction

Oral anticoagulants have been used in patients with vascular disease for over 40 years, but their role is controversial due to a number of reasons. Firstly, initial randomised control trials in patients who have experienced an MI have provided conflicting results. Secondly, anticoagulants are inconvenient to use because they require careful monitoring and dose adjustment, and in clinical trials may be more closely managed than in everyday clinical practice. Thirdly, there is debate over whether the associated risk of bleeding justifies their use. Fourthly, antiplatelet therapies have proven to be effective in reducing vascular complications and to be relatively safe.

Two important findings directed further research on anticoagulants in CAD. Rates of recurrent vascular events in patients with suspected unstable angina or MI without initial ST elevation remained high, despite the use of antiplatelet agents. [632] In addition, there was evidence of persistent biochemical stimulus to thrombosis for several months after an acute MI and in unstable angina patients, even in the presence of aspirin. [386]

These observations stimulated a number of large well conducted randomised controlled trials examining anticoagulation therapy at different intensities with and without concomitant aspirin therapy. Initially randomised controlled trials tested high intensity anticoagulation therapy, International normalised ratio (INR) = 2.8 to 4.8, versus placebo. [545], [595] The INR is a value derived from a standardized laboratory test that measures the effect of anticoagulant. The laboratory materials used in the test are calibrated against internationally accepted reference preparations, so that variability between laboratories and different reagents is minimized. Normal blood has an INR of 1. Therapeutic anticoagulation often aims to achieve an INR value of 2.0 to 3.5.

More recent randomised controlled trials have evaluated anticoagulants versus aspirin [278 598] and the combination of anticoagulants and aspirin versus aspirin alone [278 598 126 188 269] with anti-coagulation treatment in the moderate-intensity (INR = 2 to 3), and the low intensity (INR < 1.5) ranges.

6.5.2.2 Vitamin K antagonists

Two randomised control trials compared high intensity anticoagulant therapy with placebo in patients early after acute MI, both with mean follow up times of 37 months. [545 595] One study found that warfarin treatment resulted in a significant reduction in all-cause mortality (RR 24%, 95% CI 4% to 44%), reinfarction (RR 34%, 95% CI 19% to 54%) and stroke (RR 55%, 95% CI 30% to 30 to 77%). [545] The second study showed that nicoumalone or phenprocoumon treatment led to no reduction in all-cause mortality; however anticoagulant therapy did reduce recurrent MI (HR 0.47, 95% CI 0.38 to 0.59), vascular (HR 0.65, 95% CI 0.55 to 0.76) and cerebrovascular events (HR 0.60, 95% CI 0.40 to 0.90). [595] In both studies, treatment was associated with significantly more major bleeding episodes compared with placebo. [545 595]

A meta analysis of 16 randomised controlled trials of oral anticoagulant therapy in patients with established CAD found that high intensity anticoagulant therapy (INR > 2.8) reduced total mortality (OR 22%, 95% CI 13% to 31%), reinfarction (OR 42%, 95% CI 34% to 48%) and stroke (OR 48%, 95% CI 33% to 60%) compared with control, although it was associated with increased major bleeding. [23] Meta analysis of 4 randomised controlled trials of moderate intensity anticoagulation therapy (INR 2 to 3) found that anticoagulation treatment only reduced reinfarction compared with control (OR 52%, 95% CI 37% to 64%), and was also associated with increased major bleeding. [23]

6.5.2.3 Vitamin K antagonists compared to aspirin alone

Meta analysis of 7 randomised control trials in patients with CAD found that, compared with aspirin, moderate- or high-intensity anticoagulant therapy did not reduce the risk of all-cause mortality, reinfarction or stroke. [23] Major bleeding was increased with anticoagulant therapy. Subsequent to the publication of this meta analysis, two randomised controlled trials showed that high-intensity anticoagulant therapy was more effective than aspirin treatment for reducing the combination endpoint of death, non-fatal MI or stroke (warfarin versus aspirin, RR 0.81, 95% CI 0.69 to 0.95) [278] (coumadin versus aspirin, HR 0.55, 95% CI 0.3 to 1.00). [598] In the first study which recruited patients with acute MI, anticoagulation therapy compared to aspirin treatment reduced the risk of reinfarction (warfarin versus aspirin: RR 0.74, 95% CI 0.55 to 0.98) and thromboembolic stroke (warfarin versus aspirin: RR 0.52, 95% CI 0.28 to 0.97) but not mortality during a trial follow up of approximately four years. [278] In contrast, the second study found anticoagulation treatment did reduce risk of mortality compared to aspirin treatment (coumadin versus aspirin: HR 0.28, 95% CI 0.09 to 0.82), with no difference for reinfarction and stroke. [598] This study recruited patients with acute coronary syndrome of which 88% had an MI and the mean follow up was 26 months.

6.5.2.4 Vitamin K antagonists plus aspirin compared to aspirin alone

A randomised controlled trial in patients within 42 days of an acute MI and a mean follow up of 5 years found that low-dose warfarin added to aspirin therapy did not reduce the risk of the combination of cardiovascular death, reinfarction, although it did reduce the risk of stroke (aspirin 7.1% versus aspirin + warfarin 4.7%, P = 0.004) when compared to aspirin therapy alone. The combination increased the risk of bleeding. [269] Two further randomised controlled trials in patients with an acute MI up to 3 weeks earlier did not demonstrate any clinical benefit of the combination of aspirin and low intensity anticoagulation therapy over aspirin monotherapy, [126 188] although there was a significant increase in major bleeding associated with the combination. Low intensity warfarin therapy was used for these studies: one study achieved an INR of 1.04 with 1 mg warfarin plus aspirin treatment and 1.19 with 3 mg warfarin plus aspirin treatment [126] The second study achieved a mean INR value of 1.8. [188]

Two randomised controlled trials compared moderate intensity anticoagulant therapy (INR 2.0 to 2.5) plus aspirin with aspirin alone. [278] [598] One study in patients with acute coronary syndrome of which 88% had an MI found that moderate intensity coumadin therapy was more effective than aspirin alone in reducing coronary events and all-cause mortality (HR 0.28, 95%CI 0.09 to 0.82). A mean INR of 2.4 was achieved and the mean follow up was 26 months. Major bleeding rates were low in both groups. Minor bleeding in the aspirin plus coumadin group was significantly higher compared with the aspirin alone group. [598] The second study in patients hospitalised for acute MI found that aspirin plus warfarin therapy led to a lower risk of the combination outcome of death, non-fatal infarction or thromboembolic stroke compared with aspirin alone (RR 0.71, 95% CI 0.60 to 0.83). [278] Warfarin plus aspirin therapy was associated with an increased risk of non-fatal bleeding compared to aspirin alone. [278] Trial follow up was for approximately four years and a mean INR of 2.2 was achieved.

6.5.2.5 Vitamin K antagonists plus aspirin compared to warfarin alone

A randomised control trial that compared moderate intensity warfarin treatment plus aspirin with high intensity warfarin treatment alone found the combination treatment did not reduce the risk of the combination endpoint of death, non-fatal reinfarction or thromboembolic stroke compared to warfarin monotherapy. The bleeding risk was similar in the two groups. [278]

6.5.3 Health economics of vitamin K antagonists

6.5.3.1 Warfarin compared to placebo

One non UK study was identified which examined the cost effectiveness of warfarin compared with placebo. [596] This was a cost minimisation analysis and was undertaken in Holland. The authors used effectiveness data from the Anticoagulation in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) study and AntiPlatelets Trialists Collaboration study (APT). The total cost was Dfl 17 671 813 (approximately £6800 000) for the warfarin group and Dfl 19 222 590 (approximately £7400 000) for the placebo group. The savings per patient due to the intervention, discounted at 5%, was Dfl 906 (approximately £350). The incremental cost of intervention was negative suggesting that anticoagulation administration results in savings compared to placebo. These results were robust in sensitivity analysis.

6.5.3.2 Warfarin compared to aspirin

One Italian study was identified which compared warfarin with aspirin. [224]

Gianetti et al assessed the cost effectiveness of warfarin compared to aspirin, for secondary prevention of CAD, within a European context. The authors used effectiveness data from the ASPECT and the APT. This was a cost minimisation analysis since they did not synthesize the costs and benefits.

Costing was done using three different methods, which all yielded comparable results. The total cost per patient per year, using DRG mean total costs, was ECU2, 150 (approximately £1660) for warfarin and ECU2187 (approximately £1680) for aspirin. Results were sensitive to variations in the aspirin-warfarin efficacy ratio. This is a ratio that lies between 0 and 1. If the ratio is 1 or close to 1, it means there is no difference in efficacy between two interventions while the further away from 1 it follows there is a big difference in effectiveness between interventions. Warfarin was no longer the cost effective strategy in Italy once an efficacy ratio of approximately 0.72 is reached. From this analysis, it would appear that the cost effectiveness of warfarin relative to aspirin would be relatively favourable. However if the results of WARIS II are considered which found the efficacy ratio of 0.81, it appears that aspirin is the cost effective strategy compared to warfarin.

In conclusion the cost effectiveness of warfarin relative to aspirin is unclear, but largely weighs in favour of aspirin especially in light of the new evidence which shows that the efficacy ratio can be as high as 0.81.

6.9 Lipid lowering agents

Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng185

6.9.1 Evidence statements for lipid lowering agents

6.9.1.1 In a meta analysis of 14 randomised controlled trials of secondary prevention in CHD, statin therapy was associated with a reduction in all-cause mortality, CVD mortality, CHD mortality, fatal MI and coronary revascularisation compared with placebo (1++).

6.9.1.2 In a systematic review of cohort studies, randomised trials, voluntary notifications to voluntary regulatory authorities and published case reports the incidence of adverse events was low. The estimate for rhabomyolysis was 3.4 per 100,000. However, the incidence of adverse events may be increased inpatients treated with high dose statin, compared to low dose, and in patients treated with statins which are oxidised by cytochrome P450 3A4 (1++).

6.9.1.3 There is conflicting evidence that fibrates reduce cardiovascular risk in patients after MI (1++).

6.9.1.4 No studies were found testing the effectiveness of cholesterol absorption inhibitors for secondary prevention in patients after MI.

6.9.2 Clinical effectiveness of lipid lowering agents

The NICE Technology Appraisal [417] entitled 'Statins for the prevention of cardiovascular events' 2006 states that:

Statin therapy is recommended for adults with clinical evidence of cardiovascular disease

The recommendation was based on the meta analysis of 14 randomised controlled trials of secondary prevention in CHD. Of these, four were conducted in MI and / or angina patients [461 517 344 346]. Four studies recruited patients with CAD [477 128 302 575], two studies recruited patients with CAD and hypercholesterolaemia [57 498] one study recruited patients with mild CAD [408], two studies enrolled patients after coronary balloon angioplasty [535] and [56], and one study enrolled patients after percutaneous coronary intervention [534]. Statin therapy was associated with a reduction in the following clinical outcomes compared with placebo: all-cause mortality (RR 0.79, 95% CI 0.70 to 0.90), CVD mortality (RR 0.75, 95% CI 0.68 to 0.83), CHD mortality (RR 0.72, 95% CI 0.64 to 0.80), fatal MI (RR 0.57, 95% CI 0.45 to 0.72), unstable angina (RR 0.82, 95% CI 0.72 to 0.94), hospitalisation for unstable angina (RR 0.90, 95% CI 0.70 to 0.90), non-fatal stroke (RR 0.75, 95% CI 0.59 to 0.95), new or worse intermittent claudication (RR 0.64, 95% CI 0.46 to 0.91) and coronary revascularisation (RR 0.77, 95% CI 0.69 to 0.85).

The NICE Technology Appraisal [417] further states that:

The decision to initiate statin therapy should be made after an informed discussion between the responsible clinician and the individual about the risks and benefits of statin treatment, and taking into account additional factors such as comorbidity and life expectancy.

When the decision has been made to prescribe a statin, it is recommended that therapy should be initiated with a drug with a low acquisition cost (taking into account required daily dose and product price per dose).

6.9.2.1 Timing of statin therapy

No studies were identified that compared early statin with delayed statin therapy at the same dosage.

A randomised trial examined the effectiveness of early statin initiation in patients with acute coronary syndrome, in which 53% had had an acute non-Q wave MI [441]. This trial randomised patients to either high dose atorvastatin (80 mg daily) or placebo. Patients were hospitalised within 24 hours of the index event and randomised after a mean of 63 hours of hospitalisation. During or after hospitalisation for the index event, most were treated with aspirin, three quarters with beta blockers and half with ACE inhibitors or ARBs. The study period was for 16 weeks and during this period the primary end point (combination of death, non-fatal acute MI, cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischemia with objective evidence requiring emergency rehospitalisation) was reduced in patients randomised to atorvastatin, compared to those randomised to placebo, a 16% relative risk reduction. There were no significant differences in the individual outcomes of death, non-fatal MI or cardiac arrest with resuscitation, although there was a lower risk of recurrent symptomatic myocardial ischaemia with objective evidence requiring emergency rehospitalisation in the group assigned to atorvastatin. Stroke was a secondary outcome with a significant lower incidence in the atorvastatin group. The reduction in the primary endpoint did not depend on the baseline level of LDL-cholesterol with similar risk reductions in those with a baseline LDL-cholesterol above or below the median. At the end of the study, compared to baseline, LDL-cholesterol had increased by an adjusted mean of 12% in the placebo group and had decreased by an adjusted mean of 40% in the atorvastatin group. More patients in the atorvastatin group developed liver transaminase levels more than 3 times the upper limit of normal. There were no cases of myositis [441].

A study has examined early use of statin therapy within the first 24 hours of admission for acute MI using data from the National Registry of Myocardial Infarction 4 (NRMI 4)[193]. NRMI 4 is a

prospective, observational database of consecutive patients admitted with acute MI to 1230 participating hospital throughout the United States. Data was collected on 300 823 patients. A total of 174 635 patients who had had an acute MI were included in the analysis. Of these, statin therapy was used in the first 24 hours of hopsitalisation in 39 096 patients (22.4%). There were 21 978 patients who were newly started on statin therapy and 17 118 patients who were continued on statin therapy. Statin therapy was discontinued in 9411 patients. There were 126 128 patients who did not receive statins before or within the first 24 hours of hospitalisation. New initiation of statin treatment within the first 24 hours of admission was associated with a decreased risk of in-hospital mortality compared with no statin use (4.0% versus 15.4%, respectively, adjusted OR 0.62, 95% CI 0.57 to 0.67). There was also a decreased risk of in-hospital mortality in patients who continued statin therapy compared with no statin usage (5.3% versus 15.4%, respectively, adjusted OR 0.58, 95% CI 0.54 to 0.63). In contrast, those patients that had been treated with statin therapy before hospitalisation but whose statin therapy had been discontinued had a slightly higher mortality risk compared with patients who did not use statins (16.5% versus 15.4%, respectively, adjusted OR 1.12, 95% CI 1.05 to 1.20). Early stain use, whether newly initiated or continued was also associated with a decreased incidence of cardiac arrest, cardiogenic shock, cardiac rupture, and ventricular tachycardia / ventricular fibrillation. There was no reduced risk of recurrent acute MI in patients treated with early statin therapy compared with no early statin usage [193].

No randomised controlled trials were identified which examined concordance with statin treatment in patients treated before discharge compared to those treated later. However, the guideline group felt that initiation of statin treatment as soon as possible was likely to have a beneficial effect on concordance.

6.9.2.2 Adverse events

All randomised controlled trials which have examined the effectiveness of statin treatment excluded potential participants and a number of randomised controlled trials have also included a pre-randomisation run in phase during which participants were treated with an open label statin. At the end of this time some chose not to enter the trial or had some other reason not to do so, and were not randomised. Thus, tolerability may be better and the incidences of adverse events lower in the trials than in unselected patients. However, there are other sources of information which have helped inform the risk of adverse events.

In a systematic review of cohort studies, randomised trials, voluntary notifications to voluntary regulatory authorities and published case reports the incidence of rhabdomyolysis for statins other than cerivastatin was 3.4 (1.6 to 6.5) per 100 000 person years, with a case fatality of 10% [334]. The incidence of rhabdomyolysis was higher (4.2 per 100 000 person years) with lovastatin, simvastatin or atorvastatin (which are oxidised by cytochrome P450 3A4 (CYP3A4) than with pravastatin or fluvastatin (which is not oxidised by CYP3A4). The rates were about 10 times higher for cerivastatin and also for statins other than cerivastatin when taken with gemfibrozil. For cervastatin taken with gemfibrozil, the incidence was 2 000 times higher, an absolute annual incidence of about 10%. The mean incidence of myopathy in patients treated with statins was 11 per 100 000 person years. There was no significant difference in the incidence of a raised creatine kinase to ≥ 10 fold the upper limit of normal on a single measurement during routine monitoring between participants in 13 trials allocated to a statin compared to those allocated placebo (83 per 100 000 person years of statin treatment versus 60 per 100,000 person years with placebo). In two trials, neither had CK elevated on 2 consecutive measurements [334].

The incidence of liver disease attributable to statin therapy is rare. In 3 randomised trials of pravastatin, both gall bladder and hepatobiliary disorders were less common in patients allocated statins than in those allocated placebo. In randomised trials elevations in alanine aminotransferase (ALT) and or aspartate aminotransferase (AST) were reported more frequently in patients treated with statins than with placebo, and elevations of ALT (defined as ≥ 3 times the ULN, or 120 U/L) were

found in 300 statin-allocated and 200 placebo-allocated participants per 100 000 person-years. However, statistical heterogeneity across trials was noted. An elevated ALT on 2 consecutive measurements was found in 110 participants allocated to a statin and in 40 participants allocated to placebo per 100 000 person-years. Elevations in ALT were reported more frequently with higher doses of statin. The systematic review reported that in 100 000 person-years of statin use, denying 300 persons with elevated ALT the benefit of a statin (or 110 persons if repeat measures were used) would prevent liver disease in less than 1 person [334].

The guideline group noted that not treating patients with an elevated ALT prevents clinical liver disease in an extremely small number of patients. There was a consensus to recommend measurement of ALT or AST prior to starting statin treatment, so that in the event of an elevated level being found during statin treatment, it would be known if this had been present before initiation. However, patients with raised liver enzymes should not routinely be excluded from treatment with a statin [334].

Trials showed no excess of renal disease or proteinuria in statin allocated participants. There is evidence that statins cause peripheral neuropathy but the attributable risk is small (12 per 100 000 person years). No change in cognitive function was found in trials of statins in elderly patients [334].

6.9.3 Clinical effectiveness of fibrates, niacin and ezetimibe

A randomised controlled trial in patients with prior MI (≥ 6 months but <5 years before enrolment: 78%), and or stable angina pectoris compared treatment with the fibrate bezafibrate and placebo [51]. Patients were followed up for mean of 6.2 years. Treatment with bezafibrate did not confer any benefit over placebo for the primary endpoint of the combination of fatal MI, non-fatal MI or sudden death. The overall incidence of any adverse event was 69% in both groups, and the frequency of adverse event was similar in both groups [51].

In a further small randomised controlled trial in men aged less than 45 years with a prior MI 3 to 6 months earlier, treatment with bezafibrate, was associated with a reduction in the incidence of coronary events (reinfarction, CABG, PCI, sudden death or cardiovascular death) compared with placebo [137]. Concomitant drug therapy at the start of the trial was as follows: aspirin 11%, beta blockers 99%, long acting nitrates 27%, ACE inhibitors 0%. At follow up aspirin use had increased to 45% and ACE inhibitor therapy to 5%. Trial follow up was for 5 years. Total cholesterol and very low density lipoprotein cholesterol decreased in both groups, but to a significantly greater extent in the bezafibrate group. Triglyceride levels fell in the bezafibrate group, and increased in the placebo group. LDL- cholesterol did not change substantially in either group [137].

A randomised controlled trial in patients with CAD (61% had a prior MI) recruited men with an HDL-cholesterol of 1.0mmol/l or less, LDL-cholesterol 3.6mmol/l or less and triglycerides less than 3.4 mmol/l [512]. At the start of the trial the majority of participants were taking aspirin, but less than half beta blockers and less than a quarter ACE inhibitors. Patients were randomised to either the fibrate gemfibrozil or placebo. Mean trial follow up was 5.1 years. Compared with placebo, gemfibrozil therapy was associated with a reduction in the primary endpoint (combination of non-fatal MI or death from CHD) (RR 0.78, 95% CI 0.65 to 0.93) and a reduction in the incidence of the secondary combination outcome of non-fatal MI, death from CHD or stroke (RR 0.76, 95% CI 0.64 to 0.89). Compared with placebo, gemfibrozil therapy was also associated with a reduction in non-fatal MI (RR 0.77, 95% CI 0.62 to 0.96) investigator-designated stroke (RR 0.81, 95% CI 0.52 to 0.98), transient ischaemic attack (RR 0.61, 95% CI 0.25 to 0.67), carotid endarterectomy (RR 0.55, 95% CI 0.40 to 0.78) and hospitalisation for CHF (RR 0.78, 95% CI 0.62 to 0.98), but, was not associated with a reduction in death due to CHD, death from any cause, confirmed stroke, CABG or PCI and hospitalisation for unstable angina. One year after randomisation, the mean total cholesterol level was 4% lower, the mean triglyceride level 31% lower and the mean HDL-cholesterol level 6% higher

in patients assigned to gemfibrozil. Mean LDL-cholesterol levels were the same in both groups. Gemfibrozil treatment was associated with a greater incidence of dyspepsia [512].

The GDG considered that while the trial evidence for fibrate treatment in patients after MI was contradictory, two studies did report evidence of benefit in cardiovascular outcomes [137 512], and as such fibrates may be offered to those patients after MI who are intolerant of statins.

Treatment with niacin compared with placebo has been examined in a randomised controlled study in patients with a prior MI [122]. This was an early study which randomly assigned patients with prior MI to six treatment groups; low and high conjugated oestrogen therapy, clofibrate, dextrothyroxine sodium, niacin and placebo. Niacin treatment was associated with a 9.9% reduction in total cholesterol from baseline and a 26.1% reduction in triglycerides (after correcting for changes in the placebo group). Compared with placebo, niacin treatment reduced the incidence of non-fatal MI (8.9% Niacin versus 12.2% placebo, $Z = -2.88$, $P < 0.005$) and also the combination of coronary death or non-fatal MI (22.8% Niacin versus 26.2% placebo, $Z = -2.23$, $P < 0.01$), but was not associated with a reduction in the incidence of the following outcomes: all-cause mortality, the individual components of all-cause mortality, definite pulmonary embolism (fatal or non-fatal), fatal or non-fatal stroke or intermittent cerebral ischaemic attack, definite or suspected fatal or non-fatal pulmonary embolism or thrombophlebitis and also any definite or suspected fatal or non-fatal cardiovascular event. Patients in the niacin group had a greater incidence of the following side effects compared with the placebo group: the combination of diarrhoea, nausea, vomiting, black tarry stools, stomach pain, flushing, itching of skin, urticaria, other type of rash, pain or burning when urinating, decrease in appetite, unexpected weight loss, and excessive sweating [122].

No randomised controlled trials were identified comparing the cholesterol absorption agent, ezetimibe with placebo in patients after MI.

6.9.4 Health economics of lipid lowering agents

6.9.4.1 Economics of statins

The latest HTA on statins was published in 2005 [417]. The HTA covered both primary and secondary prevention and was based on models of cost effectiveness. The guidance recommended statins with the lowest acquisition cost for people with clinical evidence of CVD and its recommendations will be adopted in this guideline. Further cost effectiveness analyses, including high versus standard dose statin treatment will underpin recommendations in the lipid modification guidelines.

6.9.4.2 Economics of fibrates

Only one study [430] was found which met the inclusion criteria. This study used data from a single trial the US Department of Veterans Affairs (VA) Cooperative Studies Program HDL-C Intervention Trial (VA-HIT) [512] which compared gemfibrozil with placebo. ICERs were estimated using two sets of prices for gemfibrozil. Using the prices of gemfibrozil that were negotiated by the VA, gemfibrozil was cost saving, while using prices found outside the VA, the ICERs ranged between $6300 and $17 100/QALY.

In conclusion, treatment with gemfibrozil was cost effective in a selected group of men with CHD with low levels of HDL-cholesterol and low levels of LDL-cholesterol. This finding was robust in sensitivity analysis. However the relevance to the general post MI population not selected on the basis of an initial lipid profile or by gender is not clear.

Chapter 8 Selected patient subgroups

8.1 Patients with hypertension

The National Service framework for coronary heart disease, Department of Health (www.doh.gov.uk) states that for people with diagnosed CHD or other occlusive arterial disease the intervention for blood pressure is:

- Advice and treatment to maintain blood pressure below 140/85 mmHg.

The guideline development group agreed that in uncomplicated patients with a history of MI the optimal target blood pressure should be in accordance with NICE Hypertension Guideline 2006, which is currently ≤ 140/90 mmHg. [421] [414]

8.2.4 Patients with left ventricular dysfunction

In addition, a Technology Appraisal entitled 'Evidence summary of Technology Appraisal 95: Implantable cardioverter defibrillators for arrhythmias: NICE 2006' [543] makes recommendations regarding patients with a history of MI and LV systolic dysfunction concerning implantable cardioverter defibrillators, currently as follows:

NICE states that:

Implantable cardioverter defibrillators are recommended for patients in the following categories.

- Secondary prevention, that is, for patients who present, in the absence of treatable causes, with one of the following:
  - Having survived a cardiac arrest due to either ventricular tachycardia (VT) or ventricular fibrillation (VF)
  - Spontaneous sustained VT causing syncope or significant haemodynamic compromise
  - Sustained VT without syncope or cardiac arrest, who have an associated reduction in ejection fraction (LVEF of less than 35%) but no worse than class III of the New York Heart Association (NYHA) functional classification of heart failure.
- Primary prevention, that is, for patients who have:
  - A history of previous (more than 4 weeks) myocardial infarction (MI) and either:
  - LV dysfunction with an LVEF of less than 35% but no worse than class III of the NYHA functional class of heart failure

and

  - Non-sustained VT on Holter (24 hour electrocardiogram [ECD]) monitoring

and

  - Inducible VT on electrophysiological (EP) testing

OR

  - LV dysfunction with an LVEF of less than 30% (no worse than class III of the New York Heart Association functional classification of heart failure)

and

  - QRS duration of equal to more than 120 milliseconds.

A familial cardiac condition with a high risk of sudden death, including long QT syndrome, hypertrophic cardiomyopathy, Brugada syndrome or arrhythmic right ventricular dysphasia (ARVD), or having undergone surgical repair of congenital heart disease

Appendix Q: CG48 appendices (2007)

Q.1 Scope

Guideline title

Post MI: secondary prevention in primary and secondary care for patients following a myocardial infarction.

Short title

Post MI : secondary prevention

1. Background

The National Institute for Clinical Excellence ('NICE' or 'the Institute') has commissioned the National Collaborating Centre for Primary Care to develop a clinical guideline on secondary prevention for patients following a myocardial infarction in primary and secondary care (post MI), as part of updating the existing inherited NICE guideline 'Prophylaxis for patients who have experienced a myocardial infarction' (inherited Guideline A, April 2001) for use in the NHS in England and Wales. The guideline will provide recommendations for good practice that are based on the best available evidence of clinical and cost effectiveness.

The Institute's clinical guidelines will support the implementation of National Service Frameworks (NSFs) in those aspects of care where a Framework has been published. The statements in each NSF reflect the evidence that was used at the time the Framework was prepared. The clinical guidelines and technology appraisals published by the Institute after an NSF has been issued will have the effect of updating the Framework.

2. Clinical need for the guideline

The incidence of myocardial infarction (MI) for men aged between 30 69 is about 600 per 100,000 and for women about 200 per 100,000. From these statistics, the British Heart Foundation (2004) have estimated that there are about 147,000 MIs per year in men of all ages in the UK and 121,000 in women, giving a total of 268,000 cases. In the UK, the number of people who have had an MI at some point in their lives is 838,000 for men, and about 394,000 for women. This gives a total of over 1.2 million cases (British Heart Foundation, 2004).

MI is a complication of coronary heart disease (CHD). CHD is a preventable disease. The death rate from CHD has been falling since the early 1970s, and for people aged below 75, rates have fallen by almost 25% since 1996 (Department of Health, 2004). In spite of these improvements, when compared internationally, the UK death rate from CHD is relatively high with more than 103,000 deaths per year (Department of Health, 2003). Comparing Western European countries, only Ireland and Finland have a higher death rate from CHD than the UK (British Heart Foundation, 2004).

CHD death rates vary with age, gender, socio-economic status, ethnicity and UK geographic location.

- Death rates in men aged under 75 are nearly three times higher than in women (Department of Health, 2003).
- Death rates in affluent areas in the UK are half of those in deprived areas (Department of Health, 2003).

- People of South Asian origin have almost a 50% higher death rate compared with the general population (Wild and McKeigue, 1997).

Management

Cardiac rehabilitation programs have been consistently shown to reduce mortality rates in CHD patients (Canadian Coordinating Office for Health Technology Assessment, 2003). Cardiac rehabilitation is the coordinated sum of interventions required to ensure the best possible physical, psychological and social conditions to enable the CHD patient to preserve or resume optimal functioning in society. It also aims to slow or reverse progression of the disease. Cardiac rehabilitation cannot be regarded as an isolated form or stage of therapy, but must be integrated within secondary prevention services, of which it forms only one facet (WHO definition, 1993).

A number of drugs have been shown to improve outcome after MI.

3. The guideline

The guideline development process is described in detail in two booklets that are available from the NICE website (see 'Further information'). The guideline development process – an overview for stakeholders, the public and the NHS describes how organisations can become involved in the development of a guideline. Guideline development methods – information for National Collaborating Centres and guideline developers provides advice on the technical aspects of guideline development.

This document is the scope. It defines exactly what this guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health and Welsh Assembly Government (see Appendix).

The areas that will be addressed by the guideline are described in the following sections.

4. Population

Groups that will be covered

Adult patients (≥ 18 years) who have had an MI. The following groups are included:

a) patients following the early acute phase, which can be defined as 48 hours after admission, providing the patient is stable

b) patients who are identified as having had a proven MI at some point in the past.

Groups that will not be covered

a) Patients that have had a non-spontaneous MI (for example, a periprocedural MI, which may occur after percutaneous coronary intervention).

b) Patients who have had a non-atherosclerotic-induced MI, which is an MI in patients without underlying coronary artery disease.

5. Healthcare setting

a) The guideline will cover the care received from healthcare professionals who have direct contact with, and make decisions concerning, the care of people who have survived the early acute phase of an MI.

b) The guideline will address care in primary and secondary and, where appropriate, tertiary centres.

c) The management of patients in accident and emergency departments will not be considered.

d) The guideline will also be relevant to the work, but will not cover the practice, of those working in the occupational health services and voluntary sector.

6. Clinical management of secondary prevention

Areas that will be covered

a) The guideline will cover the management of MI following the early acute phase.

b) The guideline will cover pharmacological intervention including commencement of treatment and drug combination, monitoring of treatment and duration of treatment. The guideline will advise on the use of the following classes of drugs within the licensed indications for secondary prevention. This will include advice for those with and without left ventricular dysfunction:

i. antiplatelet drugs including aspirin

ii. beta-adrenoreceptor blocking drugs

iii. lipid modifying drugs with specific reference to the additional advice for patients post MI and incorporating the statins technology appraisal and cross referencing to the hyperlipidaemia guideline.

iv. omega-3-acid ethyl esters

v. a. angiotensin-converting enzyme inhibitors

b. angiotensin II receptor blockers

vi. calcium channel blockers

vii. potassium channel activators

viii. eplerenone

ix. vitamin K antagonists

Drugs that are subject to NICE Technology Appraisal (section 6) will be cross-referred to as appropriate.

Recommendations on treatment options will be based on the best evidence available to the guideline development group. Note that guideline recommendations will normally fall within licensed indications; exceptionally, and only where clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use the Summary of Product Characteristics/British National Formulary for information about possible side-effects and to inform their decisions for individual patients.

c) The guideline will include detection and identification of, and secondary prevention in, patients with left ventricular systolic dysfunction post MI, sign-posting, where appropriate, to the heart failure guideline and subsequent updates, and Technology Appraisals.

d) The guideline will advise on the optimal control of blood pressure post MI sign-posting to the hypertension guideline where appropriate.

e) The guideline will cover the criteria for referral for assessment for possible coronary revascularisation.

f) The guideline will cover cardiac rehabilitation. Cardiac rehabilitation is defined as the sum of activities required to influence favourably the underlying cause of the disease, as well as to ensure the patients the best possible physical, mental and social conditions so that they may, by their own efforts, preserve, or resume when lost, as normal a place as possible in the life of the community (WHO definition, 1993).

g) The guideline will cover methods for the routine assessment and recording of each individual patient's rehabilitation needs and the provision of an individualized rehabilitation plan for each patient.

h) The guideline will cover exercise, education sessions, and resumption of physical, sexual, social and vocational activities and psychological aspects of rehabilitation.

i) The guideline will include advice on the following ongoing lifestyle modifications for people following an MI:

i. diet

ii. exercise and regular physical activity

iii. alcohol consumption

iv. smoking cessation will be cross referred to the Technology Appraisal 'Guidance on the use of nicotine replacement therapy (NRT) and bupropion for smoking cessation', April 2002.

j) The guideline will pay particular attention to the clinical needs of groups which may be at risk of being excluded from secondary prevention following MI, including:

i. black and minority ethnic groups

ii. older people

iii. lower socio-economic groups

iv. women

v. rural communities.

Areas that will not be covered

a) Diagnosis of an MI either acutely or retrospectively.

b) Interventions specific to the early phase of the acute MI including (but not exclusively):

i. re-perfusion strategies in ST elevation infarcts

ii. conservative versus invasive management in non-ST elevation infarcts including angiography.

c) Different methods of assessment of cardiac status before possible coronary revascularisation.

d) The additional management of diabetes and glycaemic control in patients who have had an MI as this is more appropriately placed in the revisions of the diabetes guidelines.

e) The additional management of chronic heart failure which would be more appropriately placed in revisions of the chronic heart failure guideline.

f) Symptom control such as the management of angina.

7. Status

Scope

This is the final scope.

Guideline

The development of the guideline recommendations will begin in November 2004.

8. Further information

Information on the guideline development process is provided in:

- The guideline development process – an overview for stakeholders, the public and the NHS
- Guideline development methods –information for National Collaborating Centres and Guideline Developers.

These booklets are available as PDF files from the NICE website (www.nice.org.uk). Information on the progress of the guideline will also be available from the website.

9. Relevant NICE publications

Clinical Guidelines:

- Type 1 diabetes: diagnosis and management of type 1 diabetes in children, young people and adults, September 2004.
- Type 2 diabetes – management of blood pressure and blood lipids, October 2002.
- Type 2 Diabetes - management of blood glucose, September 2002.
- Hypertension – management of hypertension in adult patients in primary care, August 2004.
- Chronic heart failure – management of chronic heart failure in adults in primary and secondary care, October 2003.
- Hyperlipidaemia – identification and management of hyperlipidaemia as part of cardiovascular risk assessment in primary care (ongoing)
- Obesity – the prevention, identification, evaluation, treatment and weight maintenance of overweight and obesity in adults (ongoing).
- Familial hypercholesterolaemia - identification and management (ongoing)

Technology Appraisals:

- Guidance on the use of nicotine replacement therapy (NRT) and bupropion for smoking cessation, April 2002.
- Clopidogrel and modified-release dipyridamole in the prevention of occlusive vascular events , (ongoing).
- Clopidogrel in the treatment of non-ST-segment-elevation acute coronary syndrome, July 2004.

- Statins for the prevention of coronary events in patients at increased risk of developing CHD or those with established CHD (ongoing).
- Angina and myocardial infarction - myocardial perfusion scintigraphy , November 2003.
- Implantable cardioverter defibrillators (ICDs) for the treatment of arrhythmias - review of guidance no 11, (ongoing).

Q.2 Health Economic Modelling

Q.2.1 Economic analysis of cardiac rehabilitation

Q.2.1.1 Introduction

Cardiac rehabilitation (CR) after an acute myocardial infarction (MI) is a recommended therapy with established clinical effectiveness. It comprises mainly of supervised exercise training, relaxation and education. There is evidence that CR reduces the risk of total and cardiac related mortality, subsequent revascularizations, occurrence of non-fatal MI, improvements in work and physical capacity and perceived quality of life. [439], [294],[572], [110] [58]

In England the National Service Framework for Coronary heart disease (NSF-CHD) identifies patients who have survived acute MI and those who have undergone Coronary artery bypass graft (CABG) and percutaneous transluminal coronary angiography (PTCA) as initial priorities for CR [147]

The provision of exercise-based CR in the United Kingdom (UK) has increased since the early 1990s. The British Cardiac Society Working Party Report showed that 99 programmes were in place 1989 [61] [60]. By 1997 their numbers had tripled. By year 2000 in England alone 220 centres were identified in a survey of implementation of the NSF-CHD but concluded that there is still scope for improving services so that those in need are offered rehabilitation [58]

Although CR is considered effective in quickening recovery and improving prognosis, not all patients participate in a CR programme. Surveys in UK have given diverse estimates of uptake, ranging between 14-59% after MI ([58] [178],[60]

Costs of CR services vary by format of delivery. The most recent survey the British Association of cardiac rehabilitation (BACR) and the British Heart Foundation (BHF) suggest that costs per patient vary widely between £50-£712 depending on level of staffing, equipment used and intensity of the programme. In all cases staff costs ranged between 64-80% of the total [58], [60] [343]

The wider economic benefits of CR are believed to derive primarily from reduced secondary utilization of inpatient medical resources. Studies from USA [13], [439], Australia [252] and Sweden [341] have shown that CR is cost effective. However, there are no cost effectiveness studies of CR in the UK.

This study had two objectives. The first was to assess the cost effectiveness of comprehensive CR compared to no CR. A second objective was to assess the comparative cost effectiveness of some of the methods used to increase uptake of CR after an MI. The methods considered were firstly the use of telephone calls together with home visits carried out by a healthcare professional (HCP), and secondly invitation letters. Costs relevant to the National Health Service (NHS) were considered.

Q.2.1.2 Methods

Population and sub-groups

The model considered a cohort of patients who had had a recent MI. The trial evidence that the model is based on included relatively few older (>65) or black patients, so the results may not be reliable for these groups.

Interventions compared

The analysis assessed the costs and effects of CR compared with no CR. Additionally it assessed using the output from the CR model, the cost effectiveness of two methods of increasing uptake and adherence compared to 'current practice/usual care', i.e. current uptake of CR. These two methods were firstly the use of phone calls together with home visits by a HCP, in which the HCP was assumed to make contact over the phone four times, each followed by a home visit and secondly the use of two consecutive invitation letters to a CR programme over a period of 6 weeks.

Outcomes

The treatment effects were measured in terms of reduction of CVD events: non-fatal MI, revascularisation CVD-related deaths and other deaths. Health outcomes for the cost-effectiveness analysis are summarised in the form of Quality Adjusted Life Years (QALYs), where one QALY represents one year of healthy life.

Model structure and assumptions

A Markov model was developed to evaluate the incremental costs and effects of lifetime intervention with CR in secondary prevention of cardiovascular disease (CVD) events in post MI patients from a UK NHS perspective.

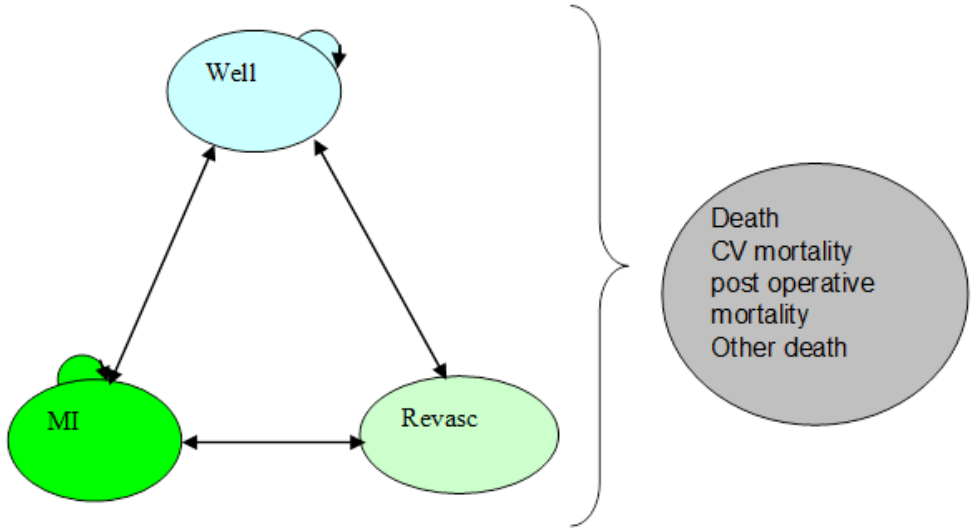
In a Markov model there are a finite number of health states. It is assumed that at any point in time, all patients must be in one and only one of the states. The model then replicates how a hypothetical cohort of people moves between the states. Figure 1 shows a schematic representation of the patients' pathways. All patients start in the event-free health state. During each six-month cycle of the model, a proportion of patients enter one of the qualifying event health states (MI, revascularisation and death) while the remainder stay in the event free state. Patients can experience more than one non-fatal event in subsequent periods of the model.

The rate at which people move through the model is regulated by transition probabilities, which describe the likelihood of moving between states over each model cycle (six months). For illustration, the equivalent annual transition probabilities for a 65-year-old patient receiving no-CR are shown in Table 185. The probabilities are derived from the placebo arms of the meta-analysis of CR trials.

The model was run first assuming that the cohort was to receive no CR. The model was then re-run assuming that the cohort all received CR and complied 100%. Transition probabilities were adjusted to reflect the expected reduction in CVD events and revascularisations. Health care costs and QALYs were then estimated for each option by weighting the time spent in the various states by mean costs and 'utilities' (health-related quality of life) of the health states. The cost and utility data used in the model are described below.

The time horizon modelled is lifetime, with an assumed upper age of 100, by which time most of the cohort have died.

Figure 1: Economic Model Structure



Baseline risks:

The risks of secondary or subsequent events, following an MI or revascularisation are shown in Table 185. Probabilities of having a re-infarction, and death were taken from the placebo arm of two recent meta-analyses [294], [110] The probabilities of having revascularisation were taken from another meta-analysis.[572] The incidence of MI following revascularisation was taken from Rita 2 and probability of post operative death was taken from the ACC/AHA 2004 Guideline Update for Coronorary Artery Bypass Graft Surgery [168].

Non-CVD related mortality by age and sex was taken from the life tables for England and Wales prepared by the Government Actuaries Department (GAD) and from the Office for National Statistics (ONS) [237], [436].. In the base case model we assumed that the post MI cohort had a 2 fold increase in risk of non-CVD death compared with the general population, because they are a high risk population (expert opinion). However, we tested this assumption in the sensitivity analysis.

Table 185: Probabilities for a 65-year-old man without Cardiac rehabilitation

Parameter	Annual probability	Source
Well to Rev	0.062	572
Well to MI	0.096	110
Well to death	0.093	110, 436
Revascu to MI	0.009	267
Revascu to post op death	0.008	168
Revascu to another revascu	0.030	572
Well to after vascu to death	0.042	267, 436
MI to revascu	0.062	572
MI to MI	0.062	294
MI to death	0.094	294, 436

Treatment effects:

The effectiveness of CR defined as the reduction in relative risks of mortality and non fatal reinfaction was obtained from systematic [110] and for revascularisation from [572]. Data on the effectiveness of the strategies aimed at increasing uptake and compliance were obtained from an HTA report [58]

Table 186: Relative risks of CR (base case analysis)

Outcome	Mean	Lower CI	Upper CI	Source
Revascularisation	0.85	0.65	1.12	[572]
MI	0.83	0.74	0.94	[110]
Post operative death	1	1	1	Assumption
Death	0.85	0.77	0.94	[110]

Table 187: Relative risks of Letters and phone calls (base case analysis)

Intervention	Results	Source
Letters	87% intervention group Compared to 57% control 0=0.0025	[58]
Telephone + HCP	57% vs. 27% in those who did not get the intervention.	[58]

Cost data

The NICE reference case specifies that costs should be measured from an NHS and personal social services perspective. These should include the direct cost of drug treatment and also potential savings from avoided treatments due to reduced incidence of CVD and hospitalisations. Costs were calculated using cost weights for each of the states of the model, multiplied by the time spent in each state. Costs are at 2005 prices. As per current NICE guidance, an annual discount rate of 3.5% was used for both costs and health benefits [418].

The costs of health states used in the model are shown in Table 188. Costs for revascularization which includes hospitalisation were taken from the NHS reference cost 2005 [148]. It was assumed that 67% of patients will have PCI and 33% will have CABG and the costs were weighted to reflect this (expert opinion). The cost of the well states was assumed to be the outpatient cost which includes the costs of medication and monitoring costs, these were taken from the NICE hypertension guideline 2006 [421]. The cost of CR was taken from a review [58] and included staff costs, equipment, and that of recruiting patients to CR. Costs of acute MI (non-fatal reinfaction) were assumed to be the same as those of patients treated with thrombolysis, which includes the cost of hospitalisation [264]. The cost of death was zero.

The costs of each strategy used to increase uptake, invitation letters or phone call contacts followed by home visits, were calculated from resource use identified in the HTA [58]. The actual unit costs were taken from the Personal Social Services Research Unit PSSRU [487].

The cost of invitation letters were calculated assuming that letters inviting participants to a CR programme were sent twice, soon after discharge and 3 weeks later. It was assumed that the letters were sent by a medical secretary, and also that 30 minutes work was required to type and send each letter.

For the HCP and phone calls [58] estimated there would be about four visits and a phone call made before each visit. Contact by the HCP was assumed to last 30 minutes and the phone call about 11 minutes. Duration for the phone call and staff costs were taken from the PSSRU [487]

Table 188: Cost of health states

				2005 UK £ PA
Parameter	Mean	Lower	Upper	Source
No event	£171	£86	£342	[417]
Rev	£8,676	£4,338	£17,352	NHS ref cost
Post Rev	£500	£250	£1,000	Assumption
MI	£4,448	£2,224	£8,896	[264]
MI (subsequent)	£500	£250	£1,000	[421]
Rev2	£8,676	£4,338	£17,352	NHS ref cost
Post Rev2	£500	£250	£1,000	Assumption
Post OPD	£0	£0	£0	
Death	£0	£0	£0	

Table 189: Other resouces

Resource use	Hourly rates	Contact time
Social worker	£38.00	30 minutes per visit x 4
Visiting costs	£1.20	4 visits
Rehabilitation nurse	£21.00	11 minutes once
Secretaries	£14.00	30 minutes to write a letter and post it on two occasions
Postage first class+paper	£0.40	Twice
Cost per minute of phone call	£0.04	

Quality of life (Utility):

In the NICE reference case, the value of health outcomes – including beneficial and harmful impacts of treatment on mortality and morbidity – is estimated using the Quality Adjusted Life Year (QALY) approach. This requires estimates of survival and quality of life associated with each health state included in the model.[418]

The utility values used in the model are shown in Table 190 and Table 191. The values were taken from literature or the Harvard cost effectiveness registry database [265]

Utilities were adjusted to reflect the fact that health related quality of life in the general population decreases with age (i.e. multiply the disease utility weight by age utility weight). Age utility weights were taken from the Department of Health, Health Survey for England [146]

One study [439], found that there was a difference of 0.052 QALYs between patients who participated in CR and those who did not using the time trade off method. This factor was applied to all the well states in the CR arm to take account of this difference in quality of life in sensitivity analysis. The weight attached to death was zero

Table 190: Health state utility weights

Health state	Utility	Mean	Lower limit	Upper limit	Source
No event	1.0	1.0	-	-	

Health state	Utility	Mean	Lower limit	Upper limit	Source
Rev	0.8	0.8	0.8	0.9	[449]
Post Rev	0.88	0.88	0.70	0.90	[265]
MI	0.76	0.76	0.70	0.90	[265]
MI (subsequent)	0.88	0.88	0.70	0.90	Assumption
Rev2	0.80	0.80	0.70	0.90	Same as Rev1
Post Rev2	0.88	0.88	0.70	0.90	Same as Rev1
Post OPD	0.00	0.00	0.00	0.00	
Death	0.00	0.00	0.00	0.00	

Table 191: Utility weight by age

Age group	Utility weight	Source
45-54	0.85	[146]
55-64	0.79	
65-74	0.78	
75+	0.73	

Cost effectiveness

The results of cost-effectiveness analysis are usually presented as Incremental Cost-Effectiveness Ratios (ICERs), which determine the additional cost of CR per additional QALY gained compared with no CR

ICERs = (cost of CR – cost of no CR)/ (QALY of CR – QALY of no CR)

Where more than two interventions are being compared, the ICERs are calculated using the following process:

i) The drugs are ranked in terms of cost (from the cheapest to the most expensive).

ii) If a drug is more expensive and less effective than the previous one, then it is said to be 'dominated' and is excluded from further analysis.

iii) ICERs are calculated for each drug compared with the next most expensive non-dominated option. If the ICER for a drug is higher than that of the next more effective strategy, then it is ruled out by 'extended dominance'. This means that there is some mixture of two other strategies that is more effective and less expensive.

iv) ICERs are recalculated excluding any drugs subject to extended dominance. [449]

Sensitivity analysis

The model includes a base case analysis supplemented with both deterministic and probabilistic sensitivity analysis. In the probabilistic sensitivity analysis all parameters in the model were allowed to vary simultaneously according to an assumed distribution reflecting the degree of uncertainty over the parameter value.

Q.2.1.3 Results

Table 192 and Table 193 below present the analysis of the incremental cost effectiveness ratio (ICER) for the base-case analysis of

a) CR versus no CR in post MI patients.

b) the comparative cost effectiveness of the methods used to increase uptake of CR after an MI

a) Cost effectiveness of Cardiac Rehabiliation vs. no Cardiac Rehabiliation.

The base case results are presented in Table 192 and Table 193 for 65-year-old men and women respectively. This suggests that CR is cost-effective for this population. The ICER of CR compared with no CR is about £7,860 and £8,360 per QALY gained for men and women respectively, which is below the level usually considered to be affordable in the NHS (about £20,000 to £30,000 per QALY).

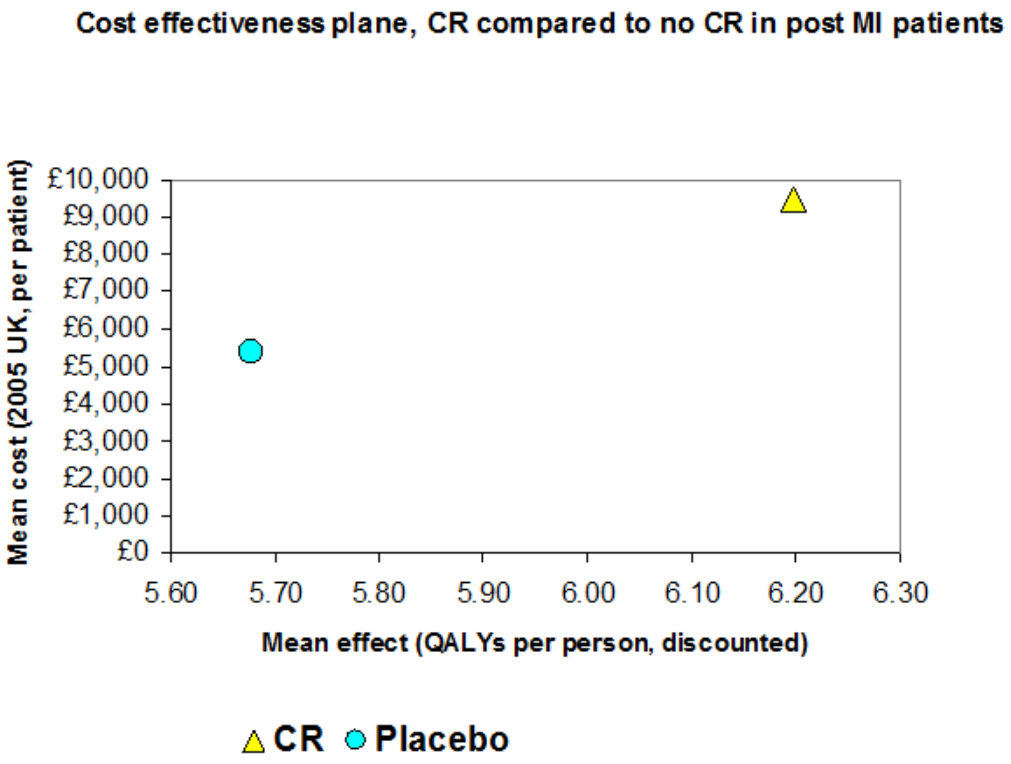
Table 192a: Incremental cost effectiveness of CR vs. No CR, base case results for 65 year old men.

	Cost (£)	Effect (QALYs)	Incremental cost (£)	Incremental effect (£)	ICER (£/QALY)
Placebo	5359.497	5.677295			
CR	9449.575	6.197696	4090.078	0.520401	7859.471

Table 8b: Incremental cost effectiveness of CR vs. No CR, base case results for 65 year old women.

	Cost (£)	Effect (QALYs)	Incremental cost (£)	Incremental effect (£)	ICER (£/QALY)
Placebo	5773.631	6.088688			
CR	10135.59	6.610674	4361.962	0.521986	8356.474

Figure 285: Cost effectiveness plane, CR compared to no CR in post MI patients



b) The comparative cost effectiveness of the methods used to increase uptake of CR after an MI

None of the strategies were ruled out on the basis of dominance. The base case model shows that the strategy of sending letters compared to usual care to increase uptake of CR is about £ 8,000/QALY. The strategy of using phone calls and home visits by a HCP compared to sending letters is about £ 8,400/QALY gained which is below the level usually considered to be affordable in the NHS (about £20,000 to £30,000 per QALY).

Table 193: Incremental cost effectiveness of the methods used to increase uptake of CR after an MI

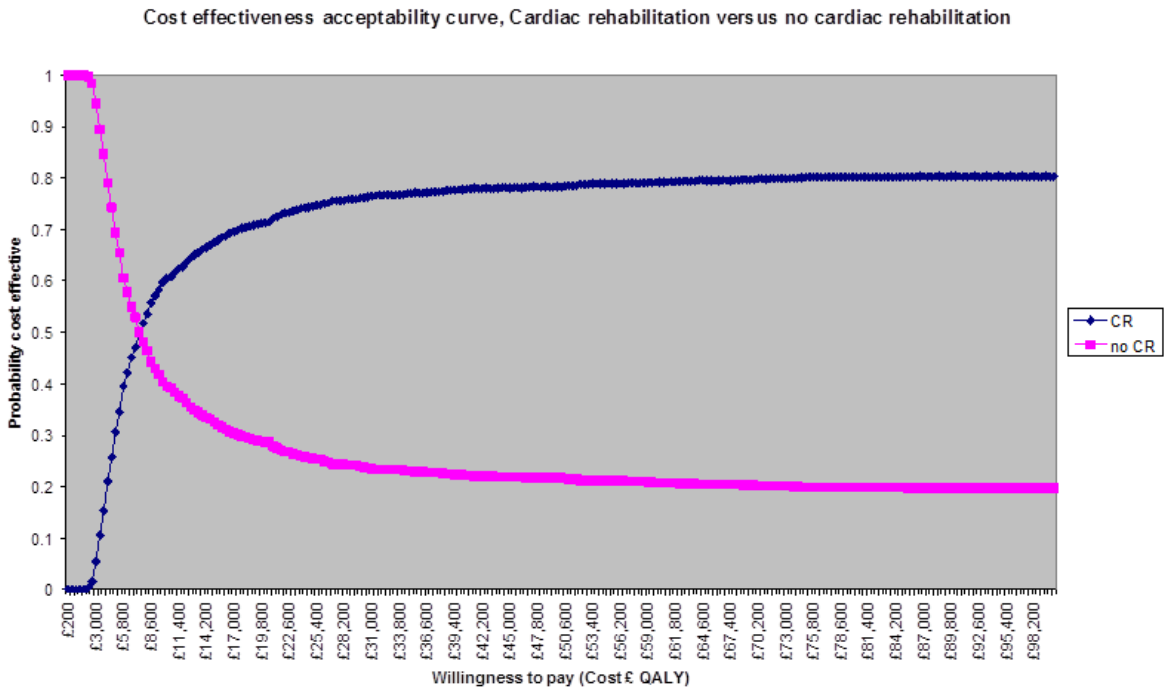
Strategy	Costs	QALY	Incre costs	Incre QALYs	ICER (£/QALY)
Usual care	£6,995,529	5885			
Letters	£7,844,705	5992	£849,176	106	£7,999
Phone + HCP	£8,896,943	6117	£1,052,239	125	£8,425

While the results of the ICER can be used to determine the optimal decision based on a comparison of mean costs and QALYs, they do not incorporate the uncertainty surrounding this decision. Figure 3 presents the base-case results in the form of cost effectiveness acceptability curves (CEACs) for CR versus no CR. Figure 295 shows the comparison between the three strategies of increasing uptake of CR. These curves detail the probability that each strategy is cost effective over a range of potential maximum values that the NHS is prepared to pay for an additional QALY.

The CEACs demonstrate that CR is highly cost effective. The probability that CR is cost effective increases as the willingness to pay increases. If the NHS is willing to pay upto £10,000 for an

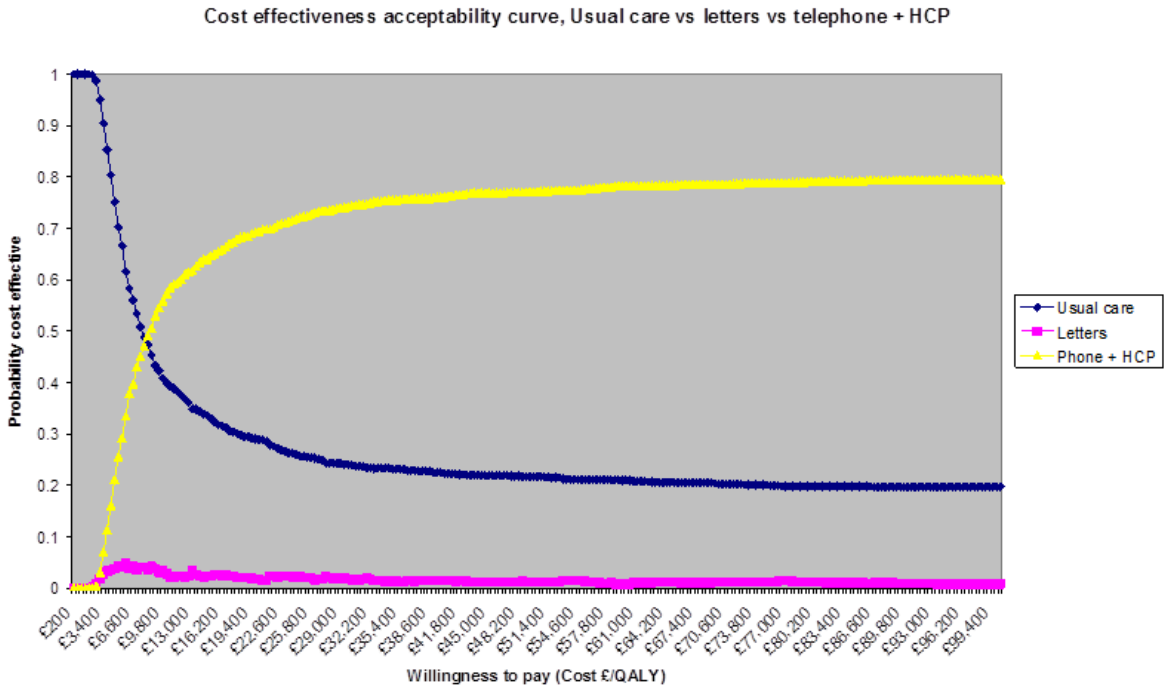
additional QALY, the probability that CR is cost effective is around 60%, increasing to 71% if the maximum willingness to pay is £20,000.

Figure 286: Cost effectiveness acceptability curve, Cardiac rehabilitation versus no cardiac rehabilitation



In Figure 295, the CEACs demonstrate that either the strategy of phone calls plus home visits by a HCP or the strategies of sending letters are cost effective. However by comparison, the strategy of using phone calls plus home visits by a HCP is the optimal strategy. If the NHS is willing to pay upto £10,000 for an additional QALY, the probability that phone calls plus home visits by a HCP is cost effective is around 57%, increasing to 69% if the maximum willingness to pay is £20,000.

Figure 287: Cost effectiveness accepability curve, Ususal care vs letters vs telephone + HCP



Other sensitivity Analysis

Sensitivity analysis was done to explore the robustness of the base case results, including the impact of age, costs of CR and CVD events, quality of life, and efficacy of CR. The model was robust to changes in assumptions about the different parameters except for quality of life.

Quality of life loss due to CR

The impact of cardiac rehabilitation on quality of life was tested. It was assumed that that cardiac rehabilitation will result in disutility or a loss in quality of life. We did a threshold analysis to find the point at which CR becomes cost ineffective due to loss in quality of life. The model estimates that a loss in quality of life due to CR of more than 3.5% will make CR cost ineffective. Thus the model is sensitive to this assumption. This is an unlikely scenario unless CR is provided to very high risk patients whose health is made worse by participating in CR.

Efficacy of CR

The efficacy of CR was tested using the upper and lower confidence intervals. When the lower confidence interval is used, the ICERs are expected to improve and when the upper confidence interval the ICERs is expected to worsen. The model remained robust when both upper and lower confidence intervals were used. Impact of CR on mortality appears to have a bigger impact on the ICERs. When the lower CI is used the ICERs fall to about £5,400/QALY and when the upper CI is used the ICERs rise to about £19,730/QALY which is borderline cost effective.

QALY gain due to CR

The model is not sensitive to changes in additional QALYs as a result of CR. The base case model assumed that there was no difference in QALYs between those who participate in CR and those that do not. We used a multiplier of 0.052 reported by Oldridge et al in the sentivity analysis. The

estimated ICERs decrease by almost half to about £4,940 per QALY gained. The model is robust to this assumption since we retrain the original conclusion..

Adherence to CR

The base case model assumed that patients will adhere to CR 100% However studies have shown that compliance rates are high in the first year and fall in subsequent years. The average for the first year is between 60 to 70% in the first 12 months, falling to between 45% to 70% after 3 years.We tested for adherence in our model. The model appears to be slightly sensitive to this assumption since compliance rates below 40% are not cost effective. For instance 40% compliance has an estimated ICER of about £20,000

Cost of CR

The results were sensitive to changes in the cost of rehabilitation but remained robust. The ICER ranged from about £2,320/QALY if the lowest cost per patient per year of £140 cited by Taylor et al is used to about £12,890/QALY when the cost is assumed to be about £800/patient per year cited by Beswich et al. As the cost of rehabilitation increases the ICER become less favourable

RR of non CVD death

The model assumed that patients after MI have a two fold increased risk of dying from any other causes than the general population. We tested this assumption in sensitivity analysis. When we assumed that there was no difference in non CVD mortality between the general population and the post MI patients the ICERs increased slightly to £8,980/QALY. Overall the model was robust to this assumption

Age and sex

Age and sex did not affect the results. However it should be acknowledged that the efficacy data available is mainly for middle aged men usually aged upto 65. Only mortality data was available a by age and sex in our model.

Discounting

The impact of the discounting was also explored. Assuming that there was no discounting, the results of the model remain robust with an estimated ICER of about £6,780/QALY. If the discount rate was raised to 6%, the ICERs slightly increased to £8,680/QALY. Thus the model was not sensitive to this parameter.

Efficacy of letters

When assumptions about the efficacy of letters were changed the model remained robust. When letters were assumed to result in a modest 1% increase in uptake, the ICERs compared to usual care increased to about £15,000/QALY. The ICERs of phone call plus home visit by a HCP improved as the efficacy of letters worsens, and worsens as the efficacy of letters improves. For instance when the efficacy of letters was assumed to result in a 100% increase in the uptake of CR letters the ICERs for letters compared to HCP + phone increased to about £11,000/QALY

Efficacy of phone calls plus home visit by HCP

In the base case model phone calls plus home visits by a HCP resulted in 111% increase in uptake of CR. We did a threshold analysis to find the point at which this intervention ceases to be cost effective. The model estimates that when the efficacy of phone call plus home visits by a HCP was

assumed to result in an increase in uptake of CR of less than 55% then phone calls plus home visits by a HCP will not be cost effective at a willingness to pay value of £20,000/QALY. For instance if the strategy of HCP + phone resulted in increase of 50% in uptake of CR, letters will dominate them. Thus the model is sensitive to this assumption, but the analysis is speculative since the ranges used in sensitivity analysis are arbitrary.

HCP used

The HCP used in the base case model was a social worker. The impact of using another HCP assuming the same efficacy observed in the social worker trial was tested. We tested the use of a healthcare assistant whose wages are half those of the social worker. The ICER when letters were compared with phone calls plus home visits by a HCP improved slightly. Other health care professionals considered were community physiotherapist and a practice nurse. The results remained robust, suggesting that the type of health care professional used to increase the uptake of CR does not matter much.

Baseline uptake of CR

The model was not sensitive to assumptions about baseline uptake of cardiac rehabilitation. Studies have shown that participation rates ranges between 14-50%. In The base case model assumed a 40% participation rate. We varied the participation rate between 14% to 85%. The ICERs were below £10,000/QALY for all comparisons thus the model remained robust to this assumption

Q.2.1.4 Limitations of the model

The assumptions about mortality and revascularisation were simplified, assuming that mortality was the same in the first year post MI and subsequent years. Study [268] demonstrated that mortality may be greater than 6 fold in the first year post MI compared to subsequent years. Revascularisation rates may also differ in the first year post MI compared to subsequent years.

The model does not consider the effect of gender. In particular, most studies of effectiveness from which the data for this model were taken were conducted in predominantly male populations. Therefore these results ought to be interpreted with caution when being generalized to women.

Lack of long term data on clinical endpoints. The follow up in the trials were averaging upto 5 years. Benefits beyond the trial period are not fully known. The model assumed that the benefits observed during the trial period will persist for lifetime. This might not necessarily be true.

Efficacy of interventions used to increase uptake of CR were drawn from very small studies of less than 100 patients in each study. These small studies might not give reliable estimates of effectiveness of these interventions.

Finally, reliable utility data for these patients are lacking. Utility weights were taken from the literature and the estimates were crude, and in some cases, old. Although we believe that the assumptions we used around health state utilities were reasonable, the model showed that the cost-effectiveness of rehabilitation is not dependent on assumptions about health state utilities.

Q.2.1.5 Conclusions

The results suggest that CR is highly cost effective when compared to no CR with 86% probability that CR is cost effective. These results are robust in sensitivity analysis except for quality life.

The results also showed that methods of increasing uptake of CR are cost effective. The ICERs were below £20,000/QALY for all comparisons in the base case model. The optimal strategy is the use of a phone plus a HCP. This result is sensitive to the efficacy of phone plus HCP. The model also shows

that the HCP delivering CR does not matter much because the model remains robust in sensitivity analysis.

Q.2.1.6 Additional information: sensitivity analysis

Table 194: Sensivity analysis for relative risk in non- CVD death

RR of non CVD death	ICER (cost/QALY)
0.5	£10,120
1	£8,980
4	£6,940
8	£6,070

Interpretation

The model assumed that patients after MI have a two fold increased risk of dying from any other causes than the general population. We tested this assumption in sensitivity analysis. When we assumed that there was no difference in non CVD mortality between the general population and the post MI patients the ICERs increased slightly to £8,980/QALY. Overall the model was robust to this assumption

Table 195: Sensivity analysis for age and sex

Age	ICER (cost/QALY) Males	ICER (cost/QALY) Females
55	£7,670	£8,210
65	£7,680	£8,360
75	£7,110	£7,610
85	£6,790	£7,050

Interpretation

Age and sex did not affect the results. However it should be acknowledged that the efficacy data available is mainly for middle aged men usually aged upto 65. Only mortality data was available a by age and sex in our model.

Table 196: Sensitivity analysis for efficacy of CR

Parameter	ICER (cost/QALY lower 95% CI)	ICER (cost/QALY upper 95% CI)
Revascularisation	£8,550	£7,330
MI	£7,300	£8,580
Death	£5,410	£19,730

Interpretation

The efficacy of CR was tested using the upper and lower confidence intervals. When the lower confidence interval is used, the ICERs are expected to improve and when the upper confidence interval the ICERs is expected to worsen. The model remained robust when both upper and lower confidence intervals were used. Impact of CR on mortality appears to have a bigger impact on the ICERs. When the lower CI is used the ICERs fall to about £5,410/QALY and when the upper CI is used the ICERs rise to about £19,730/QALY.

Table 197: Sensitivity analysis for reduction in quality of life due to CR

Reduction in QoL due to CR	ICER (Cost/QALY)

Reduction in QoL due to CR	ICER (Cost/QALY)
1%	£9,440
3%	£15,830
3.5%	£19,040
4%	£23,900

Interpretation

The impact of cardiac rehabilitation on quality of life was tested. It was assumed that that cardiac rehabilitation will result in disutility or a loss in quality of life. Arbitrary figures were used ranging between 1-4%. CR will cease to be cost effective at £20,000/QALY threshold if it resulted in quality of loss of more than 3.5%. This is an unlikely scenario unless CR is provided to very high risk patients whose health is made worse by participating in CR.

Table 198: Sensivity analysis for additional QALYs due to CR

Additional QALYs due to CR	ICER (cost/QALY)
1%	£7,060
5.2%	£4,940
10%	£3,680

Interpretation

The model is not sensitive to changes in additional QALYs as a result of CR. The base case model assumed that there was no difference in QALYs between those who participate in CR and those that do not. We assumed there would be an increase in QALY due to CR ranging from 1% to 10%. The estimated ICERs ranged from £7,060 per QALY gained.for a 1% increase in QALY to about £3,680 for a 10% increase in QALY due to CR.

Table 199: Sensitivity analysis for compliance to CR

Compliance rate	ICER (cost/QALY)
50%	£15,720
40%	£19,650
35%	£22,460
30%	£26,200

Interpretation

The base case model assumed that patients will adhere to CR 100% However studies have shown that compliance rates are high in the first year and fall in subsequent years. The average for the first year is between 60 to 70% in the first 12 months, falling to between 45% to 70% after 3 years.We tested for adherence in our model. The model appears to be slightly sensitive to this assumption since compliance rates below 40% are not cost effective. For instance 40% compliance has an estimated ICER of about £20,000

Table 200: Sensitivity analysis for Cost of CR

Cost of CR/patient/year	ICER (cost/QALY)
£140	£2,320
£300	£4,880
£600	£9,680

Cost of CR/patient/year	ICER (cost/QALY)
£800	£12,890

Interpretation

The results were sensitive to changes in the cost of rehabilitation but remained robust. The ICER ranged from about £2,320/QALY if the lowest cost per patient per year of £140 cited by Taylor et al is used to about £12,890/QALY when the cost is assumed to be about £800/patient per year. As the cost of rehabilitation increases the ICER become less favourable

Table 201: Sensitivity analysis for Cost of CVD events and procedures

Parameter	ICER Lower costs (50% less) (cost/QALY)	ICER Upper costs (100% more) (cost/QALY)
Revascularisation	£7,920	£7,750
MI	£7,730	£7,920
Subsequent MI	£7,790	£7,990

Interpretation

The model is not sensitive to outcome costs. The mean costs were reduced by 50% and increased by 100% and the results remained robust, all below £8,000/QALY.

Table 202: Sensitivity analysis for discounting

Discount rate	ICER (cost/QALY)
0%	£6,780
6%	£8,680

Interpretation

The impact of the discounting was also explored. Assuming that there was no discounting, the results of the model remain robust with an estimated ICER of about £6,780/QALY. If the discount rate was raised to 6%, the ICERs slightly increased to £8,680/QALY. Thus the model was not sensitive to this parameter.

Table 203: Sensitivity analysis for baseline uptake of CR

Baseline uptake	Letters vs. usual care	Phone call plus home visit by HCP vs. Letters
14%	£8,257	£9,474
60%	£7,952	£8,236
85%	£7,925	£8,125

Interpretation

The model was not sensitive to assumptions about baseline uptake of cardiac rehabilitation. Studies have shown that participation rates ranges between 14-50%. In The base case model assumed a 40% participation rate. We varied the participation rate between 14% to 85%. The ICERs were below £10,000/QALY for all comparisons thus the model remained robust to this assumption

Table 204: Sensitivity analysis for efficacy of letters

Efficacy of letters	Letters vs. usual care	Phone call plus home visit by HCP vs. Letters
1%	£14,969	£8,167
10%	£8,570	£8,195
20.%	£8,214	£8,232
80.00%	£7,948	£8,953
100%	£7,930	£10,943

Interpretation

When assumptions about the efficacy of letters were changed the model remained robust. When letters were assumed to result in a modest 1% increase in uptake, the ICERs compared to usual care increased to about £15,000/QALY. The ICERs of phone call plus home visit by a HCP improved as the efficacy of letters worsens, and worsens as the efficacy of letters improves. For instance when the efficacy of letters was assumed to result in a 100% increase in the uptake of CR letters the ICERs for letters compared to HCP + phone increased to about £11,000/QALY

Table 205: Sensitivity analysis for efficacy of phone plus HCP

Efficacy of phones	Letters vs. usual care	Phone call plus home visit by HCP vs. Letters
50 %	£7,998	Dominated by letters
60 %	£7,998	£11,629
80 %	£7,998	£9,029

Interpretation

In the base case model phone calls plus home visits by a HCP resulted in 111% increase in uptake of CR. We did a threshold analysis to find the point at which this intervention ceases to be cost effective. The model estimates that when the efficacy of phone call plus home visits by a HCP was assumed to result in an increase in uptake of CR of less than 55% then phone calls plus home visits by a HCP will not be cost effective at a willingness to pay value of £20,000/QALY. For instance if the strategy of HCP + phone resulted in increase of 50% in uptake of CR, letters will dominate them. Thus the model is sensitive to this assumption, but the analysis is speculative since the ranges used in sensitivity analysis are arbitrary.

Q.2.2 Economic analysis of ACE inhibitors in low risk patients with preserved LVDF

An additional analysis was undertaken to examine the cost effectiveness of treatment with ACE inhibitors compared to placebo in patients with preserved left ventricular dysfunction. The analysis used effectiveness data from a meta-analysis [19] which meta-analysed data from six trials [76], [428], [195], [29], [353] and [478].

Q.2.2.1 Methods

Population and sub-groups

The model considered a cohort of low risk post MI patients with preserved left ventricular dysfunction. Low risk is defined as the population who met the inclusion criteria of the meta-analysis [19] seen in primary and secondary care.

Interventions compared

The analysis assessed lifetime costs and effects of ACE inhibitors compared with placebo.

Outcomes

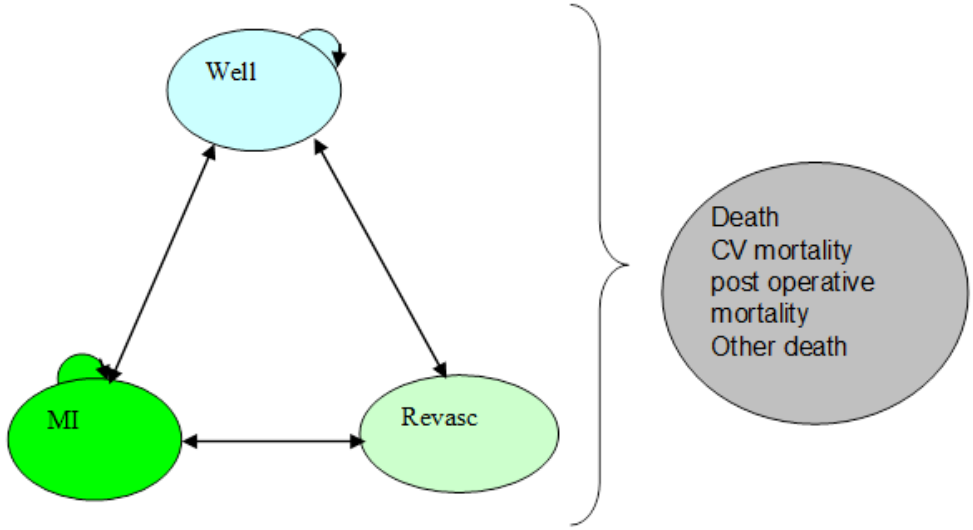
The treatment effects were measured in terms of reduction of cardiovascular events: non-fatal MI, revascularisation, unstable angina, heart failure, cardiovascular -related deaths and other deaths. Health outcomes for the cost-effectiveness analysis are summarised in the form of Quality Adjusted Life Years (QALYs).

Model structure and assumptions

A Markov model was developed to evaluate the incremental costs and effects of lifetime treatment with ACE inhibitors in secondary prevention of CVD events in low risk post MI patients from a UK NHS perspective.

In a Markov model there are a finite number of health states. It is assumed that at any point in time, all patients must be in one and only one of the states. The model then replicates how a hypothetical cohort of people moves between the states. Figure 291 shows a schematic representation of the patients' pathways. All patients start in the event-free health state. During each six-month cycle of the model, a proportion of patients enter one of the qualifying event health states (MI, heart failure, unstable angina, revascularisation and death) while the remainder stay in the event free state. Patients can experience more than one non-fatal event in subsequent periods of the model.

Figure 288: Model structure for the cost effectiveness of ACE inhibitors in low risk patients with preserved LVDF compared to placebo



The rate at which people move through the model is regulated by transition probabilities, which describe the likelihood of moving between states over each model cycle (six months). For illustration, the equivalent annual transition probabilities for a 65-year-old patient on placebo are shown in Table 206. The probabilities are derived from the placebo arm of the meta-analysis [19].

The model was run first assuming that the cohort was to receive placebo. The model was then re-run assuming that the cohort all received ACE inhibitors and complied 100% with transition probabilities adjusted to reflect the expected reduction in CVD events and revascularisations. Health care costs and QALYs were then estimated for each option by weighting the time spent in the various states by mean costs and 'utilities' (health-related quality of life) of the health states. The cost and utility data used in the model are described below.

The time horizon modelled is lifetime, with an assumed upper age of 100, by which time most of the cohort have died.

Table 206: Annual probabilities for an untreated 65 year old man

Parameter	Annual probability	Source
Well to REV	0.0189	19
Well to MI	0.01008	19
Well to unstable angina	0.01196	19
Well to heart failure	0.00328	19
Well to DEATH	0.0426298	19 436
Rev to MI	0.0189	449
Rev to unstable angina	0.0189	assumed to be the same as MI
Rev to heart failure	0.00945	assumed to be half of MI
Rev to DEATH	0.0426298	267 436
MI to REV	0.0189	19
MI to MI	0.01008	19
MI to unstable angina	0.01196	19
MI to heart failure	0.00328	19
MI to DEATH	0.0426298	19 436
Unstable angina to REV	0.0189	same as MI
Unstable angina to MI	0.01008	same as MI
Unstable angina to heart failure	0.01196	same as MI
Unstable angina to DEATH	0.0426298	same as MI
Heart failure to MI	0.023	554
Heart failure to unstable angina	0.023	554
Heart failure to heart failure	0.0545	554
Heart failure to DEATH	0.0915098	554 436

Key:

MI: myocardial infarction

UNA: unstable angina

REV: revascularisation

Q.2.2.2 Baseline risks:

The risk of secondary or subsequent events, following an MI, unstable angina, heart failure and revascularisation were taken from the placebo arm of the meta-analysis [19]. The incidence of MI following revascularisation was taken from [267].

Non-CVD related mortality by age and sex was taken from the life tables for England and Wales prepared by the Government Actuaries Department (GAD) [237] and from data on the proportion of deaths due to CVD-related causes from the Office for National Statistics [436]. In the base case model we assumed that the post MI cohort had a 2 fold increase in risk of non-CVD death compared with the general population, because they are a high risk population (expert opinion).

Figure 289: Baseline non CVD related death

Deaths by age, sex and underlying cause, 2004 registrations, England and Wales

	All cause ICD10: A00-R99		Circulatory ICD: I00-I99		Non-circulatory as proportion of all deaths (p)	
	M	F	M	F	M	F
45	12,417	8,139	3,930	1,362	0.68	0.83
55	27,117	17,649	9,330	3,541	0.66	0.80
65	52,709	37,041	19,783	11,304	0.62	0.69
75	87,367	88,404	35,607	35,958	0.59	0.59
85	51,329	109,488	20,816	46,470	0.59	0.58

Source: http://www.statistics.gov.uk/STATBASE/Expodata/Spreadsheets/D8986.xls

All cause mortality, estimated from life tables, 2002-4, England

	Annual probability of death in age band	
	M	F
45	0.0037	0.0025
55	0.0093	0.0059
65	0.0236	0.0154
75	0.0537	0.0406
85	0.0870	0.0807

Source: http://www.gad.gov.uk/Life_Tables/Interim_life_tables.htm

Relative risk of death from non-circulatory causes in cohort compared with general population: 2

Estimated non-circulatory deaths for post MI cohort

	Annual probability of death in age band	
	M	F
45	0.51%	0.41%
55	1.23%	0.94%
65	2.95%	2.14%
75	6.37%	4.82%
85	10.35%	9.30%

Treatment effects:

The effectiveness of ACE inhibitors defined as the reduction in relative risks of mortality, heart failure, revascularisation and non fatal reinfaction was obtained from the meta-analysis [19].

Table 207: Relative risks of treatment (base case analysis)

INTERVENTION		COMPARATOR		
		Relative risks		
		Mean	Lower 95% CI	Upper 95% CI
ACE inhibitors	Revascularisation	0.93	0.87	1.00
	MI	0.84	0.75	0.94
	Unstable angina	0.93	0.83	1.05
	Heart failure	0.71	0.59	0.86
	Mortality	0.87	0.81	0.94

Cost data

The NICE reference case specifies that costs should be measured from an NHS and personal social services perspective. These should include the direct cost of drug treatment and also potential savings from avoided treatments due to reduced incidence of CVD and hospitalisations. Costs were calculated using cost weights for each of the states of the model, multiplied by the time spent in each state. Costs are at 2005 prices. As per current NICE guidance, an annual discount rate of 3.5% was used for both costs and health benefits [418].

The costs of health states used in the model are shown in Table 2c. Costs for revascularization which includes hospitalisation were taken from the NHS reference cost 2005.[148] It was assumed that 67% of patients will have PCI and 33% will have CABG and the costs were weighted to reflect this (expert opinion). The cost of the well states was assumed to be the outpatient cost which includes the costs of medication and monitoring costs were taken from the Statin HTA [417]. The subsequent costs of MI and unstable angina were assumed to be the same and were taken from the NICE hypertension guideline 2006 [421]. Costs of acute MI (non-fatal reinfaction) were assumed to be the same as those of patients on thrombolysis, which includes the cost of hospitalisation, [264]. The cost of death was zero. Costs of drugs were taken from the drug tariff [484]

Cost of heart failure was taken from the NHS reference cost 2005,[148] and subsequent costs after heart failure were assumed to be the same as those seen in subsequent MI patients (expert opinion). Costs of events were reduced by 50% and doubled in sensitivity analysis.

Table 208: Costs of health states

	2005 UK £ pa				
	Mean	Lower	Upper	Source	
No event	£171	£86	£342	417	
Rev	£8,676	£4,338	£17,352	148	
Post Rev	£500	£250	£1,000	assumption	
MI	£4,448	£2,224	£8,896	264	
MI (subsequent)	£500	£250	£1,000	421	
Rev2	£8,676	£4,338	£17,352	148	
Post Rev2	£500	£250	£1,000	assumption	
post OPD	£0	£0	£0		
Death	£0	£0	£0		

Quality of life (Utility):

In the NICE reference case, the value of health outcomes – including beneficial and harmful impacts of treatment on mortality and morbidity – is estimated using the Quality Adjusted Life Year (QALY) approach. This requires estimates of survival and quality of life associated with each health state included in the model.[418]

The utility values used in the model are shown in Table 209 and Table 210. The values were taken from literature or the Harvard cost effectiveness registry database [265]

Utilities were adjusted to reflect the fact that health related quality of life in the general population decreases with age (i.e. multiply the disease utility weight by age utility weight). Age utility weights were taken from the Department of Health, Health Survey for England [146]

Table 209: Health state utility weights

Health State	Utility	Mean	Lower limit	Upper limit	Source	

No event	1.00	1.00	-	-		
Rev	0.80	0.80	0.70	0.90	[449]	
Post Rev	0.88	0.88	0.70	0.90	[265]	
MI	0.76	0.76	0.70	0.90	[265]	
MI (subsequent)	0.88	0.88	0.70	0.90	assumption	
Rev2	0.80	0.80	0.70	0.90	same as Rev 1	
Post Rev2	0.88	0.88	0.70	0.90	same as Rev 1	
post OPD	0.00	0.00	0.00	0.00		
Death	0.00	0.00	0.00	0.00		

Table 210: Utility weight by age

Age group	Age utility weight	Source
45-54	0.85	[146]
55-64	0.79	
65-74	0.78	
75+	0.73	

Q.2.2.3 Cost effectiveness

The results of cost-effectiveness analysis are presented as Incremental Cost-Effectiveness Ratios (ICERs), which determine the additional cost of ACE inhibitors per additional QALY gained compared with placebo

ICERs = (cost of ACE inhibitors – cost of placebo)/ (QALY of ACE inhibitors – QALY of placebo)

Sensitivity analysis

The model includes a base case analysis supplemented with both deterministic and probabilistic sensitivity analysis. The impact of utility, costs of revascularisation, cost of ACE inhibitors and baseline risks for mortality, revascularisation second MI, heart failure and unstable angina were assessed.

Q.2.2.4 Results

The base case results are presented for 65-year-old low risk men and women post MI with preserved left ventricular dysfunction. The results suggests ACE inhibitors are cost-effective with an estimated ICER of about £3,400/QALY gained for men and about £3,700 for women compared with placebo which is well below the level usually considered to be affordable in the NHS (about £20,000 to £30,000 per QALY).

Table 211: Base case results 65 year old male

	Cost (£)	Effect (QALYs)	Incremental cost (£)	Incremental effect (£)	ICER (£/QALY)
Placebo	£3,847	7.72			
ACE inhibitors	£5,633	8.24	£1,786	0.52	£3,424

Table 212: Base case results 65 year old female

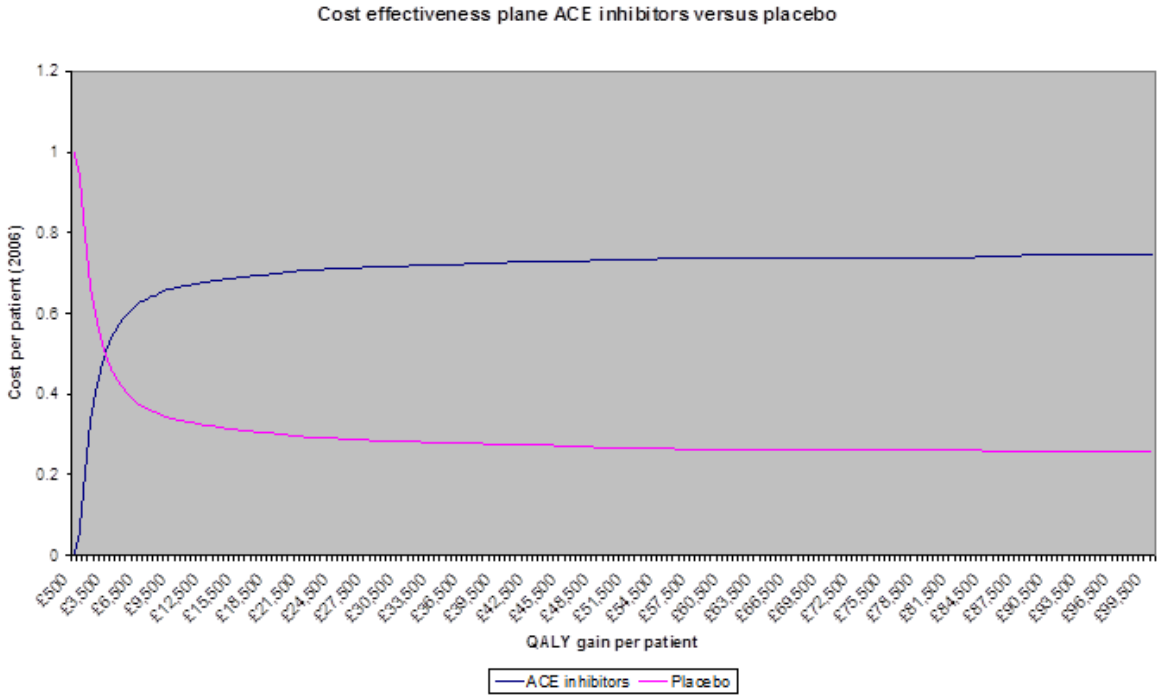
	Cost (£)	Effect (QALYs)	Incremental cost (£)	Incremental effect (£)	ICER (£/QALY)
Placebo	£4,265	8.40			
ACE inhibitors	£6,176	8.92	£1,911	0.52	£3,707

Probabilistic sensitivity analysis

A probabilistic sensitivity analysis was also done, where all parameters are assigned a distribution and are allowed to vary at the same time. The results are reported below in the form of cost effectiveness acceptability curves (CEACs). These curves detail the probability that each strategy is cost effective over a range of potential maximum willingness to pay values that the NHS can afford to pay for an additional QALY.

The CEACs demonstrate that ACE inhibitors are cost effective when compared to placebo. The probability that ACE inhibitors are cost effective is around 70% at £20,000/QALY threshold. As expected the probability that an intervention is cost effective improves as the willingness to pay increases. Thus for a threshold of £5,000/QALY the probability that ACE inhibitors are cost effective is 59%, while at £30,000/QALY the probability increases to 72%.

Figure 290: Cost effectiveness acceptibility curve



Deterministic sensitivity analysis

A range of univariate sensitivity analyses were conducted to assess the impact of different input parameters on the base case results. Detailed results for all parameters are shown in the appendix.

Quality of life

The base case model assumed that the side effect profile of ACE inhibitors was the same as in the placebo arm. However when it was assumed that ACE inhibitors will result in loss of quality due to

side effects of more than 2.1%, then ACE inhibitors would no longer be cost effective at £20,000/QALY threshold. For instance if the loss in quality of due to side effects are assumed to be about 2.5% the estimated ICERs is about £230,200/QALY. If the loss was 3% ACE inhibitors are dominated by placebo. Overall the result is sensitive to loss in quality of life due side effects of treatment.

Health state utilities were arbitrarily reduced and increased by 0.2. This did not affect the base case conclusions suggesting the model was is not sensitive to changes in health state utilities. The ICERs ranged between £3,370 to about £3,480/QALY.

Costs

Cost of events (cost of treating MI, heart failure, revascularizations, and unstable angina) were increased by 100% and reduced by 50%. The model remained robust with ICERs remaining ranging between about £3,300/QALY and £3,400/QALY in all cases examined.

Worse case scenario

A worse case scenario was examined were the cost of events were doubled, and treatment effects were set at their upper limit of the 95% confidence interval. In this case the ICERs increased to about £8,400/QALY. This is still within acceptable limits of what is usually considered affordable by the NHS. Thus the model is robust to the worse case scenario assumption.

Efficacy

Assumptions about the efficacy of treatment were tested using the 95% confidence interval. The model was robust in all cases when either the lower or the upper 95% confidence interval was used. When the upper 95% CI was used, the ICERs increased to about £6,100/QALY but were still within the range considered affordable by NHS.

RR of non CVD death, age and sex

Then model was robust to assumptions about the relative risk of death from other causes between the post MI cohort and the general population. The base case assumed a relative risk of 2. When it was assumed that there was no difference in mortality from other causes between the general population and the post MI cohort, the ICERs slightly increased to about £4,100/QALY.

The model was also robust to assumptions about age and sex. The estimated ICERs ranged between about £3,000/QALY for a 85 year old men to about and about £5,000/QALY for a 55 year old men. For women it ranged between £4,000/QALY for an 85 year old to about £5,500/QALY for 55 year old women. There was no big difference between sexes; ICERs were more favourable to men than women.

Q.2.2.5 Limitations of the model

The model was based on various assumptions that could possibly bias the results.

The first limitation of the model arises because of the nature of Markov models. These assume that the probability of an individual moving to any given health state in one time period depends only on their current health state (there is no longer 'memory' in the model). Thus the probability of heart failure for a patient whose last CVD event was an MI is assumed to be the same irrespective of how many CVD events they have previously had. Similarly, a patient's health outcome and health care costs incurred are assumed to depend only on their current health state. These assumptions are unlikely to be strictly true, and will tend to underestimate overall costs and overestimate health

outcomes for the cohort. Thus, interventions that prevent more CVD events will tend to appear rather less cost-effective than they may be in reality. So the model is conservative in this respect.

A second potentially important limitation of the model is the lack of utility data for the side effects of the drug. However sensitivity analysis was done, assuming that ACE inhibitors would result in loss of quality of life. Assuming a loss in quality of life greater than 2.1%, ACE inhibitors will no longer be cost effective at £20,000/QALY threshold suggesting that the side effects profile of ACE inhibitors affects the model results yet there is no quality of life data that is available.

There is also lack of outcome data by age and sex and non white population. This implies that it is difficult to predict the relative cost-effectiveness of ACE inhibitors in these sub-groups. There is also lack of standard errors needed for the probabilistic sensitivity analysis. In the model we assumed the standard errors were a tenth of the observed mean values used in the base case model which might not always be the case.

Another limitation of the model relates to the treatment of withdrawals and non-concordance with treatment. Since the treatment effects are based on 'intention-to-treat' analyses, the impact of withdrawals and non-concordance from the trials is already included in the model. However, the model continues to attribute drug costs for all patients throughout their lifetime. This is a conservative assumption that will tend to underestimate the cost-effectiveness of treatment.

Q.2.2.6 Conclusions

The use of ACE inhibitors in low risk patients with preserved left ventricular function is cost effective. The model is sensitive to assumptions about loss of quality of life due to assumed treatment side effects.

Q.2.2.7 Additional information: sensitivity analysis

Table 213: Sensitivity analysis; quality of life loss due to side effects

% loss of QoL due to treatment side effects	Cost/QALY
1%	£5,650
2%	£16,160
2.1%	£20,000
2.5%	£230,200
3%	DOMINATED

Interpretation:

The base case model assumed that the side effect profile of ACE inhibitors was the same as in the placebo arm. However when a threshold analysis was done, if ACE inhibitors treatment resulted in loss of quality of more than 2.1%, then ACE inhibitors would no longer be cost effective at £20,000/QALY threshold. For instance if the loss in quality of due to side effects are assumed to be about 2.5% the estimated ICERs is about £230,200/QALY. If the loss was 3% ACE inhibitors are dominated by placebo. Overall the result is sensitive to loss in quality of life due side effects of treatment. This however should be interpreted with caution since there was no published evidence supporting the idea that ACE inhibitor treatment resulted in side effects that were significantly different from placebo.

Table 214: Sensitivity analysis; health state utilities ± 0.2

Health state	(-0.2) cost /QALY	(+ 0.2) cost/QALY
Revasularisation	£3,420	£3,420

Health state	(-0.2) cost /QALY	(+ 0.2) cost/QALY
Post Revasularisation	£3,520	£3,370
MI	£3,420	£3,430
Post MI	£3,400	£3,440
Unstable angina	£3,420	£3,430
Post unstable angina	£3,480	£3,370
Heart failure	£3,420	£3,430
Post HF	£3,390	£3,450

Interpretation:

Health state utilities were arbitrarily reduced and increased by 0.2. This did not affect the base case conclusions suggesting the model was is not sensitive to changes in health state utilities. The ICERs ranged between £3,370 to about £3,480/QALY.

Table 215: Sensitivity analysis cost of CVD events/health state costs

Cost of events	50% less (cost/QALY)	100% more (cost/QALY)
No event	£3,320	£3,630
Revasularisation	£3,430	£3,420
Post Revasularisation	£3,380	£3,510
MI	£3,450	£3,370
MI (subsequent)	£3,440	£3,400
Unstable angina	£3,430	£3,420
Unstable angina subsequent	£3,390	£3,480
Heart failure	£3,440	£3,390
Post HF	£3,440	£3,400

Interpretation:

Cost of events (cost of treating MI, heart failure, revascularizations, and unstable angina) were increased by 100% and reduced by 50%. The model remained robust with ICERs remaining ranging between about £3,300/QALY and £3,400/QALY in all cases examined.

Table 216: Sensitivity analysis; worse case scenario 1, doubling the cost of events and using upper confidence limit of the 95% CI

	Cost (£)	Effect (QALYs)	ICER (£/QALY)
Placebo	£7,690	7.7193	
ACE inhibitors	£9,530	7.9394	£8,360

Interpretation:

A worse case scenario was examined were the cost of events were doubled, and treatment effect was set at its upper limit of the 95% confidence interval. In this case the ICERs increased £8,400. This is still within acceptable limits of what is usually considered affordable by the NHS. Thus the model is sensitive to the worse case scenario assumption.

Table 217: Sensitivity analysis; efficacy of ACE inhibitors treatment

Outcome	Lower 95% CI	Upper 95% CI

Outcome	Lower 95% CI	Upper 95% CI
Revasularisation	£3,270	£3,600
MI	£3,320	£3,540
Unstable angina	£3,280	£3,600
Heart failure	£3,330	£3,550
Mortality	£2,600	£6,090

Interpretation:

Assumptions about the efficacy of treatment were tested using the 95% confidence interval. The model was robust in all cases when either the lower or the upper 95% confidence interval was used. When the upper 95% CI was used, the ICERs increased to about £6,100/QALY but were still within the range considered affordable by NHS.

Table 218: Sensitivity analysis; relative risk of non-CVD death

Relative risk of non CVD death	cost/QALY
1	£4,060
2	£3,420
4	£2,960
8	£2,540

Interpretation:

Then model was robust to assumptions about the relative risk of death from other causes between the post MI cohort and the general population. The base case assumed a relative risk of 2. When it was assumed that there was no difference in mortality from other causes between the general population and the post MI cohort, the ICERs slightly increased to about £4,100/QALY.

Table 219: Sensitivity analysis; age and sex

Age	cost/QALY (Males)	cost/QALY (Females)
55	£4,740	£5,520
65	£3,420	£4,060
75	£2,990	£3,790
85	£2,890	£4,040

Interpretation:

The model was also robust to assumptions about age and sex. The estimated ICERs ranged between about £3,000/QALY for a 85 year old men to about and about £5,000/QALY for a 55 year old men. For women it ranged between £4,000/QALY for an 85 year old to about £5,500/QALY for 55 year old women. There was no big difference between sexes; ICERs were more favourable to men than women.

Q.2.3 Beta blockers economic model results

An additional analysis was undertaken which examined the cost effectiveness of a "new" generation beta blocker carvedilol in selected in post MI patients. Only one trial [135] was identified which compared carvedilol with placebo. An economic analysis was performed using data from this trial and the results are presented below

Q.2.3.1 Methods

Population and sub-groups

The model considered post MI patients with left ventricular dysfunction who met the inclusion criteria of the Carvedilol Post Infarct Survival Control in left ventricular Dysfunction (CAPRICORN) trial [135]. The model was run separately for different cohorts, defined by age (65, 75 and 85) and sex. The base case analysis is presented for 65-year-old men and women. However the trial evidence that the model this is based on included relatively few women (27%) or black patients, so the results may not be reliable for these sub-groups.

Interventions compared

The analysis assessed the costs and effects of carvedilol compared with placebo.

Outcomes

The treatment effects were measured in terms of prevention of cardiovascular events: non-fatal MI, hospital admission for heart failure, and cardiovascular -related deaths. Other cardiovascular events, including onset of stable or unstable angina, stroke, and peripheral vascular disease were not modelled, as they were not reported in the trial. Health outcomes for the cost-effectiveness analysis are summarised in the form of Quality Adjusted Life Years (QALYs), where one QALY represents one year of healthy life.

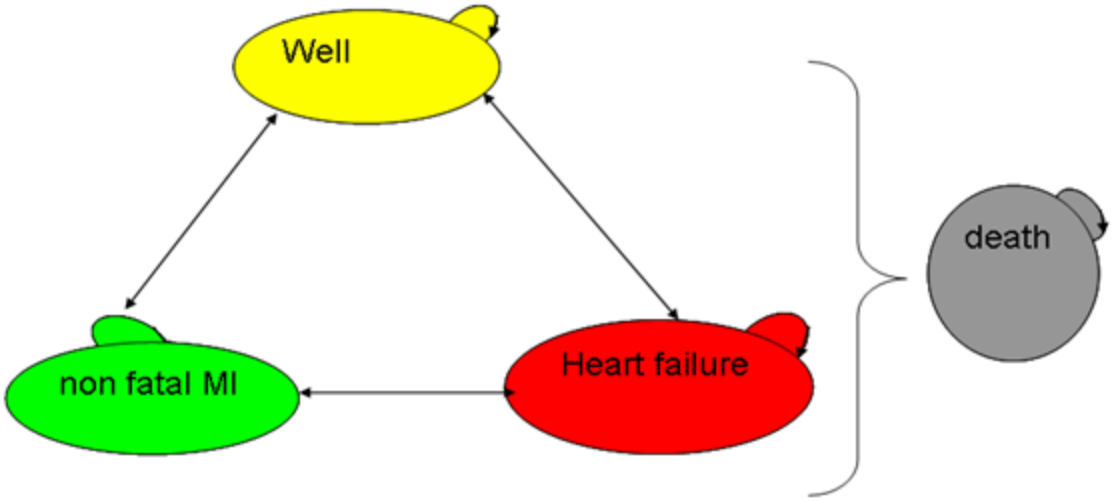
Model structure and assumptions

A Markov model was developed to evaluate the incremental costs and effects of lifetime treatment with third generation beta blockers for post MI patients with left ventricular dysfunction seen in primary care from a UK NHS perspective.

In a Markov model there are a finite number of health states. It is assumed that at any point in time, all patients must be in one and only one of the states. The model then replicates how a hypothetical cohort of people moves between the states.

Figure 291 shows a schematic representation of the patients' pathways. All patients start in the event-free health state. During each six-month cycle of the model, a proportion of patients enter one of the qualifying event health states (MI, heart failure, or death) while the remainder remains in the event free state. Patients can experience more than one non-fatal event in subsequent periods of the model.

Figure 291: Model structure for third generation beta blockers



The rate at which people move through the model is regulated by transition probabilities, which describe the likelihood of moving between states over each model cycle (six months). These transition probabilities are adjusted for each subgroup by age and sex. For illustration, the equivalent annual transition probabilities for untreated 65-year-old men are shown in Table 220.

The model was run first assuming that the cohort received no intervention (placebo). The model was then re-run for the treatment arm with transition probabilities adjusted to reflect the expected reduction in CVD events from the clinical trial data. Health care costs and QALYs are then estimated for each option by weighting the time spent in the various states by mean costs and 'utilities' (health-related quality of life) of the health states. The cost and utility data used in the model are described below.

The time horizon modelled is lifetime, with an assumed upper age limit of 100, by which time most of the cohort have died.

Table 220: Probabilities for a 65-year-old untreated man

Parameter	Annual probability	Source
Well to MI	0.0480	135
Well to heart failure	0.1120	135
Well to death	0.1268	135
MI to MI	0.0480	135
MI to heart failure	0.1120	135
MI to death	0.1268	135
heart failure to heart failure	0.1120	135
heart failure to MI	0.0480	135

heart failure to death	0.2118	[136]

Q.2.3.2 Baseline risks:

The probabilities of secondary cardiovascular events were taken from the placebo arm of the CAPRICORN trial [135] Non- cardiovascular related mortality by age and sex was taken from the life tables for England and Wales prepared by the Government Actuaries Department (GAD) [237] In the base case model we assumed that post MI cohort is at increased risk of non- cardiovascular death (2 fold risk) compared with the general population (expert opinion).

Figure 292: Baseline non-CVD related death

Deaths by age, sex and underlying cause, 2004 registrations, England and Wales

	All cause ICD10: A00-R99		Circulatory ICD: I00-I99		Non-circulatory as proportion of all deaths (p)	
	M	F	M	F	M	F
45	12,417	8,139	3,930	1,362	0.68	0.83
55	27,117	17,649	9,330	3,541	0.66	0.80
65	52,709	37,041	19,783	11,304	0.62	0.69
75	87,367	88,404	35,607	35,958	0.59	0.59
85	51,329	109,488	20,816	46,470	0.59	0.58

Source: http://www.statistics.gov.uk/STATBASE/Expodata/Spreadsheets/D8986.xls

All cause mortaliy, estimated from life tables, 2002-4, England

	Annual probability of death in age band	
	M	F
45	0.0037	0.0025
55	0.0093	0.0059
65	0.0236	0.0154
75	0.0537	0.0406
85	0.0870	0.0807

Source: http://www.gad.gov.uk/Life_Tables/Interim_life_tables.htm

Relative risk of death from non-circulatory causes in cohort compared with general population: 2

Estimated non-circulatory deaths for post MI cohort

	Annual probability of death in age band	
	M	F
45	0.51%	0.41%
55	1.23%	0.94%
65	2.95%	2.14%
75	6.37%	4.82%
85	10.35%	9.30%

Treatment effects:

The relative treatment effects of third generation beta blockers were taken from the CAPRICON trial [135].

Table 221: Relative risks of third generation beta blokers (base case analysis)

INTERVENTION		Relative risks		
		Mean	Lower CL	Upper CL
Beta blockers	MI	0.59	0.39	0.90
	heart failure	0.86	0.67	1.09
	Death	0.75	0.58	0.96

Cost data:

The NICE reference case specifies that costs should be measured from an NHS and personal social services perspective. These should include the direct cost of drug treatment and also potential savings from avoided treatments due to reduced incidence of CVD disease. Costs were calculated using cost weights for each of the states of the model, multiplied by the time spent in each state. Costs are at 2005/06 prices. As per current NICE guidance, an annual discount rate of 3.5% was used for both costs and health benefits. [418]

The cost of health states used in the model are shown in Table 222. Costs of acute MI (non-fatal reinfaction) were assumed to be the same as those of patients on thrombolysis, which includes the cost of hospitalisation Hartwell 2005 [264]. Costs of heart failure were taken from NHS reference costs.

Subsequent MI costs were taken from NHS hypertension guideline 2006.[421] Subsequent heart failure costs were assumed to be the same as those of MI (expert opinion)

Drug costs were taken from the prices quoted in the Drug Tariff, [484] based on the usual dose for post MI patients. In the base case model a conservative approach was taken, using the most expensive dose of carvedilol 25mg and the use of the smaller dose of 6.25mg was tested in sensitivity analysis.

Table 222: Costs of health states

Health state	£ Cost/year	Source
MI	£4,448	264
Subsequent MI costs	£500	421
Heart failure	£2,350	148
Post heart failure costs	£500	assumption
Death	£0	449

Table 223: Drug costs

Drug	Cost per year (£)	
	Drug used in the model (25mg)	6.25 mg
Carvedilol	£113.67	£81.08

Source: Prescription Pricing Authority (PPA) February 2006

Q.2.3.3 Quality of life (Utility):

In the NICE reference case, the value of health outcomes – including beneficial and harmful impacts of treatment on mortality and morbidity – is estimated using the Quality Adjusted Life Year (QALY) approach. This requires estimates of survival and quality of life associated with each health state included in the model [418].

The utility estimates for MI was taken from study [449], heart failure and post MI were taken from the Harvard cost effectiveness registry [265]. Post heart failure was assumed to be the same as heart failure state.

Utilities were adjusted to reflect the fact that health related quality of life in the general population decreases with age (i.e. multiply the disease utility weight by age utility weight). Age utility weights were taken from the Department of Health, Health Survey for England (1996) [146].

The base case model assumed that there was no loss in quality of life due to treatment side effects. This assumption was tested in the sensitivity analysis, assuming that treatment resulted in a reduction in quality of life of up to 10%.

Table 224: Health state utility weights

Heath state	Utility weight	Source
MI	0.80	449
Post MI	0.88	265
heart failure	0.71	265
Death	0	265

Table 225: Utility weight by age

Age group	Age utility weight	Source
45-54	0.85	146
55-64	0.79	

Age group	Age utility weight	Source
65-74	0.78	
75+	0.73	

Cost effectiveness:

The results of cost-effectiveness analysis are usually presented as Incremental Cost-Effectiveness Ratios (ICERs), which determine the additional cost of using one drug (X) per additional QALY gained compared with no intervention or another drug (Y):

ICERs = (cost of X – cost of Y)/ (QALY of X – QALY of Y)

Sensitivity Analysis:

The model includes a base case analysis supplemented with both univariate deterministic and probabilistic sensitivity analyses to test the impact of uncertainty over various model parameters and assumptions.

Q.2.3.4 Results

The base case results are presented in tables Table 226 and Table 227 for 65-year-old men and women post MI with left ventricular dysfunction. The results suggests that third generation beta blockers are highly cost-effective for this population with an estimated ICER of about £1,100/QALY gained, compared with placebo which is well below the level usually considered to be affordable in the NHS (about £20,000 to £30,000 per QALY).

Table 226: Base case results 65 year old male

	Cost (£)	Effect (QALYs)	Incremental cost (£)	Incremental effect (£)	ICER (£/QALY)
Placebo	£2,414	3.40			
Beta Blockers	£3,286	4.20	£872	0.80	£1,091

Table 227: Base case results 65 year old female

	Cost (£)	Effect (QALYs)	Incremental cost (£)	Incremental effect (£)	ICER (£/QALY)
Placebo	£2,533	3.54			
Beta Blockers	£3,439	4.36	£906	0.82	£1,102

Figure 293: Base case results 65-year-old male, cost-effectiveness plane

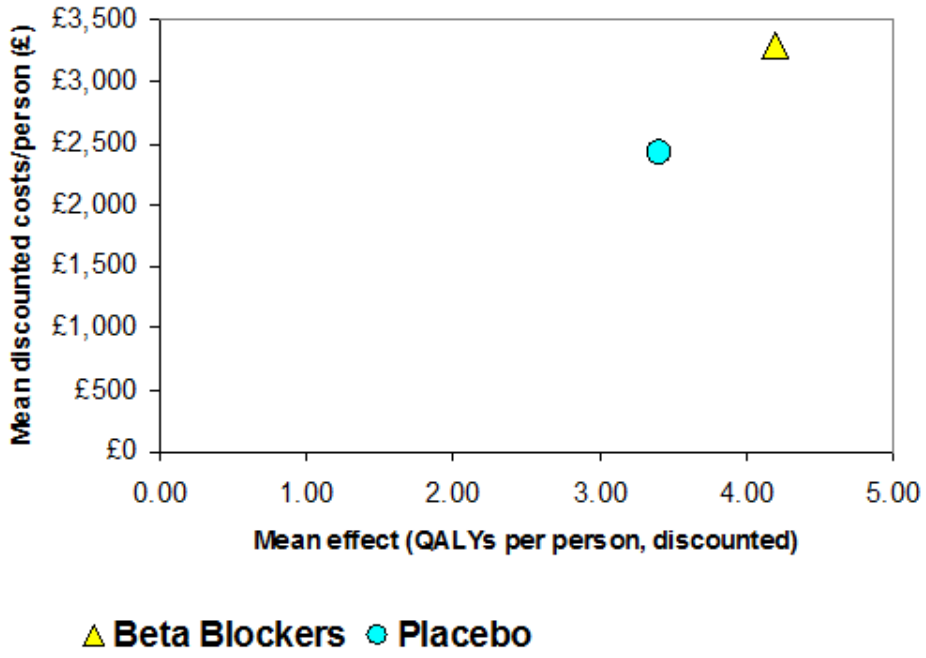
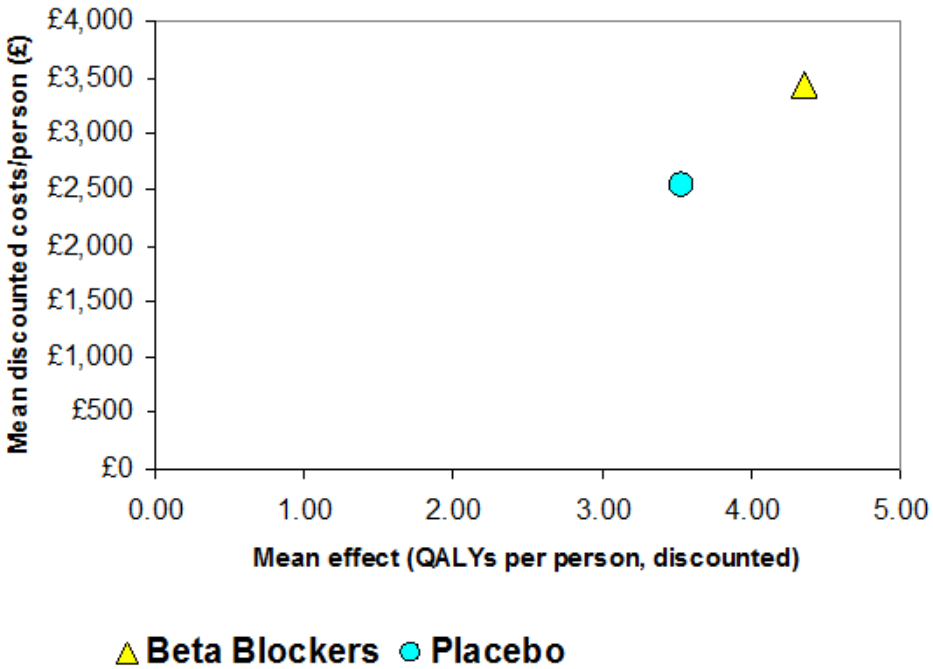


Figure 294: Base case results 65-year-old female, cost-effectiveness plane

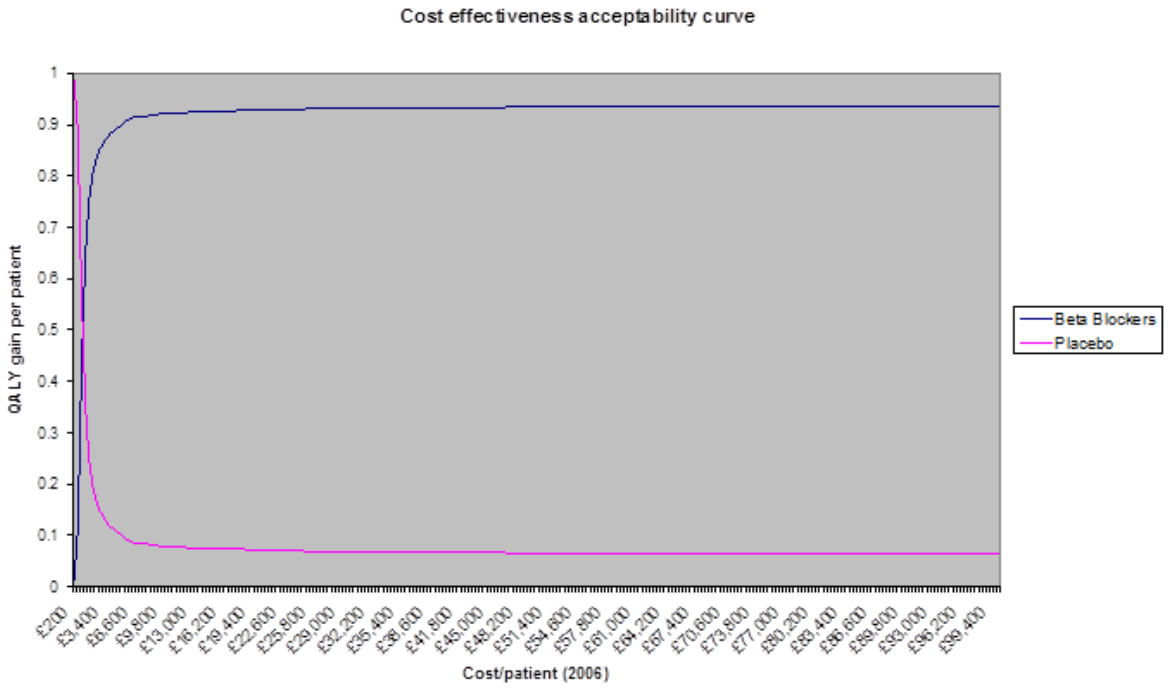


Probabilistic sensitivity analysis

A probabilistic sensitivity analysis was also done, where all parameters are allowed to vary at the same time. The results are reported below in the form of cost effectiveness acceptability curves (CEACs). These curves detail the probability that each strategy is cost effective over a range of potential maximum willingness to pay values that the NHS can afford to pay for an additional QALY.

The CEACs demonstrate that beta blockers are cost effective when compared to placebo. The probability that beta blockers are cost effective is around 93% at £20,000/QALY threshold. Even at lower thresholds such as £5,000/QALY beta blockers are still highly cost effective with a 90% probability of being cost effective. This suggests that beta blocker treatment in patients with left ventricular dysfunction is value for money.

Figure 295: Cost effectiveness acceptability curve



Deterministic sensitivity analysis

A range of univariate sensitivity analyses were conducted to assess the impact of different input parameters on the base case results. Detailed results for all parameters are shown in the appendix. The following parameters were tested costs of drugs, cost of events, discount rate, utility, age, and relative risk of non-CVD deaths and efficacy of treatment.

Efficacy of treatment

The results are not sensitive to uncertainty over the magnitude of treatment effects estimated from the CAPRICON trial [135]. When the relative risks of carvedilol compared with no intervention were increased to their upper 95% confidence limits and reduced to their lower 95% confidence limits the results remained robust. The ICERs ranged between about £800/QALY to about £1500/QALY when both lower and upper confidence intervals are used.

Relative risk of non CVD death

Relative risk of non CVD mortality does not affect the conclusions of the model. If its assumed that patients post MI have the same risk of dying from non circulatory causes as the general population, the ICERs increase by £20 to £1110. If it was assumed that post MI patients have a six fold increase in risk of dying from non circulatory causes, the ICERs slightly fell by £60 to £1030/QALY. This suggests that the model is robust to this assumption.

Quality of life loss due to treatment side effects

The model is robust assumptions about loss of quality of life as a result of treatment side effects. If it was assumed that beta blocker treatment would result in a 1% loss in quality of life, the estimated ICERs would be about £1090/QALY and if the loss was assumed to be as big as 10%, the ICERs will increase four fold to £4360/QALY, still within the range considered affordable by NHS.

Health state utilities

The results are not sensitive to assumptions about the health state utilities used in the base case model. When the observed health state utilities were arbitrarily reduced by 0.2, the model remained robust. When they increased by 0.2 the results did not change. The ICERs ranged between about £1100 to about £1200/QALY.

Cost of health states

The model is not sensitive to assumptions about the health state costs. When they were doubled or reduced by 50% the ICERs ranged between about £1,000/QALY to about £1,300/QALY.

Age and sex

The model is robust to assumptions about age and sex. However it should be noted that efficacy data by age and sex is not available except for baseline mortality. The trial data mainly had male population aged between 60-65 years. For ages below 55 and above 70 and to females the results need to be interpreted with caution.

Worse case scenarios

A worse case scenario was examined were the cost of events were doubled, and treatment effect was set at its upper 95% confidence interval. In this case the ICERs increased by ten fold, to about £11,000/QALY. This however was still within the range of what is considered affordable by the NHS. Thus in this worse case scenario, the model remained robust.

Another scenario was tested where in addition to doubling the costs of events and using the upper 95% confidence interval for treatment effect, it was also assumed that ACE inhibitors will result in a 1% loss in quality of life due to side effects of treatment. The ICER increased to about £55,000/QALY. The model was not robust to this worse case scenario. It is however important to note that this is an unlikely scenario since the cost of events/ health states are not as high as suggested in this assumption and the efficacy of beta-blockers is not as low as again suggested in this assumption.

Q.2.3.5 Limitations of the model

The model was based on various assumptions that could possibly bias the results.

The first limitation of the model arises because of the nature of Markov models. These assume that the probability of an individual moving to any given health state in one time period depends only their current health state (there is no longer 'memory' in the model). Thus the probability of heart

failure for a patient whose last CVD event was an MI is assumed to be the same irrespective of how many CVD events they have previously had. Similarly, a patient's health outcome and health care costs incurred are assumed to depend only on their current health state. These assumptions are unlikely to be strictly true, and will tend to underestimate overall costs and overestimate health outcomes for the cohort. Thus, interventions that prevent more CVD events will tend to appear rather less cost-effective than they may be in reality. So the model is conservative in this respect.

A second potentially important limitation of the model is the lack of utility data for the side effects of the drug. However exploratory sensitivity analysis was done assuming that carvedilol would result in loss of quality of life of upto 10%, but the results remained robust. This suggests that side effects profile might not affect the base case conclusions.

There is also lack of outcome data by age and sex and non white population. This implies that it is difficult to predict the relative cost-effectiveness of third generation beta blockers in these sub-groups. There is also lack of standard errors needed for the probabilistic sensitivity analysis. In the model we assumed the standard errors were a tenth of the observed mean values used in the base case model which might not always be the case.

Another limitation of the model relates to the treatment of withdrawals and non-concordance with treatment. Since the treatment effects are based on 'intention-to-treat' analyses, the impact of withdrawals and non-concordance from the trials is already included in the model. In CAPRICON [135] 20% of patients were permanently withdrawn from treatment. However, the model continues to attribute drug costs for all patients throughout their lifetime. This is a conservative assumption that will tend to underestimate the cost-effectiveness of treatment.

Q.2.3.6 Conclusions

This analysis suggests that treatment with third generation beta blockers is cost effective. This result is robust for all the parameters tested in sensitivity analysis including a worse case scenario.

Q.2.3.7 Additional information: Sensitivity analysis

All sensitivity analysis applies to 65 year old men

Table 228: Sensitivity analysis, efficacy of beta blocker treatment (95% CI)

Outcome	ICER for Lower 95% CI	ICER for Upper 95% CI
MI	£880	£1,420
Heart failure	£790	£1,530
Mortality	£1,060	£1,530

Interpretation:

The model is stable to assumptions about the efficacy of treatment. The ICERs ranges between about £800/QALY to about £1500/QALY when both lower and upper confidence intervals are used.

Sensitivity analysis, quality of life loss due to treatment side effects

Table 229: Sensitivity analysis, quality of life loss due to treatment side effects

Quality of life loss due to treatment side effects	cost/QALY
1%	£1,180
2%	£1,180
5%	£1,750
10%	£4,360

Interpretation:

The model is robust assumptions about loss of quality of life as a result of treatment side effects. If it was assumed that beta blocker treatment would result in a 1% loss in quality of life, the estimated ICERs would be about £1090/QALY and if the loss was assumed to be as big as 10%, the ICERs will increase four fold to £4360/QALY, still within the range considered affordable by NHS.

Table 230: Sensitivity analysis; health state utilities ± 0.2

Health state	(0.2 less) cost/QALY	(0.2 more) cost/QALY
MI	£1,090	£1,100
well post MI	£1,100	£1,090
Heart failure	£1,090	£1,090
well post heart failure	£1,180	£1,020

Interpretation:

The results are not sensitive to assumptions about the health state utilities used in the base case model. When the observed health state utilities were arbitrarily reduced by 0.2, the model remained robust. When they increased by 0.2 the results did not change. The ICERs ranged between about £1100 to about £1200/QALY.

The model is very robust to all assumptions tested with ICERs remaining the same as in the base case or differing very slightly as shown in the table above.

Table 231: Sensitivity analysis; relative risk of non-CVD death

Relative risk of non CVD mortality	ICER (Cost/QALY)
1	£1,110
2	£1,090
4	£1,060
6	£1,030

Interpretation:

Relative risk of non CVD mortality does not affect the conclusions of the model. If its assumed that patients post MI have the same risk of dying from non circulatory causes as the general population, the ICERs increase by £20 to £1110. If it was assumed that post MI patients have a six fold increase in risk of dying from non circulatory causes, the ICERs slightly fell by £60 to £1030/QALY. This suggests that the model is robust to this assumption.

Table 232: Sensitivity analysis; health state costs

Cost of health state	50% less (cost/QALY)	100% more (cost/QALY)
WELL	£1,010	£1,260
MI (ACUTE)	£1,150	£980
Well post MI	£1,080	£1,110
Heart Failure	£1,100	£1,070
Well post heart failure	£970	£1,330

Interpretation:

The model is not sensitive to assumptions about the health state costs. When they were doubled or reduced by 50% the ICERs ranged between about £1,000/QALY to about £1,300/QALY.

Table 233: Sensitivity analysis; Age and sex

AGE	MALE cost/QALY	FEMALE cost/QALY
55	£1,070	£1,080
65	£1,090	£1,100
75	£1,110	£1,120
85	£1,070	£1,080

Interpretation:

The model is robust to assumptions about age and sex. However it should be noted that efficacy data by age and sex is not available except for baseline mortality. The trial data mainly had male population aged between 60-65 years. For ages below 55 and above 70 and to females the results need to be interpreted with caution.

Table 234: Sensitivity analysis; Worse case scenario 1, costs of health state doubled, treatment effects set the upper limit of the 95% CI

	Cost (£)	Effect (QALYs)	ICER (£/QALY)
Placebo	£4830	3.402509	
Beta Blockers	£5500	3.4643036	£10870

Interpretation:

A worse case scenario was examined were the cost of events were doubled, and treatment effect was set at its upper 95% confidence interval. In this case the ICERs increased by ten fold, to about £11,000/QALY. This however was still within the range of what is considered affordable by the NHS. Thus in this worse case scenario, the model remained robust.

Table 235: Sensitivity analysis; Worse case scenario 2, costs of health states doubled, treatment effects set at the upper limit of the 95% CI, 1% loss in quality of life due to treatment side effects

	Cost (£)	Effect (QALYs)	Incremental cost (£)	Incremental effect (£)	ICER (£/QALY)
Placebo	£4,828	3.402509			
Beta Blockers	£5,499	3.4148236	£671.42	0.0123147	£54,522

Interpretation:

Another scenario was tested where in addition to doubling the costs of events and using the upper 95% confidence interval for treatment effect, it was also assumed that ACE inhibitors will result in a 1% loss in quality of life due to side effects of treatment. The ICER increased to about £55,000/QALY. The model was not robust to this worse case scenario. It is however important to note that this is an unlikely scenario since the cost of events/ health states are not as high as suggested in this assumption and the efficacy of beta-blockers is not as low as again suggested in this assumption.

Q.2.4 Economic analysis of omega-3 fatty acid supplementation compared to no supplements for patients following MI

Q.2.4.1 Introduction

During validation of the Post Myocardial Infarction guideline some questions were raised about the robustness of the evidence of effectiveness and cost-effectiveness for the recommendation on use of omega-3 fatty acid supplements. NICE's Guidance Executive has asked the NCC and GDG to reconsider this evidence and do a further economic analysis on the cost-effectiveness of omega-3 fatty acids.

Q.2.4.2 Clinical evidence

The recommendation in the draft guideline was based on the GISSI-P trial[228], which found a reduced incidence of cardiovascular deaths in patients recruited within 3 months of an acute MI treated with an omega-3-acid ethyl ester supplement (850-882mg EPA and DHA as ethyl esters in the average ratio of EPA/DHA of 1:2.

There are many other trials of omega-3 fatty acids, dietary and supplemental, in various patient populations at different levels of cardiovascular risk. A Cochrane review[273] found significant heterogeneity in these data, essentially due to one large study in patients with angina[87]. When this study was taken out, the heterogeneity was removed and the meta-analysis suggested a significant reduction in mortality with omega 3, largely due to two studies in patients recruited shortly after acute myocardial infarction DART1[86] and GISSI-P[228]. The negative effects of DART2 appeared to offset the positive effects in DART1 and GISSI-P.

The Cochrane review[273] considered various possible explanations for this difference and concluded:

"It may be that the effect of omega 3 fats on cardiovascular disease is smaller than previously thought (if indeed the effect does exist). Alternatively it may be that effects in those who have had a myocardial infarction are protective of death, but the effects in men with angina and no infarction are not…" (p16 Hooper et al 2004[273])

The researchers on the DART1 and DART2 studies suggested that the effect might be due to interaction between fish oil and medication in angina patients.(Burr, Dunstan and George 2005) Other hypotheses are that the benefits of omega-3 could be due to promotion of electrical stability, reduced platelet thrombogenicity or avoidance of damage from unstable plaques in the early post-MI period.

Q.2.4.3 Cost-effectiveness evidence

Two cost-effectiveness analyses based on GISSI-P were available to the GDG – one from a company submission from Solvay 2004[284], and another from a published study[198], part funded by another company (Pharmacia & Upjohn). The Solvay submission estimated an incremental cost effectiveness ratio (ICER) of £15,189 over the four-year trial period, and £3,717 per QALY extrapolated over the patients' lifetimes. Though generally of good methodological quality, the Solvay submission did not report the sensitivity of their findings to the effectiveness data or assumptions.

The published analysis by Franzosi and colleagues[198] used rather more conservative assumptions, and estimated an ICER of 24,603 euros per life year gained (LYG) (with a range of 15,721 to 52,524 euros for a best-case and worst-case analysis). It is unclear whether this estimate would lie below the NICE threshold of £20-30,000 per QALY.

Another cost-effectiveness analysis based on the GISSI-P trial has since been published by Lamotte et al [330]. This analysis, also funded by Solvay, presented results from the perspective of the Australian,

Canadian, German, Polish and Belgian health care systems. It used a different modelling approach to that in the Solvay submission, but arrived at similar results (5,346 to 8,315 euro per LYG, compared with £2,812 per LYG in the submission). Lamotte et al estimated that treatment would still be cost-effective (relative to the five countries' maximum willingness-to-pay), if the risk of cardiovascular death with treatment were up to 24% to 40% higher than observed in GISSI-P. They also conducted a probabilistic sensitivity analysis, in which they estimated the impact of uncertainty over the relative risk reductions, as reflected in the 95% confidence intervals from the GISSI-P trial. According to this analysis, the probability that supplementation is cost-effective was estimated at around 98%. However, this did not allow for uncertainty over other model assumptions or parameters. For example, the model assumed that patients dying in the study period lost 12-13 years of life and this was not tested in sensitivity analysis.

On balance the current evidence suggests that omega-3 supplements may be a cost-effective intervention for patients after MI. However, there is considerable uncertainty over this finding. In particular, it was unclear whether the cost-effectiveness of supplements is robust to different methods of estimating their clinical effectiveness.

Q.2.4.4 Aim for further economic analysis

To estimate the cost-effectiveness of omega-3 fatty acid supplementation for patients following MI who cannot comply with dietary recommendations.

Q.2.4.5 Methods for economic analysis

Population

Patients who have had an MI within 3 months and who are unable to eat sufficient oily fish of 2-4 portions per week to meet the recommended intake of approximately 3.5g eicosapentaenoic acid (EPA) and 2.5g decosahexaenoic acid (DHA) per week. Subgroup analysis was performed to estimate the cost-effectiveness of supplementation for people who partially comply with the recommended dietary intake of oily fish.

Intervention

The analysis compared increased intake of omega-3 fatty acids from supplemental sources compared with no supplementation. The supplements considered were:

- 1g per day omega-3-acid ethyl esters (460mg EPA, 380mg DHA per capsule) (Omacor)
- 3g per day omega-3-marine triglycerides (170mg EPA, 115mg DHA per capsule) (Maxepa)

Both of the above options provide the recommended levels of EPA and DHA, assuming no dietary intake. The cost-effectiveness of supplements for patients who partially meet the recommended dietary intake of oily fish was estimated by assuming that patients use half the above doses: one capsule every other day for Omacor; or for Maxepa, instead of taking the supplements twice a day they will take them once a day.

The use of other over-the-counter supplements was not considered due to potential concerns about contamination in unlicensed products. The Cochrane review[273] discusses potential concerns over cancers and neurological deficits that could possibly be increased due to dioxin and PCB contamination of fish oils. Although they found no direct evidence for this in the RCT or cohort data, they note that there is a lack of data on important outcomes. They conclude "independent analysis of the levels of toxins in named brands of fish oil supplements and oily fish sold for food should be more widely available" (p20 Hooper et al 2004[273]).

Source of effectiveness data

In the absence of evidence of a difference in effect between dietary and supplemental sources of omega-3 fats, we assume equivalence (at equivalent doses of EPA/DHA). Thus evidence from trials of dietary or supplemental sources was pooled where relevant. Thus estimates of effectiveness for the base case analysis were taken from a meta-analysis of the results of DART 1[86] and GISSI-P trials.[228] In addition data from GISSI-P and DART 1 was considered in the sensitivity analysis. This is based on the hypothesis that the effect observed in these trials is specific to patients who have recently had an MI, and that the results of the other main trial DART2[87] are not relevant to this population.

The outcomes considered were total deaths, non-fatal MI, non-fatal stroke and revascularisations. Other outcomes such as heart failure, peripheral artery disease were not considered because very few events were recorded in both trials.

Table 236: Treatment effect used in the model

	Meta-analysis (base model)			GISSI-P alone			DART1 alone		
Outcome	**Mean**	**Lower CL**	**Upper CL**	**Mean**	**Lower CL**	**Upper CL**	**Mean**	**Lower CL**	**Upper CL**
MI	1.14	0.75	1.74	0.96	0.80	1.14	1.49	0.97	2.30
Stroke	1.22	0.91	1.64	1.19	0.88	1.61	2.51	0.49	12.89
Revascularisation	1.05	0.97	1.13	1.05	0.97	1.13	1.05	0.97	1.13
CVD death	0.79	0.67	0.93	0.84	0.72	0.97	0.70	0.53	0.91
Total mortality	0.81	0.68	0.96	0.86	0.77	0.97	0.71	0.55	0.92

The company submission used the results of a four way analysis from the GISSI-P trial, and for our base model, we used the same results from the meta-analysis and did sensitivity analysis to estimate the impact of uncertainty over the treatment effects (as reflected in the 95% confidence intervals estimated from the meta-analysis) and various other model parameters.

The model was not adjusted for non-compliance. We assumed compliance issues were accounted for in the intention-to-treat results. Assuming 100% compliance tend to over-estimate costs, thus our model is conservative biasing the results against treatment.

The Cochrane review[273] found no evidence of long-term side effects of omega-3. However, they did find that increased omega-3 intake was significantly associated with drop outs due to side effects and gastrointestinal (GI) side effects. The model included a loss of quality-of-life due to GI side effects, based on the estimated incidence in the Cochrane review, pooling results across all levels of cardiovascular risk. This assumes that the rates of such side effects do not differ for the post-MI population.

Estimation of costs and effects

The costs and effects of treatment were estimated over a lifetime horizon using a cohort Markov modelling approach. We used a twelve-month model cycle length. This period was deemed sufficiently short to ensure that it is unlikely that patients would experience two events within the same cycle.

Baseline non-CVD mortality rates in the absence of additional omega-3 were estimated by age from population data for England and Wales. That is Governments Actuary's Department and Office for National Statistics[237,436] and adjusted for assumed increased risks following a first MI. Incidence rates for CVD mortality, non-fatal MI and stroke following a first MI, in the absence of treatment, were estimated from the observed rates in the trial control groups. Estimates for sensitivity analysis were also taken from a cohort study by Kaplan 2002 [306], in which 2677 patients were followed up for an

average of 3.4 years after an MI. The Kaplan data was also used to estimate the distribution of CVD death, non-fatal MI and non-fatal stroke by age, and the proportion of these events that occurred in the first year after an initial MI. Risks of stroke following a first stroke were estimated from a cohort study by Hardie et al 2004 [260]. The incidence of revascularisation by age was estimated from Johansen et al 1998 [292].

It has been reported that the survival benefits of omega-3 following myocardial infarction appear early and do not persist in the longer term Ness et al 2002 [422]. In the base case analysis we assumed that treatment effects do not persist beyond the longest trial period (3.5 years for GISSI-P), and that supplements are only used for this time. We tested these assumptions in sensitivity analysis.

Costs were estimated from the perspective of the NHS and discounted at an annual rate of 3.5% in accordance with NICE guidance [418]. The cost of omega-3 supplements were taken from the BNF [79]. The cost for non-fatal MI and strokes were based on those reported in the NICE technology appraisal of statins Ward et al 2005 [417], adjusted for inflation.

Outcomes were estimated in the form of quality adjusted life years (QALYs). The quality of life ('utility') associated with various health states in the post-MI population was also taken from the NICE statin technology appraisal [417] Utility was adjusted for age, using estimates from a representative general population sample in the Health survey of England 1996 [146]. QALYs were discounted at 3.5% per annum.

Cost effectiveness

The results of cost-effectiveness analysis are presented as incremental cost-effectiveness ratios (ICERs), which estimate the additional cost per additional QALY gained using omega-3 supplements compared with no supplements.

Sensitivity analysis

The model includes a base case analysis supplemented with univariate deterministic sensitivity analyses to test the impact of uncertainty over various model parameters and assumptions.

Q.2.4.6 Results

The base case results are presented for patients aged 55 years in Table 237. These suggest that for post-MI patients who do not comply with dietary advice to eat 2-4 portions of oily fish per week, omega-3-acid ethyl esters supplements are cost-effective, with an estimated ICER of about £12,500 per QALY.

Table 237: Base case results for omega-3-acid ethyl esters supplements compared with no supplements in 55 year old patients after MI who do not comply with dietary recommendations

	Cost (£)	Effect (QALYs)	Incremental cost (£)	Incremental effect (£)	ICER (£/QALY)
No supplements	£14,164	9.10	-	-	-
Supplements	£15,237	9.19	£1,073	0.09	£12,480

The supplements are estimated to be rather less cost-effective for younger patients and more cost-effective for older patients (see Table 238 below).

Table 238: Estimated cost-effectiveness by age – base case assumptions

	No supplements	Supplements	

	No supplements		Supplements		
Age	Cost (£)	Effect (QALYs)	Cost (£)	Effect (QALYs)	ICER (£/QALY)
45	£16,529	11.64	£17,653	11.70	£19,424
55	£14,164	9.10	£15,237	9.19	£12,480
65	£11,535	6.51	£12,592	6.66	£7,020
75	£8,694	4.03	£9,704	4.24	£4,639

It will be more cost-effective from an NHS perspective if some or all of the recommended intake of omega 3 fatty acids could be obtained from dietary sources. For example, if only half the quantity of supplements is required, the estimated ICER for a 55 year old falls to £9,267 per QALY.

Duration of treatment costs and effects

In the base model we assumed that the benefits and costs of supplementation persist for 3.5 years, as this was the longest duration of demonstrated effectiveness [228]. The duration of the other included trial [86] was two years, and a long-term follow-up study found that treatment effects did not persist beyond two years [422] If we assume that treatment costs and effects only last for two years, omega 3 supplementation appears to be less cost-effective (Table 239). At age 55 the estimated ICER is £23,400, which is above the £20,000 threshold. Conversely, if we assume that treatment effects and costs persist for life, supplementation appears to be more cost-effective: £6,600 per QALY for 55 year olds.

Clearly if the benefit of omega 3 is of limited duration, it will not be cost-effective to continue using, and paying for, supplements beyond this period. If we assume that the benefits will cease at 3.5 years and costs will persist for life – that is that people continue to receive omega 3 supplements but they do not derive any benefit from them - omega-3-acid ethyl esters supplements would only appear to be cost-effective for older patients (age 65 and over).

Table 239: Sensitivity to duration of treatment costs and effects

	ICER (£/QALY)			
Costs	2 years	3.5 years	Lifetime	Lifetime
Effects	2 years	3.5 years	3.5 years	Lifetime
Age 45	£44,088	£19,424	£53,077	£8,343
Age 55	£23,429	£12,480	£29,950	£6,584
Age 65	£10,829	£7,020	£13,590	£5,065
Age 75	£6,495	£4,639	£7,069	£3,912

Source of effectiveness data

The base model used estimates of treatment effects from a meta-analysis of DART 1 and GISSI-P trials. When we considered results of the GISSI-P trial alone, the ICERs increased slightly (Table 240). Treatment remained cost-effective with the GISSI-P data, except for the 45 year old group, for whom the estimated ICER was above the £20,000 per QALY threshold. The results using the DART1 data alone were very similar to those using the pooled data.

Table 240: Sensitivity to source of effectiveness estimates

	ICER (£/QALY)		
	DART1	GISSI-P	Pooled
Age 45	£19,640	£27,393	£19,424

	ICER (£/QALY)		
Age 55	£12,206	£16,603	£12,480
Age 65	£7,337	£8,834	£7,020
Age 75	£5,157	£5,596	£4,639

Uncertainty over the size of treatment effects

The robustness of the results to uncertainty over the size of treatment effects was assessed using the upper and lower 95% confidence intervals from the meta-analysis (Table 241). The model results remained robust when the treatment effects were improved (set to their lower confidence interval) and worsened (upper confidence interval) for all outcomes except for all cause mortality. When the upper 95% confidence limits were used for all cause mortality, omega-3-acid ethyl esters supplements were no longer cost effective at the £20,000/QALY threshold. The estimated ICER was about £130,700 per QALY for a person aged 55 years, £37,800 for a 65 year old and £20,400 for a 75 year old.

Table 241: Sensitivity to upper and lower confidence limits of treatment effects: age 55

	Relative risks		ICER (£/QALY)	
	Mean	95% CI	Lower limit	Upper limit
Non-fatal MI	1.14	(0.75 to 1.74)	£11,672	£13,792
Non-fatal stroke	1.22	(0.91 to 1.64)	£11,174	£14,533
Revascularisation	1.05	(0.97 to 1.13)	£12,067	£12,885
All cause mortality	0.81	(0.68 to 0.96)	£7,472	£130,705

Outcomes included in model

In the meta-analysis, only all cause mortality was found to be significantly different between treatment groups. If we assume no effect for the other outcomes (non-fatal MI, non-fatal stroke and revascularisation) and model mortality alone, the results become slightly more favourable (Table 242). Thus the model results are largely driven by the treatment effect on all cause mortality.

Table 242: Sensitivity to inclusion of non-fatal outcomes (MI, stroke and revascularisation)

	ICER (£/QALY)	
	All outcomes	All cause mortality only
Age 45	£19,424	£16,327
Age 55	£12,480	£11,021
Age 65	£7,020	£6,253
Age 75	£4,639	£4,111

Source of baseline event rates

In the base case model, the annual risks of cardiovascular disease events (non-fatal MI, non-fatal stroke, revascularisation and cardiovascular disease-related mortality) in the absence of supplements was taken from the rates observed in the control groups of the included trials [86] and [228] These included 6,676 patients followed up for an average of 3.3 years. Estimates from a cohort study [306] gave rather higher ICERs (less cost-effective) (Table 243). Supplements still appeared to be cost-effective for people aged 55 and older, but not for 45 year olds (based on the £20,000 per QALY cost-effectiveness threshold).

Table 243: Sensitivity to source of baseline cardiovascular disease risks (MI, stroke, revascularisation, cardiovascular disease-related death)

	ICER (£/QALY)	
	All outcomes	All cause mortality only
Age 45	£19,424	£16,327
Age 55	£12,480	£11,021
Age 65	£7,020	£6,253
Age 75	£4,639	£4,111

Relative risk of non cardiovascular disease mortality

Packham C et al [448] and Robinson M et al [504] estimated that the relative risk of dying from non cardiovascular disease in a cohort of patients with coronary heart disease compared with the general population lies between 2 and 8. We used a conservative estimate of 2 for the base case model. If we assume that there is no difference in non cardiovascular mortality between the general population and those with coronary heart diseases, the ICERs rise and treatment no longer appears to be cost-effective for younger patients (Table 244). When the risk is assumed to be around 4, the ICERs fall.

Table 244: Sensitivity to assumed relative risk of non-cardiovascular disease mortality

	ICER (£/QALY)		
	RR=1	RR=2	RR=4
Age 45	£24,004	£19,424	£14,417
Age 55	£15,856	£12,480	£9,177
Age 65	£8,469	£7,020	£5,541
Age 75	£5,345	£4,639	£3,943

Cost of supplements

The base model used Maxepa, which was used in the DART1 trial and costs about £150 a year. We also tested the use of the supplement used in the GISSI-P trial (Omacor), which is slightly more expensive (£181 a year). The model results remained cost effective, although for younger patients the estimated ICER was very close to the £20,000 per QALY threshold (Table 245). If we assume clinical equivalence between these supplements, it will not be cost-effective to use the more expensive product.

Table 245: Sensitivity to price of supplements

	ICER (£/QALY)	
	Maxepa £150 pa	Omacor £181 pa
Age 45	£19,424	£21,472
Age 55	£12,480	£13,843
Age 65	£7,020	£7,772
Age 75	£4,639	£5,119

Impact of treatment side effects

The base model assumes that there is a 0.07% loss in quality of life due to treatment side effects. This is probably an over-estimate, as it is based on the assumption that the additional 5% of patients who reported gastrointestinal (GI) side effects in omega-3-acid ethyl esters supplement trials (Hooper et al 2004) all experience a permanent loss of quality of life of 1.4%, which is an estimate for of the quality of life loss due to "nausea, vomiting or diarrhoea for 5 days" Anderson 1985 [25]. In

reality many of these patients would have only experienced transient effects, and those with longer lasting or more serious effects would have been likely to stop taking the supplements.

The Hooper review [273] found that there were significantly more drop outs due to side effects with omega 3 than in the control groups, although overall drop out rates were not significantly different. Any loss of effectiveness due to drop outs is included in the model through the intention-to-treat estimates of treatment effects. No adjustment is made for the reduced cost of supplements due to drop outs, but if anything this will tend to bias the model against supplementation.

In addition to the quality of life loss, the base case model assumes that an additional GP visit (cost £24) is required per patient per year to treat side effects. This is also likely to be conservative, since only a minority of patients report side effects and these appear to be relatively minor in nature.

Assumptions about the cost and quality of life loss due to side effects made little difference to the base case results, which still showed that omega-3-acid ethyl esters supplements were cost effective, except possibly for younger patients with particularly high treatment costs for side effects (2 or 3 additional GP visits for every patient each year) – see Table 246.

Table 246: Sensitivity to cost and quality of life loss due to side effects

	ICER (£/QALY)					
Quality of life loss	0.001%			0.07%		
Extra GP visits	1	2	3	1	2	3
Age 45	£16,248	£22,068	£27,889	£19,424	£26,383	£33,342
Age 55	£11,264	£14,730	£18,196	£12,480	£16,319	£20,159
Age 65	£6,713	£8,268	£9,822	£7,020	£8,645	£10,271
Age 75	£4,543	£5,281	£6,019	£4,639	£5,393	£6,147

Discounting

NICE [418] recommends we discount both cost and benefits at 3.5% per annum. We tested three different scenarios: no discounting, 3.5% for effects and 6% for costs, and 6% for both costs and effects. The model was not sensitive to assumptions (Table 247).

Table 247: Sensitivity to discount rates for costs and effects (QALYs)

	ICER (£/QALY)			
Costs	0%	3.5%	6%	6%
Effects	0%	3.5%	3.5%	6%
Age 45	£15,301	£19,424	£16,818	£22,924
Age 55	£10,170	£12,480	£11,068	£14,366
Age 65	£6,041	£7,020	£6,350	£7,781
Age 75	£4,173	£4,639	£4,269	£4,990

Health state utilities

The health state utilities used in the model were obtained from the literature. We tested the assumption that the mean health state utilities were 0.2 less or more than the ones we got from the literature. The model was not sensitive to this assumption.

Table 248: Sensitivity to health state utility values: age 55

	Utility values (0-1)		ICER (£/QALY)	
Health State	**Base case**	**Range**	**Lower limit**	**Upper limit**

	Utility values (0-1)		ICER (£/QALY)	
MI (year one)	0.76	(0.56 to 0.96)	£12,654	£12,310
Post MI	0.88	(0.68 to 1.00)	£13,389	£11,991
Stroke (year one)	0.63	(0.43 to 0.83)	£12,550	£12,410
Post stroke	0.63	(0.43 to 0.83)	£13,004	£11,996
Revascularisation (year one)	0.80	(0.60 to 1.00)	£12,685	£12,281
Post revascularisation	0.88	(0.68 to 1.00)	£14,259	£11,610

Costs of cardiovascular disease events

The costs of cardiovascular disease events do not affect the model results. When the costs were increased by 100% or reduced by 50%, the ICERs changed very little (Table 249).

Table 249: Sensitivity to cost of cardiovascular disease events

	Costs (£ pa)		ICER (£/QALY)	
Health State	**Base case**	**Range**	**Lower limit**	**Upper limit**
MI (year one)	£4,537	(£2,268 to £9,074)	£12,280	£12,879
Post MI	£510	(£255 to £1,020)	£12,368	£12,703
Stroke (year one)	£8,207	(£4,103 to £16,414)	£12,333	£12,772
Post stroke	£2,206	(£1,103 to £4,413)	£12,193	£13,054
Revascularisation (year one)	£3,082	(£1,541 to £6,163)	£12,322	£12,795
Post revascularisation	£510	(£255 to £1,020)	£12,275	£12,889

Q.2.4.7 Discussion

Our results are broadly consistent with other published economic evaluations. [198] and [330] all concluded that omega 3 supplements were cost effective compared with no supplements.

The submission by Solvay 2004 [284] estimated an incremental cost effectiveness ratio (ICER) of £15,189 over the four-year trial period, and £3,717 per QALY extrapolated over the patients' lifetimes. Their estimated ICERs are comparable with ours which we estimated to be £12,500 over 3.5 years and £6,600/QALY over lifetime. If we use the same effectiveness data (GISSI-P alone) and drug costs (Omacor) as used in the Solvay analysis, our model gives an estimate ICER of £18,500 per QALY for a 55 year old.

The Solvay model was of good methodological quality. Their main limitation was that they did not report the sensitivity of their findings to the effectiveness data or assumptions. Our results were highly sensitive to uncertainty over the treatment effects: at the upper 95% confidence limit for the relative risk of total mortality, omega 3 supplementation was not cost-effective, with an ICER of over £130,000 per QALY.

Our model slightly differed from the Solvay model [284]. We included the outcome of revascularisation while their model did not. However, this made little difference to the results. Our base model used pooled treatment effects from [86] and [228], while the Solvay submission used data from [228] alone. We tested this in sensitivity analysis and this did not change model results. We also modelled loss of quality of life of due to treatment side effects which the Solvay model did not consider. Again, this made little difference to the results. Despite these identified methodological differences, our conclusions are similar.

Our analysis had some weakness especially with regards to lack of data on relative treatment effects for under-55s and over 75 year olds. This means that it is difficult to predict the relative cost-

effectiveness of omega-3-acid ethyl esters in these age groups. Most of the efficacy data relates to mainly middle aged men 60-75 years. As such extrapolating this evidence to longer-term outcomes (cardiovascular disease events) is more difficult for these age groups.

The model also assumes that a patient's health outcome and health care costs incurred are assumed to depend only on their current health state. This is unlikely to be strictly true, and will tend to underestimate overall costs and overestimate health outcomes for the cohort. Thus, interventions that prevent more CVD events will tend to appear rather less cost-effective than they may be in reality. So the model is conservative in this respect.

Q.2.4.8 Conclusions

Our analysis found that omega-3-acid ethyl esters supplements are cost effective when compared with no supplements in patients soon after MI. Using the best available data and assumptions, we estimated ICERs of about £12,500. This result was sensitive to uncertainty over the size of treatment effects - supplements did not appear to be cost-effective at the upper confidence limit for the relative risk of mortality.

These results depend on the assumption that treatment effects do not persist beyond the longest trial period, 3.5 years for the GISSI-P trial,[228] and that supplements are not continued after this time. DART1, [86]was of shorter duration (2 years), and benefits were not observed to continue beyond this in a follow-up study Ness et al 2002 [422]. Although this was beyond the intervention time, and while there were still differences in fish intake between the two groups, the differences were less than during the trial period [422] If we assume that treatment costs and effects only last for two years, supplements are of borderline cost-effectiveness (£23,400 per QALY).

We assumed clinical equivalence for dietary and supplemental sources of omega 3 supplements, provided that the patient consumes the correct quantities of omega 3 fatty acids. From an NHS perspective, it will clearly be more cost-effective for patients to obtain this from dietary sources. But if a patient is unable to do this, provision of supplements does appear to be a cost-effective use of NHS resources. We assumed use of the cheapest available supplement with the correct quantities of EPA and DHA (Maxepa). Although the other such supplement (Omacor) also appears to be cost-effective compared with no supplementation, it will not be cost-effective compared with the cheaper alternative (assuming clinical equivalence between these products).

Finally, the validity of this analysis depends on acceptance of the proposition that the benefits of omega 3 are confined to people with a recent MI. We only included effectiveness data from the two trials in this population (DART1 and GISSI-P). If we were to broaden this evidence base to include the DART2 trial in angina patients, omega-3 supplementation would not appear to be effective or cost-effective.

Q.3 Clinical Evidence extractions

Table 250: What is the effectiveness of adding ACE inhibitors versus placebo to improve outcome in…

Grading: 1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number: 3093 Pfeffer MA;McMurray JJ;Velazquez EJ;Rouleau JL;Kober L;Maggioni AP;Solomon SD;Swedberg K;Van de WF;White H;Leimberger JD;Henis M;Edwards S;Zelenkofske S;Sellers MA;Califf RM; Valsartan, captopril, or both in myocardial infarction complicated	Randomised Controlled Trial	Inclusion criteria: At least 18 years mean (valsartan 65.0± 11.8 years, captopril 65.4, valsartan plus captopril 64.9±11.8 years). Men and women (31.1%). MI complicated by clinical or radiologic signs of HF, evidence of LV systolic dysfunction.	Valsartan 20 mg initially, dose increased in 4 steps, goal of step 3: 80 mg valsartan twice daily during initial hospitalizatio n, step 4: by 3 month visit 160 mg twice daily: 4909 patients.	Captopril 6.25 mg initially, goal of step 3: 25 mg captopril three times daily during initial hospitalization, step 4: by 3 month visit 50 mg three times daily: 4909 patients.	Follow-up: average 24.7 months years.	Primary outcome: all cause mortality. Secondary outcomes: Death from CV causes, or MI or HF, resuscitation after cardiac arrest or stroke, hospitalization for MI or HF, tolerability.	Novartis Pharm.	Primary outcome: all cause mortality: valsartan 979 (19.9%), valsartan + captopril 941 (19.3%), captopril 958 (19.5). Hazard ratio valsartan versus captopril : 1.00 (97.5% CI 0.90-1.11, P = 0.98). Hazard ratio valsartan + captopril versus captopril : 0.98 (97.5% CI 0.89-1.09, P = 073). Secondary outcomes: Valsartan versus captopril hazard ratios. Death from CV causes 0.98 (97.5% CI 0.87 to 1.09, P = 0.62). Death from CV causes or MI 0.95 (97.5% CI 0.87 to 1.05, P = 0.25). Death from CV causes or HF 0.97 (97.5% CI 0.90 to 1.05, P = 0.51). Death from CV causes, MI or HF 0.95 (97.5% CI 0.88 to 1.03, P =

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
by heart failure, left ventricular dysfunction, or 2003 349 New England Journal of Medicine								0.20). Death from CV causes, MI, HF, resuscitation after cardiac arrest or stroke 0.96 (97.5% CI 0.89 to 1.04, P = 0.25). Valsartan + captopril versus captopril. Death from CV causes 1.00 (97.5% CI 0.89 to 1.11, P = 0.95). Death from CV causes or MI 0.96 (97.5% CI 0.88 to 1.09, P = 0.40). Death from CV causes or HF 1.00 (97.5% CI 0.92 to 1.09, P = 0.94). Death from CV causes, MI or HF 0.97 (97.5% CI 0.89 to 1.05, P = 0.37). Death from CV causes, MI, HF, resuscitation after cardiac arrest or stroke 0.96 (97.5 %CI 0.89 to 1.04, P = 0.26). Hospitalization for MI or HF: Valsartan group 919 patients (18.7%) had a total of 1447 hospitalizations. Valsartan + captopril group 834 patients (17.1%) had a total of 1297 hospitalizations. Captopril group 945

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								patients (19.3%) had a total of 1437 hospitalizations. Valsartan versus captopril group P = 0.50 for comparison of proportion of patients and P = 0.51 for comparison of admissions. Valsartan + captopril group versus captopril group P = 0.005 for comparison of proportion of patients and P = 0.007 for comparison of admissions. Tolerability: Proportion of patients no longer taking medication at 1 year: valsartan group 15.3%, valsartan + captopril group 19.0% captopril group 16.8%. Valsartan + captopril group versus captopril group, P = 0.007. Mean doses of patients taking medication at 1 year: valsartan group 116±53 mg, valsartan + captopril group, valsartan 116±53 mg, captopril 107±53 mg, captopril group 117± 53 mg. Discontinuation

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								reasons: Hypotension: Valsartan 70/4885 (1.4%)* Valsartan+captopril 90/4862 (1.9%)* Captopril 41/4879 (0.8%). Cough: Valsartan 70/4885 (1.4%)* Valsartan+captopril 90/4862 (1.9%)* Captopril 41/4879 (0.8%). Rash: Valsartan 30/4885 (1.4%)* Valsartan+captopril 101/4862 (2.1%) Captopril 122/4879 (2.5%). Angiodema: Valsartan 9/4885 (0.2%)* Valsartan+captopril 0.2/4862 (1.9%) Captopril 13/4879 (0.3%). Taste disturbance: Valsartan 9/4885 (0.2%)* Valsartan+captopril 16/4862 (0.3%) Captopril 21/4879 (0.4%). Key: * the difference from the captopril group is significant at P < 0.05. Note: Valsartan is licensed in the UK for

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								post MI patients with LV dysfunction.

Grading: 1+ Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number: 3251 Arnold JMO;Yusuf S;Young J;Mathew J;Johnstone D;Avezum A;Lonn E;Pogue J;Bosch J; Prevention of heart failure in patients in the Heart Outcomes Prevention Evaluation (HOPE) study 2003 107 Circulation	Randomised Controlled Trial	Men & women at least 55 years, mean age 66 years, 26.7% women. Before random assignment all eligible participants entered a run-in phase, during which 2.5 mg of ramipril was administered daily for 7 days, followed by a matching placebo for 10 to 14 days. History of CAD, stroke, PAD or diabetes plus one CV risk factor, 80.6% previous CV	Ramipril, 10 mg OD.	Matching placebo	4.5 years.	Primary: composite MI / stroke / death from CV causes. Secondary: hospitalisations for HF and unstable angina, worsening angina, heart failure rate (composite of heart failure requiring hospitalisations, fatal heart failure, heart failure signs and symptoms and heart failure requiring open label ACEIs).	MRC Canada, Hoechst-Marion Roussel, Astra-Zeneca, King Pharm., Natural Source Vit E Assn and Negma, Heart and Stroke Foundn of Ontario.	Mean follow-up 4.5 years: there were 482 (10.4%) patients with clinical MI and unexpected CV deaths in ramipril group compared with 604 (12.9%) in the placebo group (RRR 21%, 95%CI 11 to 30; P < 0.0003). Ramipril reduced heart failure rate from 11.5% to 9% (RR 0.77; 95%CI 0.68 to 0.87; P < 0.0001). Ramipril patients had a reduced RR of nonfatal MI of 23% (9 to 34); P < 0.0019, either Q-wave MI (18% , -9 to 38) or non-Q-wave MI (24%, 8 to 37), ramipril 5.6% versus placebo 7.2%. Risk reductions in MI were documented in subjects taking or not taking beta

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
		event, 53% previous MI, 43.4% PAD, 10.8% stroke or transient ischemic attack, 38.3% diabetes mellitus, hypertension history 46.5%, dyslipidemia 65.8%. Trial entry: 76.8% subjects taking antiplatelet agent, 28.9% lipid-lowering agent, 39.5% beta blocker, 47.0% calcium channel blocker, 15.1% diuretic. Exclusions: HF, LVEF < 0.40, taking ACE inhibitor, uncontrolled hypertension, overt nephropathy, MI / stoke within 4 weeks recruitment,						blockers, lipid lowering and / or antiplatelet agents. Ramipril had no effect on hospitalizations for unstable angina or heart failure hospitalizations but reduced worsening and new angina, 27.2% versus 30.0%; RRR, 12%; (5 to 18) P < 0.0014, and coronary revascularization 12.5% versus 14.8%; RRR, 18%; (8 to 26) P < 0.0005.

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
		hyper-sensitivity to ACE.						
Reference number: 1770 Braunwald E;Domanski MJ;Fowler SE;Geller NL;Gersh BJ;Hsia J;Pfeffer MA;Rice MM;Rosenberg YD;Rouleau JL;PEACE T; Angiotensin-converting-enzyme inhibition in stable coronary artery disease. 2004 351 New England Journal of Medicine	Randomised Controlled Trial	50 years or older, mean age 65 years, women 18%. CAD at least 1 of following: MI at least 3 months prior to ecruitment 55%, CABG / PTCA at least 3 months prior to recruitment, obstruction greater / equal to 50% of luminal diameter of 1 native vessel, LVEF < 40%, toleration medication & successful completion of run-in phase, compliance. Diabetes mellitus 17%. Exclusions:	Trandolapril, target dose 4 mg OD.	Matching placebo.	7 years, median 4.8 years.	Primary: composite of death from CV causes, non fatal MI, coronary revascular-isation. Other: combination of CV death, nonfatal MI, revascularisation, unstable angina, HF, stroke, PAD, cardiac arrhythmia.	NHLB Inst., Knoll Pharm., Abbott Labs.	The incidence of the primary endpoint (composite of death from CV causes, non fatal MI, or coronary revascularization) was 21.9% in the Trandolapril group compared with 22.5% in the placebo group (HR in Trandolapril group 0.96, 95% CI 0.88 to 1.06, P = 0.45). Drop out: 3 in treatment and 8 in placebo did not return for a follow-up visit. Compliance: Treatment, at 1 year: 81.9% on treatment, at 2 years: 78.5%, at 3 years: 74.5%. Among patients in placebo, 1.5% were receiving ACEI at 1 year, 4.6% at 2 years and 8.3% at 3 years. 68.6% of treatment group and 77.7% of placebo group were taking target dose 4 mg placebo / placebo per day. Side effects: The rates of cough (39.1%

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
		current ACE / ARB usage, hospitalization for unstable angina 2 months prior, valvular HD requiring surgery, CADG / PTCA within 3 months prior, planned revascular-isation, serum creatinine > 2.0 mg/dl, serum K > 5.5 mmol/l, limited 5 year survival chance,psychos ocial risk adherence, no consent, female not using contraception, involved in non FDA / HP Canadian NHW approved trial. There was a 4 week run-in period. The participants was instructed to						versus 27.5% P = 0.01) and syncope (4.8% versus 3.9% P = 0.04) were greater in the Trandolapril group compared with the control group.

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
		take 2 mg of trandolapril daily, and they recruited if they compliant and tolerated the treatment. The median follow-up was 4.8 years. There were 9297 patients enrolled with						
Reference number: 3228 Flather MD;Yusuf S;Kober L;Pfeffer M;Hall A;Murray G;Ball S;Pogue J;Moye L;Braunwald E; Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular	Systematic Review						MRC Canada, Hoechst-Marion Roussel, Sqibb, Merck Frosst Canada, Merck Sharpe & Dohme UAS, Bristol Myers, Zeneca.	Median treatment duration in SAVE, AIRE and TRACE was 31 (IQR 19-41) months. Treatment was associated with a reduction of mortality in the three post MI trials, SAVE 1992, AIRE 1993 and TRACE 1995 (N = 5966, treatment deaths 702/2995 (23.4%) versus placebo deaths 866/297 (29.1%), OR 0.74, 95% CI 0.66 to 0.83). Similarly, readmission for heart failure (treatment 11.9% versus placebo 15.5%, OR 0.73, 95% CI 0.63 to 0.85), recurrent myocardial

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
dysfunction: a systematic overview of data from individual patients								infarction (treatment 10.8% versus placebo 13.2%, OR 0.80, 95% CI 0.69 to 0.94), or the composite of these events (treatment 35.5% versus placebo 41.9%, OR 0.75, 95% CI 0.67 to 0.83) were reduced. Combining all five trials (SAVE 1992, AIRE 1993 and TRACE 1995 + SOLVD 1991 / 1992) the treatment decreased mortality (N = 12 763), treatment deaths 1467/6391 (23.0%) versus placebo deaths 1710/6372 (26.8%), OR 0.80, 95% CI 0.74 to 0.87). Treatment also reduced readmission for heart failure (treatment 13.7% versus placebo 18.9%, OR 0.67, 95% CI 0.61 to 0.74), re-infarction (treatment 8.9% versus placebo 11.0%, OR 0.79, 95% CI 0.70 to 0.89), or the composite of these events (treatment 33.8% versus placebo 41.0%, OR 0.72, 95% CI 0.67 to

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								0.78).
Fox KM;EURopean t; Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study).[see comment] 2003 362 Lancet	Randomised Controlled Trial	Age > 18, mean age 60 years, 15% female. Run-in period: for 2 weeks participants were given 4 Characteristics mg of perindopril once daily in the morning in addition to their normal medication. If 4 mg was tolerated, perindopril was increased to 8 mg once daily in the morning for 2 weeks. Patients aged 70 years or older were given 2 mg daily in the first week, followed by 4 mg daily in the second week, and 8 mg daily in the last	Perindopril 8mg OD.	Matched placebo.	Average 4.2 years follow-up.	Primary: composite of CV death, non-fatal MI, cardiac arrest with successful resuscitation. Secondary: the composite of total mortality, non fatal MI, hospital admission for unstable angina, cardiac arrest with successful resuscitation, plus these individual components, revascularisation, stroke, admission for HF.	Servier, France.	Perindopril treatment was associated with reduction in primary endpoint 20% RRR (95% CI 9 to 29, P = 0.0003), 1.9% absolute risk reduction. Perindopril was associated with reductions in all secondary endpoints, although some were not statistically significant (not significant: unstable angina, total mortality, cardiovascular mortality, cardiac arrest, stroke, revascularization). See Figure 3, Table 1. Of note, perindopril treatment resulted in a 14% reduction in the composite outcome of total mortality, non-fatal MI, unstable angina and cardiac arrest (95% CI 6 to 21, P = 0.0009).

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
		2 weeks. Documented CAD, post MI < 3 months 64%, PCI or CABG < 6 months, 55%, narrowing of at least one main coronary artery, history of chest pain, positive electro-cardiogram, echo or nuclear stress test. Diabetes mellitus 12%. Most patients used antiplatelet agent > 90%. Exclusions: HF, planned revascularizatio n, hypo-tension, uncontrolled hyper-tension, recent ACE / ARB use, renal in-sufficiency creatinine > 150 micromol/L serum K . 5.5						

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
		mmol/L.						
Reference number: 3402 Granger CB;McMurray JJ;Yusuf S;Held P;Michelson EL;Olofsson B;Ostergren J;Pfeffer MA;Swedberg K; Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial 2003 362	Randomised Controlled Trial	Inclusion criteria: Aged 18 years or older, male and female (68% male in treatment group, 68% male in placebo group), symptomatic HF of at least 4 weeks duration, LVEF≤40%, previous intolerance to ACE inhibitors.	Candesartan 32 mg daily, 1011 patients.	Placebo: 1014 patients.	Median follow-up 33.7 months.	Primary: Composite of unplanned hospital admission for the management of worsening CHF or CV death. Secondary: CV death, hospital admission for CHF or MI, CV death, hospital admission for CHF, MI or stroke.	Astra-Zeneca R&D, Molndal, Sweden.	Primary: Composite of unplanned hospital admission for the management of worsening CHF or CV death: candesartan versus placebo HR 0.70 95% CI 0.60 to 0.81, P < 0.001. Secondary: CV death: candesartan versus placebo HR 0.80 95% CI 0.66 to 0.96, P = 0.02. Hospital admission for CHF: candesartan versus placebo HR 0.61 95% CI 0.51 to 0.73, P < 0.001. CV death, hospital admission for CHF or MI: candesartan versus placebo HR 0.72 95% CI 0.62 to 0.83, P < 0.001. CV death, hospital admission for CHF, MI or stroke: candesartan versus placebo HR 0.74 95% CI 0.64 to 0.85, P < 0.001. CV death, hospital admission for CHF, MI, stroke or coronary revascularization: candesartan versus placebo HR 0.76 95% CI

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								0.66 to 0.87, P < 0.001. Discontinuation reasons: Hypotension: Candesartan 37/1013 (1.4%)** Placebo 9/1015 (0.8%). Intolerance due to previous hypotension: Candesartan 13/143 (9.1%) Placebo 5/113 (4.2%). Cough: Candesartan 2/4885 (0.2%) Placebo 4/4879 (0.4%). Intolerance due to previous cough: Candesartan 2/704 (0.3%) Placebo 4/751 (0.5%). Increase in creatinine: Candesartan 62/4885 (6.1%)** Placebo 27/4879 (2.7%). Intolerance due to previous renal dysfunction: Candesartan 31/134 (23.1%) Placebo 12/100 (12%). Angioedema: Candesartan 1/4885 (0.1%) Placebo 0/4879. Intolerance due to previous angioedema / anaphylaxis: Candesartan 1/28 (2.6%) Placebo 0/44 (0.4%). Hyperkalaemia:

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								Candesartan 19/4885 (1.9%)* Placebo 3/4879 (0.3%). Intolerance due to previous hyperkalaemia: Candesartan 8/134 (13.6%) Placebo 1/100 (1.0%). Key: * the difference from the candesartan group is significant at P = 0.0005, ** the difference from the candesartan group is significant at P < 0.0001.
Reference number: 3183 Investigators H.O.P.E.; Effects of ramipril on coronary events in high-risk persons: results of the Heart Outcomes Prevention Evaluation Study 2001 104	Randomised Controlled Trial	Men & women at least 55 years, mean age 66 years, 26.7% women. Before random assignment all eligible participants entered a run-in phase, during which 2.5 mg of ramipril was administered daily for 7 days, followed by a matching placebo for 10	Ramipril, 10 mg OD.	Matching placebo	4.5 years	Primary: composite MI / stroke / death from CV causes. Secondary: hospitalisations for HF and unstable angina, worsening angina, heart failure rate (composite of heart failure requiring hospitalisations, fatal heart failure, heart failure signs and	MRC Canada, Hoechst-Marion Rousses, Astra-Zeneca, King Pharm., Natural Source Vit E Assn and Negma, Heart and Stroke Foundn	Mean follow-up 4.5 years: there were 482 (10.4%) patients with clinical MI and unexpected CV deaths in ramipril group compared with 604 (12.9%) in the placebo group (RRR 21%, 95%CI 11 to 30; P < 0.0003). Ramipril reduced heart failure rate from 11.5% to 9% (RR 0.77; 95%CI 0.68 to 0.87; P < 0.0001). Ramipril patients had a reduced RR of nonfatal MI of 23% (9 to 34); P < 0.0019, either Q-wave MI

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Circulation		to 14 days. History of CAD, stroke, PAD or diabetes plus one CV risk factor, 80.6% previous CV event, 53% previous MI, 43.4% PAD, 10.8% stroke or transient ischemic attack, 38.3% diabetes mellitus, hypertension history 46.5%, dyslipidemia 65.8%. Trial entry: 76.8% subjects taking antiplatelet agent, 28.9% lipid-lowering agent, 39.5% beta blocker, 47.0% calcium channel blocker, 15.1% diuretic. Exclusions: HF, LVEF < 0.40, taking ACE inhibitor,				symptoms and heart failure requiring open label ACEIs).	of Ontario.	(18% , -9 to 38) or non-Q-wave MI (24%, 8 to 37), ramipril 5.6% versus placebo 7.2%. Risk reductions in MI were documented in subjects taking or not taking beta blockers, lipid lowering and / or antiplatelet agents. Ramipril had no effect on hospitalizations for unstable angina or heart failure hospitalizations but reduced worsening and new angina, 27.2% versus 30.0%; RRR, 12%; (5 to 18) P < 0.0014, and coronary revascularization 12.5% versus 14.8%; RRR, 18%; (8 to 26) P < 0.0005.

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
		uncontrolled hypertension, overt nephropathy, MI / stoke within 4 weeks recruitment, hyper-sensitivity to ACE.						

Grading: 1- Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number: 1764 Kondo J;Sone T;Tsuboi H;Mukawa H;Morishima I;Uesugi M;Kono T;Kosaka T;Yoshida T;Numaguchi Y;Matsui H;Murohara T;Okumura K; Effects of low-	Randomised Controlled Trial	Inclusion criteria: Male and female (74% male in treatment group, 77% male in placebo group), history of coronary intervention. Patients with a history of coronary intervention and no significant coronary	Candesartan 4 mg daily, 203 patients.	Placebo, no tablet given, 203 patients.	Mean follow-up 24 months.	Primary: Composite of revascularisation, nonfatal MI, CV death. Secondary: Composite of worsening angina, congestive heart failure.	Not listed.	Composite of revascularization, nonfatal MI, CV death: 12 / 194 recruits candesartan group versus 25 / 203 recruits control group, P = 0.03. Composite of worsening angina, congestive heart failure 9 / 194 recruits candesartan group versus 16/203 recruits control group, P = 0.14. Note: Candesartan is not licensed in the UK for post MI patients.

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
dose angiotensin II receptor blocker candesartan on cardiovascular events in patients with coronary artery disease.[see comment] 2003 146 American Heart Journal		stenosis on follow up afterintervention (MI: treatment group 67%, placebo group 70%). Exclusion criteria: Congestive heart failure EF < 0.40, receiving dialysis,						

Table 251: What is the effectiveness of adding ACEi versus ARBs to improve outcome in….

Grading: 1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number: 3134 Dickstein K;Kjekshus J;OPTIMAAL Steering Committee of	Randomised Controlled Trial	Inclusion criteria: At least 50 years mean 67.5±9.8 years, men and women, MI (at least 2 of the following:	Losartan 12.5 mg once daily titrated to 50 mg daily as tolerated, 2551 patients.	Captopril 12.5 mg three times daily to 50 mg three times daily as tolerated, 2733 patients.	Follow-up: average 2.7 years (0.9).	Primary outcome: all cause mortality. Secondary outcomes: sudden cardiac death / resuscitated	Merck, Sharpe and Dohme Re-search Labs., USA.	Primary outcome: all cause mortality: losartan 499 (18.2%) versus captopril 447 (16.4%), relative risk (95% CI) 1.13 (0.99-1.28) P = 0.069. Secondary outcomes: sudden cardiac death /

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
the OPTIMAAL Study Group; Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Optimal Trial in Myocardial Infarction with Angiotensin II 2002 360 Lancet		history of chest pain > 20 min, ST elevation on electrocardiograph, or an increase in cardiac markers). MI patients with signs and symptoms of HF during the acute phase (defined as treatment with diuretic or intravenous vasodilator therapy for HF, pulmonary rates, third heart rate sound, persistent sinus tachycardia > 100 bpm, or radiographic evidence of pulmonary congestion). Patients with acute MI and EF < 35% or LV end-diastolic dimension > 65				cardiac arrest, MI (fatal / non fatal), MI/total mortality, CV death, stroke (fatal / non fatal), CABG, PTCA, revascular-isation, first all cause admission, first admission for HF, cardio-vascular admission, non-cardio-vascular admission, tolerability.		resuscitated cardiac arrest losartan 239 (8.7%) versus captopril 203 (7.4%), relative risk (95% CI) 1.19 (0.99-1.43) P = 0.072, MI (fatal / non fatal) losartan 384 (14.0%) versus captopril 379 (13.9%), relative risk (95% CI) 1.03 (0.89-1.18) P = 0.722, MI / total mortality losartan 746 (27.2%) versus captopril 689 (25.2%), relative risk (95% CI) 1.10 (0.99-1.22) P = 0.085, CV death losartan 420 (15.3%) versus captopril 363 (13.3%), relative risk (95% CI) 1.17 (1.01-1.34) P = 0.032, Stroke (fatal / non fatal) losartan 140 (5.1%) versus captopril 132 (4.8%), relative risk (95% CI) 1.07 (084-1.36) P = 0.587, CABG losartan 404 (14.7%) versus captopril 375 (13.7%), relative risk (95% CI) 1.09 (0.95-1.26) P = 0.228. PTCA losartan 466 (17.0%) versus

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
		mm and/or new Q-wave anterior-wall acute MI, or previous pathological Q-waves in the anterior wall. Patients enrolled within 10 days of onset of symptoms (median 3 days). Exclusion criteria: Suprine systolic arterial blood pressure < 100 mm Hg at randomization, current receipt ACE inhibitor or angiotensin II antagonist, unstable angina, haemodynamic ally significant dysrhymia, haemodynamic ally significant stenotic valvular						captopril 493 (18.0%), relative risk (95% CI) 0.94 (0.83-1.07) P = 0.358, revascularization losartan 845 (30.8%) versus captopril 827 (30.3%), relative risk (95% CI) 1.03 (0.93-1.13) P = 0.620, first all cause admission losartan 1806 (65.8%) versus captopril 1774 (64.9%), relative risk (95% CI) 1.03 (0.97-1.10) P = 0.362, first admission for HF losartan 306 (11.2%) versus captopril 265 (9.7%), relative risk (95% CI) 1.16 (0.98-1.37) P = 0.0.72, cardiovascular admission losartan 1480 (53.9%) versus captopril 1421 (52.0%), relative risk (95% CI) 1.06 (0.99-1.14) P = 0.108, non-cardiovascular admission losartan 855 (32.3%) versus captopril 905 (33.1%), relative risk (95% CI) 0.98 (0.90-1.08) P = 0.719. Tolerability: Losartan was better tolerated than captopril. Discontinuation due to adverse experience

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
		heart disease and planned revascularization.						losartan 202 (7.0%) versus captopril 387 (14.0%), relative risk (95% CI) 0.94 (0.42-0.59) P < 0.0001. Discontinuation reasons: Hypotension: Losartan 47/2744 (1.7%) Captopril 61/2733 (2.2%), Cough: Losartan 28/2744 (0.4%)*** Captopril 113/2733 (0.8%), Rash: Losartan 3/2744(1.0%)** Captopril 18/2733(0.7%), Angioedema: Losartan 4/2744(0.1%)* Captopril 142733(0.5%), Taste disturbance: Losartan 1/2744(0.0%)*** Captopril 17/2733(0.5%) (* the difference from the captopril group is significant at P = 0.0.19, ** the difference from the captopril group is significant at P = 0.008, *** the difference from the captopril group is significant at P < 0.0001). Note: Losartan is not licensed in the UK for post MI patients.

Table 252: Is there an optimum time for ACEI to be administered in the non-acute phase?

Grading: 1+ Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number: 3379 Pfeffer MA;Greaves SC;Arnold JM;Glynn RJ;LaMotte FS;Lee RT;Menapace FJ;Rapaport E;Ridker PM;Rouleau JL;Solomon SD;Hennekens CH; Early versus delayed angiotensin-converting enzyme inhibition therapy in acute myocardial infarction. The healing and early afterload reducing	Randomised Controlled Trial	Men and women (22%), > 21 years with MI within 24 hours post MI. Mean age 60.6 years. Exclusion criteria: Need of ACEI for CHF, serum creatinine ≥ 2.5 mg/dl, presence of major complication of infarction that was not stabilized before infarction (e.g. cardiac shock, persistent ischemia, or unstable rhythm), systolic blood pressure > 100 mm HG, or failure to complete all	Early (1 day) ramipril, 3 groups: 117 recruits early placebo/late full dose ramipril group, 116 recruits early low 0.625 mg ramipril/late low 0.625 mg ramipril, 119 recruits early full dose ramipril/late full dose ramipril. Ramipril highest achievable dose in early phase, first 14 days up to 10 mg (full dose). Initial dose 1.25 mg ramipril 2.5 mg at 12	Delayed, late (14 day ramipril).	90 days.	LV Ejection fraction (LVEF). Akinesis and dyskinesis (% LV that was non-contractile).	Hoechst Marion Roussel, Upjohn.	First 14 days: LVEF increased in all 3 groups, but greatest in the full dose ramipril group. Improvements were 2.4±8.8 units, 3.9±8.2 units and 4.8±10.0 units for placebo, low dose ramipril and high dose ramipril, respectively, P = 0.47 for trend. Regression model of early change in EF demonstrated by ramipril demonstrated a significant improvement with the use of ramipril (P = 0.011). Akinesis/dyskinesis decreased in all groups. Late phase: Continued reduction in the proportion of the LV that was assessed as either akinetic or dyskinetic in all groups. However, only the group who received ramipril for the first time during the late period (placebo to full dose) showed a statistically

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
therapy trial 1997 95 Circulation		pre-randomization evaluations within 24 hours from the onset of chest pain.	hours, subsequently titrated up to 10 mg ramipril in 24 hour intervals.					significant improvement in wall motion (P = 0.02).

Table 253: What is the effectiveness of adding aspirin versus placebo to improve outcome in patients after MI?

Grading: 1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number: 1784 Baigent C;Sudlow C;Collins R;Peto R; Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients	Systematic Review	Previous MI.	Aspirin, dipyridamole, sulfinpyrazone. 9984 patients	Placebo: 10022 patients.			MRC UK, Stroke Assn., BHF, Imperial Cancer Res. Fund, EU Biomed Program, Well-come, Chest Heart & Stroke Scotl.	For post MI patients treated for a mean duration of 27 months, treatment resulted in 36 (SE 5) fewer serious vascular events per 1000 (non fatal MI: 18 (SE 3) fewer per 1000, P < 0.001; vascular death: 14 (SE 4) fewer per 1000 P < 0.0006; non-fatal stroke: 5 (SE 1) fewer per 1000, P < 0.002). The estimated risk of extra-cranial bleeds due to antiplatelet therapy was calculated as approximately 1 patient per 1000 per year.

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
2002 324British Medical Journal								
Reference number: 3740 Chan FK; Ching JY; Wong VW; Leung VK; Kung NN; Hui AJ; Wu JC; Leung WK; Lee VW; Lee KK; Lau JY; To KF; Chan HL; Sung JJ Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding 2005 352 New england Journal of Medicine	Randomised Controlled Trial	Inclusion criteria: Previous upper GI bleeding, treated and endoscopy performed 8 weeks post eradication therapy. Endoscopically confirmed ulcer healing, negative test for H. pylori Exclusion criteria: Use of NSAIDs, Cox-2 inhibitors, anticoagulants, other antiplatelets, or corticosteroids, history gastric surgery, aspirin or clopidogrel allergy, presence of erosive	Clopidogrel 75 mg daily plus esomeprazole placebo twice daily.	Aspirin 80 mg daily plus esomeprazole 20mg twice daily.	12 months.	Primary: recurrent ulcer bleeding. Secondary: lower GI bleeding.	Division Gastro-enterology and Haeptology at the Chinese University of Hong Kong.	Recurrent bleeding: 13/161 clopidogrel, 1/159 aspirin plus esomeprazole. Cumulative incidence of recurrent bleeding: clopidogrel 8.6% (95%CI 4.1 to 13.1%) versus aspirin plus esomeprazole 0.7% (95%CI 0 to 2%), P = 0.001. Cumulative incidence of lower GI bleeding:clopidogrel 4.6% (95%CI 1.7 to 7.9%) versus aspirin plus esomeprazole 4.6% (95%CI 1.3 to

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
		esophagotis, gastric-outlet obstruction, renal failure requiring dialysis, terminal illness, or cancer.						

Grading: 1+ Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number: 1161 A randomized, controlled trial of aspirin in persons recovered from myocardial infarction 1980 243 JAMA	Randomised Controlled Trial	Inclusion criteria: post MI, men and women (12%), aged between 30-69 years, mean age 54 years, > 85% patients recruited 6 month post MI, interval between infarct and entry to trial: mean 25 months (range 2 -60 months). Exclusion criteria:	Asprin: 1000 mg once daily. 2267 patients.	Placebo: 2257 patients.	3 years months, mean follow-up 38 months.	Primary: Total mortality. Secondary: CHD mortality (MI + sudden death), coronary incidence (CHD mortality or non-fatal MI), fatal or non-fatal stroke.	NHLB Institute	Total mortality: treatment 10.8% versus 9.7% placebo, not significant. CHD mortality: treatment 8.7% versus 8.0% placebo, not significant. Sudden death: treatment 2.7% versus 2.0% placebo, not significant. Coronary incidence: treatment 14.1% versus 14.8% placebo, not significant. Symptoms suggestive of peptic ulcer, gastritis, or erosion of gastric mucosa: treatment 23.7% versus 14.9% placebo, Z value 7.52, significant.

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
		Anticoagulation, aspirin dipyridamole or sulfinpyrazone therapy, severe ulcer disease, sensitivity to aspirin, previous						
Reference number: 1151 Aspirin in coronary heart disease. The Coronary Drug Project Research Group 1980 62 Circulation	Randomised Controlled Trial	Inclusion criteria: MI patients who survived 4-6 weeks post infarct, male, age 45-70 years. Exclusion criteria: none listed.	Aspirin, 324 mg, three times daily, 758 patients.	Placebo: 771 patients.	Mean follow-up: 22 months.	Primary: Mortality; Secondary: Coronary death, sudden coronary death, nonfatal MI	Not listed	Mortality: treatment 5.8% versus placebo 8.3%, Z value - 1.9. Coronary death: treatment 4.6% versus placebo 6.4%, Z value - 1.49. Sudden coronary death: treatment 2.6% versus placebo 3.2%, Z value 0.70. Nonfatal MI: treatment 3.6% versus placebo 2.2%, Z value 0.48. Upper GI irritation: treatment 12.5% versus placebo 6.3%, Z value 4.08.
Reference number: 1163 Breddin K;Loew D;Lechner K;Uberla K;Walter E; Secondary	Randomised Controlled Trial	Inclusion criteria: acute MI patients who survived 4-6 weeks, age 45 to 70 years, male and female (21.5%). Exclusion	Aspirin, 1500mg, 317 patients.	Placebo: 309 patients.	Mean follow-up 24 months.	Primary: Coronary death (fatal MI + sudden death), coronary events (non fatal MI, fatal MI + sudden death). Secondary:	Not listed.	Coronary death (fatal MI + sudden death): aspirin 13/317 versus placebo 22/309, P < 0.05. Coronary events (non fatal MI, fatal MI + sudden death): aspirin 24/317 versus placebo 37/309, P < 0.05.

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
prevention of myocardial infarction. Comparison of acetylsalicylic acid, phenprocoumon and placebo. A multicenter two-year prospective study 1979 41 Thrombosis & Haemostasis		criteria: contraindications to aspirin.				Stomach complaints / ulcer.		Stomach complaints / ulcer: aspirin 20/317 versus placebo 12/309
Elwood PC CABMSPW; A randomized controlled trial of acetyl salicylic acid in the secondary prevention of mortality from myocardial infarction 1974 1 British Medical Journal	Randomised Controlled Trial	Inclusion criteria: post MI, men under 65 years, mean age 56 years, interval between infarct and entry to trial: mean 70 days (range ½ -6 months). Exclusion criteria: Anticoagulation therapy,evidence of peptic ulcer.	Aspirin 300mg once daily: 615 patients.	Placebo: 624 patients.	1 year.	Mortality.	Not listed.	Mortality: treatment 8.3% versus 10.9% placebo, not significant.
Reference	Randomised	Inclusion	Aspirin:	Placebo: 878 patients.	1 year.	Mortality,	Not	Mortality: treatment

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
number: 1162 Elwood PC;Sweetnam PM; Aspirin and secondary mortality after myocardial infarction 1979 2 Lancet	Controlled Trial	criteria: post MI, men and women (15%), mean age 56 years, interval between infarct and entry to trial: < 6 weeks 50%, 6-13 weeks 26%, 14 weeks > 24%, mean interval 10 months. Exclusion criteria: Anticoagulation therapy, evidence of peptic ulcer, sensitivity to aspirin.	300mg three times daily. 847 patients.			Cardiovascular mortality, non-fatal MI, total mortality plus non-fatal vascular events.	listed.	14.8% versus 12.3% placebo, not significant, cardiovascular mortality: treatment 11.6% versus 13.9% placebo, not significant, non-fatal MI treatment 7.1% versus 10.9% placebo, P < 0.05, total mortality plus vascular events treatment 27.4% versus 35.8% placebo, P < 0.05, withdrawal due to bleeding: treatment 8/847 patients versus 4/878 placebo Authors state that the study was underpowered with respect to recruitment to detect a 25% reduction as significant at P < 0.05.
Reference number: 1052 Verheugt FW;van d;Funke-Kupper AJ;Sterkman LG;Galema TW;Roos JP;	Randomised Controlled Trial	Inclusion criteria: First anterior wall acute MI < 12 h (ST-segment elevation > 2 mm in precordial leads in absence of precordial Q wave), Men and	Aspirin, 100 mg once daily, 50 patients.	Placebo: 50 patients.	3 months.	Primary: Infarct size. Secondary: Death, reinfarction, unstable angina, revascularisation.	Not listed.	Infarct size assessed as 72 hour cumulative lactate dehydrogenase release: treatment 1431±782 U/l versus placebo 1592±1082 U/l (P = 0.35). Mortality: treatment 10/50 versus placebo 12/50, not significant. Reinfarction: treatment 2/50 versus placebo 9/50

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Effects of early intervention with low-dose aspirin (100 mg) on infarct size, reinfarction and mortality in anterior wall acute myocardial infarction 1990 66 American Journal of Cardiology		women (26%), age range 27 to 91 years, mean, aspirin: 61 years, placebo: 64 years. Exclusion criteria: contraindication to aspirin.						(P < 0.03). Unstable angina: treatment 14/50 versus placebo 11/50, not significant. CABG/PTCA: treatment 2/50 versus placebo 1/50, not significant.

Table 254: What is the effectiveness of adding aspirin versus clopidogrel to improve outcome in patients after MI?

Grading: 1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number: 3730 Gent M; A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of	Randomised Controlled Trial	Inclusion criteria: MI onset ≤ 35 days before randomization, two of a) characteristic ischaemic pain for 20 min,	Clopidogrel 75 mg once daily: 3143 patients, MI subgroup, 3233 patients stroke subgroup,	Aspirin 325 mg once daily: 3159 patients MI subgroup, 3198 patients stroke subgroup, 3229 patients PAD subgroup.	Mean follow-up 1.91 years.	Primary: Incidence of first occurrence of ischemic stroke, MI or vascular death.	Sanofi, Bristol-Myers Squibb.	RR reduction of primary outcome measure for post MI patient subgroup: clopidogrel versus aspirin = -3.7% (-22 to 12.0), P = 0.66. Clopidogrel 291/3159 versus aspirin 283/3159. RR reduction of primary outcome

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
ischaemic events (CAPRIE) 1996 348 Lancet		b) elevation of CK, CK-MB, LDL or AST to 2x upper limit of laboratory normal with no other explanation, c) development of new ≥ 40 Q waves in.	3233 patients PAD subgroup.					measure for stoke patient subgroup: clopidogrel versus aspirin = 7.3% (-5.7 to 18.7), P = 0.26. Clopidogrel 433/3233 versus aspirin 461/3198. RR reduction of primary outcome measure for PAD patient subgroup: clopidogrel versus aspirin = 23.8% (8.9 to 36.2), P = 0.0028. Clopidogrel 433/3233 versus aspirin 461/3198. RR reduction of primary outcome measure for ALL patient subgroup: clopidogrel versus aspirin = 8.7% (0.3 to 16.5), P = 0.043. Clopidogrel 939/9599 versus aspirin 1021/9586.

Grading: 1+ Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number 2278: Sabatine MS;Cannon CP;Gibson CM;L¾pez-	Randomised Controlled Trial	Inclusion criteria: enrolled within 12 h after onset ST-elevation MI, aged 18 to 75	Clopidogrel 300 mg loading dose, followed by 75 mg once daily. Aspirin.	Clopidogrel placebo. Aspirin. Fibrinolytic agent: 1739 patients.	30 days.	Primary: Composite occluded infarct related artery on angiography, death or	Sanofi-Aventis, Bristol-Myers Squibb.	Before angiography: Rates of the primary efficacy endpoint 21.7% in placebo group and 15.0% in clopidogrel group: 36% odds

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Send¾n JL;Montalescot G;Theroux P;Claeys MJ;Cools F;Hill KA;Skene AM;McCabe CH;Braunwald E; Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation 2005 352 New England Journal of Medicine		years, mean 57 years, men and women (20%), scheduled to receive a fibrinolytic agent, an anticoagulant (if a fibrin-specific lytic agent was prescribed), aspirin and undergo angiography 48 to 192 hours after the start of study medication Exclusion criteria: treatment with clopidogrel within 7 days before enrolment or planned treatment with Clopidogrel or a glycoprotein 11b/11a inhibitor before angiography, contraindication	Fibrinolytic agent: 1752 patients.			recurrent MI before angiography. Composite death from CV causes, recurrent MI, recurrent ischemia requiring revascularisation at 30 days.		reduction with clopidogrel therapy (95% CI 24 to 47%, P < 0.001). At 30 days: Primary endpoint: clopidogrel therapy odds reduction = 20%, P < 0.03. There was no significant difference in major or minor bleeding between the two treatment

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
		s to fibrinolytic therapy, planned angiography within 48 h in the absence of a new clinical indication, cardiac shock, prior CABG, weight 67 kg or less and receipt of more than 4000-U bolus of unfractionated heparin, weight more than 67 kg and receipt of more than 5000-U bolus of unfractionated heparin, or receipt of more than standard dose of low-molecular-weight heparin.						

Table 255: What is the effectiveness of adding aspirin versus aspirin and clopidogrel to improve outcome in…

Grading: 1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number: 5183 Bhatt DL;Fox KAA;Hacke W;Berger PB;Black HR;Boden WE;Cacoub P;Cohen EA;Creager MA;Easton JD;Flather MD;Haffner SM;Hamm CW;Hankey GJ;Johnston SC;Mak KH;Mas JL;Montalescot G;Pearson TA;Steg PG;Steinhubl SR;Weber MA;Brennan DM;Fabry-Ribaudo L;Booth J;Topol E	Randomised Controlled Trial	Inclusion criteria: Aged 45 years or older and one of the following conditions: Multiple atherothrombotic risk factors such as diabetes, diabetic nephropathy, ankle-brachial < 0.9, asymptomatic carotid stenosis ≥ 70% of luminal diameter, ≥ 1 carotid.	Clopidogrel 75 mg once daily plus aspirin 75 mg once daily: 7802 patients.	Placebo once daily plus aspirin 75 mg once daily: 7801 patients.	Median follow-up 28 months.	Primary: Composite of myocardial infarction, stroke (of any cause), or death from cardiovascular causes (including haemorrhage). Secondary: Composite of myocardial infarction, stroke (of any cause), death from cardiovascular causes, hospitalisation.	Sanofi-Aventis, Bristol-Myers Squibb.	Primary: First occurrence of composite of myocardial infarction, stroke (from any cause) or death from cardiovascular causes: 534/7802 (6.8%) clopidogrel plus aspirin versus 573/7801 (7.3%) placebo plus aspirin, RR of 0.93 (95% CI 0.83 to 1.05, P = 0.22). Secondary: Composite of myocardial infarction, stroke, death from cardiovascular causes, hospitalisation for unstable angina, transient ischaemic attack, or revascularisation: 1301/7802 (16.7%) clopidogrel plus aspirin versus 1395/7801 (17.9%) placebo plus aspirin, RR of 0.92 (95% CI 0.82 to 0.98, P = 0.04). Death from any cause: 371/7802 (4.8%) clopidogrel plus aspirin versus 374/7801 (4.8%) placebo plus

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Clopidogrel and aspirin versus aspirin alone for the prevention of Atherothrombotic events 2006 354 New England Journal of Medicine								aspirin, RR of 0.99 (95% CI 0.86 to 1.14, P = 0.90). Death from cardiovascular causes: 238/7802 (3.1%) clopidogrel plus aspirin versus 229/7801 (2.9%) placebo plus aspirin, RR of 1.04 (95% CI 0.87 to 1.25, P = 0.68). Nonfatal MI: 147/7802 (1.9%) clopidogrel plus aspirin versus 1.59/7801 (2.0%) placebo plus aspirin, RR of 0.92 (95% CI 0.74 to 1.16, P = 0.48). Nonfatal ischaemic stroke: 132/7802 (1.7%) clopidogrel plus aspirin versus 160/7801 (2.1%) placebo plus aspirin, RR of 0.82 (95% CI 0.66 to 1.04, P = 0.10). Nonfatal stroke: 149/7802 (1.9%) clopidogrel plus aspirin versus 185/7801 (2.4%) placebo plus aspirin, RR of 0.80 (95% CI 0.65 to 0.997, P = 0.05). Hospitalisation for unstable angina, transient ischaemic attack or revascular-isation: 886/7802 (11.1%)

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								clopidogrel plus aspirin versus 957/7801 (12.3%) placebo plus aspirin, RR of 0.90 (95% CI 0.82 to 0.98, P = 0.02). Subgroup analysis: Documented CV disease 'symptomatic': Enrolled with multiple vascular risk factors 'asymptomatic' (some of whom had a reported history of cardiovascular events: 10.4% prior MI, 5.8% prior stroke, 5.2% prior TIA, 7.7% had undergone PCI and 9.8% prior CABG although did not meet the criteria for established cardiovascular disease as defined in the study). Primary endpoint: Among 3284 asymptomatic patients, there was a 20% relative increase in primary events with clopidogrel plus aspirin compared with placebo plus aspirin (6.6% versus 5.5% respectively, P = 0.20). Among 12153 symptomatic patients there was a marginal

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								significant reduction in the primary endpoint with clopidogrel plus aspirin compared with placebo plus aspirin (6.9% versus 7.9% respectively, P = 0.046). Death from all causes and cardiovascular cause: Among 3284 asymptomatic patients, there was a significant increase in death from any cause with clopidogrel plus aspirin compared with placebo plus aspirin (5.4% versus 3.8% respectively, P = 0.04), as well as a significant increase in the rate of death from cardiovascular disease with clopidogrel plus aspirin compared with placebo plus aspirin (3.9% versus 2.2% respectively, P = 0.01). In contrast, the addition of clopidogrel had no significant effect on death from cardiovascular causes in the symptomatic subgroup. Safety end points: Severe bleeding: 130/7802

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								(1.7%) clopidogrel plus aspirin versus 104/7801 (1.3%) placebo plus aspirin, RR of 1.25 (95% CI 0.97 to 1.61, P = 0.09). Fatal bleeding: 26/7802 (0.3%) clopidogrel plus aspirin versus 17/7801 (0.2%) placebo plus aspirin, RR of 1.53 (95% CI 0.83 to 2.82, P = 0.17). Primary intracranial haemorrhage: 26/7802 (0.3%) clopidogrel plus aspirin versus 27/7801 (0.3%) placebo plus aspirin, RR of 0.96 (95% CI 0.56 to 1.65, P = 0.89). Moderate bleeding: 164/7802 (2.1%) clopidogrel plus aspirin versus 101/7801 (1.3%) placebo plus aspirin, RR of 1.62 (95% CI 1.27 to 2.1, P < 0.001). Subgroup analysis Severe bleeding: Asymptomatic patients: Clopidogrel plus aspirin: 2%, Placebo plus aspirin 1.2% (P = 0.07). Symptomatic patients: Clopidogrel plus aspirin: 1.6%, Placebo plus aspirin 1.4% (P = 0.39). Moderate

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								bleeding: Asymptomatic patients: Clopidogrel plus aspirin: 2.2%, Placebo plus aspirin 1.4% (P = 0.08). Symptomatic patients: Clopidogrel plus aspirin: 2.1% Placebo plus aspirin 1.3% (P < 0.001).
Reference number: 1822 Yusuf S;Zhao F;Mehta SR;Chrolavicius S;Tognoni G;Fox KK; Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment 2001 345 New England Journal of Medicine	Randomised Controlled Trial	Inclusion criteria: Hospitalised within 24 h of onset of symptoms of acute coronary syndromes without ST elevation. Exclusion criteria: contraindications to antiplatelet / anticoagulant therapy, high risk for bleeding or heart failure, taking oral coagulants, revascularization in previous 3 months,	Clopidogrel 300 mg immediately followed by 75 mg daily plus aspirin. 6259 patients.	Placebo plus aspirin. 6303 patients.	3 to 12 months, mean duration of treatment 9 months, no patient < 3 months.	Primary: Death from CV causes non fatal MI or stroke. Death from CV causes, nonfatal MI, stroke or refractory ischemia. Reinfarction. Secondary: Revascularization .	Not listed.	Death from CV causes, non fatal MI or stroke: clopidogrel 582/6259 (9.3%) versus placebo 719/6303 (11.4%), RR 0.80 (95%CI 0.72 to 0.90, P < 0.001). Death from CV causes, nonfatal MI, stroke or refractory ischemia: clopidogrel 1035/6259 (16.5%) versus placebo 1187/6303 (18.8%), RR 0.86 (95%CI 0.79 to 0.94, P < 0.001). Reinfarction: clopidogrel 85/6259 (1.4%) versus placebo 126/6303 (2.0%), RR 0.69 (95%CI 0.52 to 0.90, P < 0.007). Slightly fewer patients in the clopidogrel group underwent revascularization: 36% versus placebo 36.5%.

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
		received intravenous glycoprotein IIb / IIIa receptor inhibitors in previous 3						Major bleeding was significantly higher in clopidogrel group (3.7%) versus placebo (2.7%), RR 1.38 95% CI 1.13 to 1.67, P = 0.001. but there were not significantly more patients with episodes of life-threatening bleeding or hemorrhagic strokes (Clopidogrel 2.2% versus placebo 1.8%, RR 1.21, 95%CI 0.95 to 1.56).

Grading: 1+ Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number: 2279 Sabatine MS;Cannon CP;Gibson CM;L¾pez-Send¾n JL;Montalescot G;Theroux P;Claeys MJ;Cools F;Hill KA;Skene	Randomised Controlled Trial	Inclusion criteria: enrolled within 12 h after onset ST-elevation MI, aged 18 to 75 years, mean 57 years, men and women (20%), scheduled to receive a fibrinolytic agent, an anticoagulant (if	Clopidogrel 300 mg loading dose, followed by 75 mg once daily. Aspirin. Fibrinolytic agent: 1752 patients.	Clopidogrel placebo. Aspirin. Fibrinolytic agent: 1739 patients.	30 days.	Primary: Composite occluded infarct related artery on angiography, death or recurrent MI before angiography. Composite death from CV causes, recurrent MI, recurrent ischemia	Sanofi-Aventis, Bristol-Myers Squibb.	Before angiography: Rates of the primary efficacy endpoint 21.7% in placebo group and 15.0% in clopidogrel group: 36% odds reduction with clopidogrel therapy (95% CI 24 to 47%, P < 0.001). At 30 days: Primary endpoint: clopidogrel therapy odds reduction = 20%, P < 0.03. There was no significant difference

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
AM;McCabe CH;Braunwald E; Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation 2005 352 New England Journal of Medicine		a fibrin-specific lytic agent was prescribed), aspirin and undergo angiography 48 to 192 hours after the start of study medication. Exclusion criteria: treatment with clopidogrel within 7 days before enrolment or planned treatment with Clopidogrel or a glycoprotein 11b/11a inhibitor before angiography, contraindications to fibrinolytic therapy, planned angiography within 48 h in the absence of a new clinical				requiring revascularisation at 30 days.		in major or minor bleeding between the two treatment

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
		indication, cardiac shock, prior CABG, weight 67 kg or less and receipt of more than 4000-U bolus of unfractionated heparin, weight more than 67 kg and receipt of more than 5000-U bolus of unfractionated heparin, or receipt of more than standard dose of low-molecular-weight heparin.						

Table 256: What is the effectiveness of adding a beta blocker versus placebo to improve outcome in...

Grading: 1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number: 3841 Chen ZM;Jiang	Randomised Controlled Trial	Inclusion criteria: Post MI recruited within 24 h of suspected acute	Immediately: 162 mg aspirin plus 75 mg clopidogrel.	Immediately: 162 mg aspirin plus placebo. Subsequently: 162 mg aspirin plus placebo once	Up to 4 weeks.	Primary: Composite of death, reinfarction, or stroke. Death	Sanofi-Aventis, Bristol-Myers Squibb,	Primary: Composite of death, reinfarction, or stroke: 2121/22961 (9.2%) treatment versus 2310/22891 (10.1%)

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
LX;Chen YP;Xie JX;Pan HC;Peto R;Collins R; Addition of clopidogrel to aspirin in 45852 patients with acute myocardial infarction:randomised placebo-controlled trial 2005 366		MI onset (ST elevation (87%), left bundle block (6%), or ST depression (7%)). Mean age ± SD = 61 ± 11 years, male and female (28%). Patients with hypertension: 8%.	Subsequently : 162 mg aspirin plus 75 mg clopidogrel once daily for up to 4 weeks (or, if earlier, until hospital discharge or death): 22 961 patients.	daily for up to 4 weeks (or, if earlier, until hospital discharge or death): 22 891 patients.		from any cause. Secondary: Re-infarction, stroke, cardiogenic shock, heart failure, presumed cardiac rupture, ventricular fibrillation, other cardiac arrest, pulmonary embolism.	Astra-Zeneca, MRC UK, BHF, Cancer Research UK.	placebo, OR of 0.91 (95% CI 0.86 to 0.97, P = 0.002). About 2 weeks of clopidogrel therapy associated with 9 (SE 3) fewer patients with death, reinfarction or stroke in hospital per 1000 allocated treatments. Death from any cause: 1726/22961 (7.5%) treatment versus 1845/22891 (8.1%) placebo, OR of 0.93 (95% CI 0.87 to 0.99, P = 0.03). Arrhythmia: 432/22961 (1.9%) treatment versus 454/22891 (2.0%) placebo. Asystole: 642/22961 (2.8%) treatment versus 697/22891 (2.0%) placebo. Cardiac rupture: 188/22961 (0.8%) treatment versus 210/22891 (0.9%) placebo. Cardiogenic shock: 503/22961 (2.2%) treatment versus 562/22891 (2.5%) placebo. Reinfarction: 133/22961 (0.5%) treatment versus

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								101/22891 (0.4%) placebo. Stroke: 72/22961 (0.3%) treatment versus 87/22891 (0.4%) placebo. Other: 92/22961 (0.4%) treatment versus 103/22891 (0.4%) placebo. Secondary: Reinfarction: Died, any cause: 209/22961 (0.9%) treatment versus 223/22891 (1.0%) placebo, OR of 0.93 (95% CI 0.77 to 1.13, P = 0.46). Survived: 270/22961 (1.2%) treatment versus 330/22891 (1.4%) placebo, OR of 0.81 (95% CI 0.69 to 0.95, P = 0.01). All: 479/22961 (2.1%) treatment versus 553/22891 (2.4%) placebo, OR of 0.86 (95% CI 0.76 to 0.97, P = 0.02). Allocation to clopidogrel produced 14% (95% CI 3-4) proportional reduction in the risk of any reinfarction. Stroke: Ischaemic (or unknown): 164/22961 (0.7%) treatment versus

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								194/22891 (0.8%) placebo, OR of 0.84 (95% CI 0.68 to 1.03, P = 0.10). Haemorrhagic: 53/22961 (0.2%) treatment versus 56/22891 (0.2%) placebo, OR of 0.98 (95% CI 0.67 to 1.42, P = 0.90). Died, any cause: 90/22961 (0.4%) treatment versus 108/22891 (0.5%) placebo, OR of 0.83 (95% CI 0.63 to 1.10, P = 0.19). Survived: 127/22961 (0.6%) treatment versus 142/22891 (0.6%) placebo, OR of 0.89 (95% CI 0.70 to 1.13, P = 0.33). All: 217/22961 (0.9%) treatment versus 250/22891 (1.1%) placebo, OR of 0.86 (95% CI 0.72 to 1.03, P = 0.11). Cardiogenic shock: 983/22961 (4.3%) treatment versus 1043/22891 (4.6%) placebo, OR of 0.94 (95% CI 0.86 to 1.02, P = 0.15). Heart failure: 3033/22961 (13.2%) treatment versus 3093/22891 (13.5%) placebo, OR of 0.97 (95% CI 0.92 to 1.03, P = 0.34).

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								Presumed cardiac rupture: 209/22961 (0.9%) treatment versus 224/22891 (1.0%) placebo, OR of 0.93 (95% CI 0.77 to 1.12, P = 0.45). Ventricular fibrillation: 624/22961 (2.7%) treatment versus 655/22891 (2.9%) placebo, OR of 0.95 (95% CI 0.85 to 1.06, P = 0.35). Other cardiac arrest: 867/22961 (3.8%) treatment versus 913/22891 (8.1%) placebo, OR of 0.94 (95% CI 0.86 to 1.04, P = 0.24). Pulmonary embolism: 32/22961 (0.1%) treatment versus 33/22891 (0.1%) placebo, OR of 0.97 (95% CI 0.59 to 0.91.57, P = 0.03). Safety: Bleeding: Fatal: 73/22961 (0.32%) treatment versus 74/22891 (0.32%) placebo, excess per 1000 (SE) = -0.1 (0.5), P = 0.92. Cerebral: 39/22961 (0.17%) treatment versus 41/22891 (0.18%) placebo. Non-cerebral: 36/22961 (0.16%)

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								treatment versus 37/22891 (0.16%) placebo. Non-fatal: 61/22961 (0.27%) treatment versus 51/22891 (0.22%) placebo, excess per 1000 (SE) = 0.4 (0.5), P = 0.35. Cerebral: 16/22961 (0.07%) treatment versus 15/22891 (0.07%) placebo. Transfused: 46/22961 (0.20%) treatment versus 36/22891 (0.16%) placebo. Any: 134/22961 (0.58%) treatment versus 125/22891 (0.55%) placebo, excess per 1000 (SE) = 0.4 (0.7), P = 0.59. Additional drug therapy during hospital stay: Non-study antiplatelet therapy: 10% patients. Anticoagulation therapy (chiefly heparin): 75%.
Reference number: 368 Dargie HJ; Effect of carvedilol on	Randomised Controlled Trial	Inclusion criteria: Confirmed MI occurring within the previous 21 days, aged > 18	Carvediol Up-titration phase to 25 mg. Initial dose 6.25 mg, if	Placebo: 984 patients.	Mean follow-up: 1.3 years. Minimum time 3 months.	Primary: All cause mortality. Composite of all cause mortality or cardiovascular-cause hospital	None listed.	Primary: All cause mortality: Treatment 116/975 (12%) versus placebo 151/984 (15%), hazard ratio 0.77 (95%CI 0.60 to 0.98), P = 0.031.

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. 2001 357 Lancet		years, mean age 63 years (25-90), male and female (27%), LV ejection fraction ≤ 40% (mean directly by 2D electrocardiography radionuclide or contrast ventriculography) or indirectly by wall motion score index ≤ 1.3, concurrent treatment with ACE inhibitor for > 48 h with the dose being stable for > 24 h unless proven intolerance of ACE inhibitors. Exclusion criteria: Continued requirement for IV inotropic therapy or	tolerated continued on a twice daily basis. If not tolerated, same dose was re-administered 12 h later. If again not tolerated two further attempts to introduce drug were made, but at the lower dose of 3.123 mg. If that dose was not tolerated patients were followed up off study medication. Following successful initial dosing, patient returned to			admission. Secondary: Sudden death. Hospitalization for heart failure.		Composite of all cause mortality or cardiovascular-cause hospital admission: Treatment 340/975 (35%) versus placebo 367/984 (37%), hazard ratio 0.92 (95%CI 0.80 to 1.07), P = 0.296. Secondary: Sudden death: Treatment 51/975 (5%) versus placebo 69/984 (7%), hazard ratio 0.74 (95%CI 0.51 to 1.06), P = 0.098. Hospitalization for heart failure: Treatment 118/975 (12%) versus placebo 138/984 (14%), hazard ratio 0.86 (95%CI 0.67 to 1.09), P = 0.215. Other: Cardiovascular-cause mortality: Treatment 104/975 (11%) versus placebo 139/984 (14%), hazard ratio 0.75 (95%CI 0.58 to 0.96), P = 0.024. Death due to heart failure: Treatment 18/975 (2%) versus placebo 30/984 (3%), hazard ratio 0.60 (95%CI 0.33 to 1.07), P = 0.083. Non-fatal MI: Treatment 34/975 (3%) versus placebo 57/984

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
		uncontrolled heart failure, ongoing or expected need for b-blockage, complicating clinical conditions including unstable angina, uncorrected significant valve disease, hypotension < 90 mmHg, bradycardia < 60 bpm., uncontrolled hypertension, unstable IDDM, significant pulmonary, hepatic or renal impairment, ongoing therapy with inhaled beta-2 agonists or steroids, rate-limiting calcium channel blockers, antiarrythmics	outpatients at 3-10 day intervals for up-titartion to target of 25 mg or maximum dose tolerated. Up-titration phase lasted approximately 4 to 6 weeks and dose of ACE inhibitor was not altered. 975 patients.					(6%), hazard ratio 0.59 (95%CI 0.39 to 0.90), P = 0.014. All cause mortality or non-fatal MI: Treatment 139/975 (14%) versus placebo 192/984 (20%). hazard ratio 0.71 (95%CI 0.57 to 0.89), P = 0.002.

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
		(except amiodarone), immunosuppressive agents, pregnancy, continuing lactation or planned pregnancy, inability or unwillingness to give informed consent.						
Reference number: 3755 Freemantle N;Cleland J;Young P;Mason J;Harrison J; Beta-blockade after myocardial infarction: systematic review and meta regression analysis 1999 318B MJ	Systematic Review	Post MI patients. Acute phase, long term therapy.	β blockers	placebo.	Short term trials: up to 6 weeks after onset of pain (51 RCTs). Long term trials: 6 weeks to 48 months (31 RCTs).	Mortality. Reinfarction.	Not listed.	Short term trials: Overall 3062/29260 died (10.1%). Of the 51 RCTs identified, only 45 observed deaths in either in treatment or placebo groups. The quality of group of trials may be influenced by the small numbers of patients recruited in some of the trials and also the small numbers of deaths. Pooled random effects odds ratio: 0.96 (95%CI 0.85 to 1.08), a 4% reduction in odds of death. Equates to an annual reduction of 0.4 deaths in 100 patients for treatment up to six

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								weeks, not significant (-0.2 to 10). 50 patients would require treatment to avoid one death (100 to ∞). Long term trials: Overall 2415/24975 died (9.7%) in 31 trials. Pooled random effects odds ratio: 0.77 (0.69 to 0.85), a 23% reduction in odds of death. Equates to an annual reduction of 1.2 deaths in 100 patients (0.6 to 1.7), 84 patients would require treatment to avoid one death. For reinfarction (22 trials): annual reduction in reinfarction of 0.9 events in every 100 (0.3 to 1.6), 107 patients would need to be treated to avoid one non-fatal infarction. Predictors of benefit: initial intravenous dose of β blocker on mortality in long term trials. Applying covariate term in the analysis suggested no additional benefit among patients treated in this manner, odds ratio 0.87 (95%CI 0.61 to 1.22). Equally this analysis

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								indicated that there is no reason to delay treatment with a β blocker. Early initiation will lead to a greater period when benefits may be accrued from treatment. Choice of drug: Individually, only four drugs achieved a reduction in the odds of death: Propranolol: OR 0.71 (95%CI 0.59 to 0.85), Timolol: OR 0.59 (95%CI 0.46 to 0.77), Metoprolol: OR 0.80 (95%CI 0.66 to 0.96), Acebutolol: OR 0.49 (95%CI 0.25 to 0.93). Acebutolol is supported by a single moderately sized study (open to considerable measurement error). RCTs including propranolol, timolol and metoprol include 63% of the available evidence on the long term effect of β blockage in post MI patients. Other β blockers that did not show a reduction in odds of death: Atenolol, Labetalol, Oxprenolol, Pindolol, Practolol.

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number: 3783 Ko DT;Hebert PR;Coffey CS;Sedrakyan A;Curtis JP;Krumholz HM; Beta-blocker therapy and symptoms of depression, fatigue, and sexual dysfunction 2002 288 JAMA	Systematic Review	Post MI patients, RCTs that enrolled ≥ 100 patients and ≥ 6 months of follow-up.	β blockerrs.	Placebo.	Follow-up range: 6 to 59 months.	Adverse effects: Fatigue 10 trials, 17 682 patients. Sexual dysfunction 6 trials, 14 897 patients. Depressive symptoms 7 studies, 10 662 patients.	Not stated.	Fatigue: Weighted event rates: β blockers 34% versus placebo 30%., RRI (95%CI) = 15% (2 to 26). Withdrawal because of fatigue: β blockers 1.8% versus placebo 0.5%., RRI (95%CI) = 163% (16 to 494). Sexual dysfunction: Weighted event rates: β blockers 19% versus placebo 17%. RRI (95%CI) = 10% (-4 to 25), not significant. Withdrawal because of sexual dysfunction: β blockers 1.2% versus placebo 0.3%. RRI (95%CI) = 397% (203 to 716). Depressive symptoms: Withdrawal because of depressive symptoms: β blockers 21.7% versus placebo 20.5%. RRI (95%CI) = 12% (-11 to 41), not significant.

Table 257: Is there an optimum time for beta-blockers to be initiated in unselected patients after MI?

Grading: 1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number: 2994 Rees K;Bennett P;West R;Davey SG;Ebrahim S; Psychological interventions for coronary heart disease 2004	Systematic Review							Meta-analysis of 22 trails (10634 patients) reporting this outcome (OR 0.78, 95% CI 0.67 to 0.90). There was significant heterogeneity of effects in some of these clinical outcomes, and there was evidence of publication bias for the non-fatal myocardial infarction findings. The evidence was dominated by two large trials (ENRICHD, Jones), both of which produced null findings for all clinical outcomes. Anxiety was measured in only 9 trials. A small but statistically significant reduction in anxiety with the intervention was seen, where the SMD was -0.08 (-0.16, -0.01). Depression was measured in 11 trials overall (4535 patients), again using a number of different measures. There was significant

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								heterogeneity between trials. Across all trials there was a significant reduction in depression (SMD -0.3 (-0.48, -0.13) random effects model). Several studies reported composite measures for anxiety, depression and mental health, and these form a separate category. For the 5 trials overall (347 patients) there is a significant beneficial reduction (SMD -0.22 (-0.44, -0.01)). Eighteen trials were identified that included some form of stress management (SM). Results were presented on 18 trials with any stress management intervention +/- other rehabilitation versus usual care/other rehabilitation. There was no strong evidence of effect of SM on total mortality in the 10 trials (3425 patients) reporting this as an

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								outcome (OR 0.88, 95% CI 0.67 to 1.15). Cardiac mortality was reported in 4 trials where weak evidence of a reduction in the number of deaths was seen in the intervention group (pooled effect estimate OR 0.62, 95% CI 0.38 to 0.99), and of a 31% reduction in non-fatal myocardial infarction in the intervention group in the 8 trials (3990 patients) reporting this outcome (OR 0.69, 95% CI 0.52 to 0.92). One of these 8 trials recruited patients with identified levels of psychopathology prior to randomisation (Stern). Only one of these 8 trials examined the effects of a stress management intervention without the influence of other rehabilitation interventions (Jones). For anxiety, there was only weak evidence of a small decrease in

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								anxiety with the intervention (SMD -0.07 (-0.15, 0.01)). For depression, there was evidence of a reduction in depression scores in the intervention group (SMD -0.32 (-0.56, -0.08) - random effects model). Results are dominated by one large trial (Jones) which showed a null effect, and hence significant heterogeneity between studies (SMD -0.3 (-0.48, -0.13) random effects model). Several studies reported composite measures for anxiety, depression and mental health. For the 5 trials overall (347 patients), there was evidence of a reduction (SMD -0.22 (-0.44, -0.01).

Grading: 1+ Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference	Randomised	Post MI< 65	Session	Usual care from	3 months.	Illness Perception	Heart	At 3 months, there was a

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
number: 1346 Petrie KJ;Cameron LD;Ellis CJ;Buick D;Weinman J; Changing illness perceptions after myocardial infarction: an early intervention randomized controlled trial 2002 64 Psychosomatic Medicine	Controlled Trial	years.	lasted 30-40 minutes, was conducted by a psychologist during the hospital stay. 1st session/ Individualised according to Illness Perception Questionnaire. Explained pathophysiology of MI, examined patient's belief, addressed misconcep-tions.	rehabilitation nurses.		Questionnaire (IPQ). Return to work.	Found. NZ	significant success in changing patient's belief to a more positive and controllable view of MI, as determined by the IPQ, compared to control patients.The intervention group had a shorter delay in return to work rate compared with control.

Table 258: What is the effectiveness of adding calcium blocker versus placebo to improve outcome in…

Grading: 1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number: 1290 National Institute for	Guideline	Post MI.	Calcium channel blockers.	Mortality, Non-fatal MI.			NHS.	Mortality: treatment versus placebo OR of 0.99 (95% CI 0.89 to 1.10 not significant) fixed effects.

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Clinical Excellence; A Prophylaxis for patients who have experienced a myocardial infarction 2001 National Institute for Clinical Excellence								OR of 0.99 (95% CI 0.87 to 1.12 not significant) random effects. Non-fatal MI: treatment versus placebo OR of 0.80 (95% CI 0.70 to 0.92) fixed effects. OR of 0.81 (95% CI 0.69 to 0.96) random effects. 1000 patients treated for 1 year, 10 non-fatal MIs avoided (95% CI 2 to 19).

Grading: 1+ Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number: 57 Effect of verapamil on mortality and major events after acute myocardial infarction (the Danish Verapamil Infarction Trial II--DAVIT II) 1990 66	Randomised Controlled Trial	Inclusion criteria: Post MI patients recruited during hospitalization from day 7 to 15 after admission. Aged under 75 years. Male and female (20%). Exclusion criteria: Heart failure, systolic blood pressure	Verapamil 120 mg three times daily: 878 patients.	Placebo: 897 patients.	18 months.	Total mortality. First major event (first reinfarction or death). Cardiac death. Sudden death. First reinfarction. First cardiac event (first reinfarction or cardiac death).	Knoll, Germany.	Total mortality: 95/878 (11.1%) treatment versus 119/897 (13.8%) placebo, HR of 0.80 (95% CI 0.61 to 1.05, P = 0.11). First major event (first reinfarction or death): 146/878 (18.0%) treatment versus 180/897 (21.6%) placebo, HR of 0.80 (95% CI 0.66 to 0.99, P = 0.03). Cardiac death: 84/878 (9.9%) treatment versus 107/897 (12.3%) placebo, HR of 0.79 (95%

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
American Journal of Cardiology		below 90 mmHg.						CI 0.59 to 1.05, P = 0.10). Sudden death: 46/878 (5.6%) treatment versus 63/897 (7.4%) placebo, HR of 0.74 (95% CI 0.50 to 1.07, P = 0.10). First reinfarction: 84/878 (11.0%) treatment versus 107/897 (13.2%) placebo, HR of 0.77 (95% CI 0.58 to 1.03, P = 0.04). First cardiac event (first reinfarction or cardiac death): 137/878(17.0%) treatment versus 170/897 (20.2%) placebo, HR of 0.80 (95% CI 0.64 to 1.00, P = 0.03). Patients without heart failure had a significantly better prognosis than patients with heart failure. Treatment with verapamil did not confer any benefit on patients with heart failure compared with placebo. Thus the overall benefit of verapamil was found in patients without heart failure immediately before randomisation.
Reference	Randomised	Inclusion	Amlodipine 5	Placebo: 408 patients.	36 months.	Primary:	Pfizer.	Primary outcome: Mean 3

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
number: 3832 Pitt B;Byington RP;Furberg CD;Hunninghake DB;Mancini GB;Miller ME;Riley W; Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events. PREVENT Investigators 2000 102 Circulation	Controlled Trial	criteria: Men and women (20%), 30-80 years mean age 57 years, with angiographic evidence of CAD, angiographic evidence of 1 focal coronary lesion ≤30% diameter stenosis and the presence of ≥ 1 lesion with 5% to 20% stenosis that was not in a vessel with a ≤ 60% lesion. Diastolic BP <95 mmHg, total cholesterol <325 mg/dl, fasting blood glucose of <200 mg/dl. Patient population, Post MI: 45%, Stroke 3%, Angina 68%.	mg QD, after 2 weeks increased to 10 mg if tolerated 417 patients.			Reduction in the progression of early athlero-sclerotic segments as measured by change in mean minimal diameter with quantitative coronary angiography. Secondary: Reduction in progression of athlero-sclerosis as assessed with B-mode ultrasono-grapgy. Progression based on mean of 3 year regression slopes of the maximum IMT measurements estimated in each of the separate wall segments. All-cause mortality, reinfarction, stroke, congestive heart failure, unstable		year change in minimum diameter in segments of ≤30% stenosis Amilodipine and placebo had nearly identical average reductions in minimal diameter: 0.95 mm versus 0. 84 mm, respectively (P = 0.38). Secondary outcomes: Progression of carotid atherosclerosis Amilodipine reduced progression: placebo group 0.033 mm increase in IMT versus amilodipine 0.013 mm increase (P < 0.007). Mortality: 6/417 treatment versus 8/408 placebo, HR of 0.74 (95% CI 0.28 to 2.12, not significant). Reinfarction: 19/417 treatment versus 20/408 placebo, HR of 0.94 (95% CI 0.50 to 1.76, not significant). Stroke: 5/417 treatment versus 5/408 placebo, HR of 0.74 (95% CI 0.28 to 2.12, not significant). Congestive heart failure: 1/417 treatment versus 5/408

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
						angina, CABG, other major procedure (angioplasty, stenting,		placebo, HR of 0.20 (95% CI 0.02 to 1.67, not significant). Unstable angina: 60/417 treatment versus 85/408 placebo, HR of 0.67 (95% CI 0.48 to 0.93). CABG: 17/417 treatment versus 29/408 placebo, HR of 0.57 (95% CI 0.31 to 1.03, not significant). Other major procedures: 40/417 treatment versus 67/408 placebo, HR of 0.56 (95% CI 0.38 to 0.83).

Table 259: What is the effectiveness of adding potassium channel activators versus placebo to improve outcomes in patients after MI?

Grading: 1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number: 3817 IONA Study Group; Effect of nicorandil on coronary events in patients with stable angina:	Randomised Controlled Trial	History of clearly established coronary artery disease (either had MI, previous CABG or CHD by angiography) or positive exercise test	Nicorandil 10 mg twice daily thereafter 20 mg twice daily: 2565 patients.	Placebo: 2561 placebo.	Mean follow-up 1.6 years.	Primary: Composite of coronary heart disease death, non-fatal MI, or unplanned hospital admission for cardiac chest pain. Secondary: Coronary heart	Merck Pharm, Aventis Pharma, Chugai Pharm. Co.	Primary: Composite of coronary heart disease death, non-fatal MI, or unplanned hospital admission for cardiac chest pain: nicorandil 337/2565 (13.1%) versus placebo 398/2561 (15.5%), HR of 0.83 (95% CI 0.72 to 0.97), P = 0.014. Secondary: Coronary

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
the Impact Of Nicorandil in Angina (IONA) randomised trial 2002 359		with additional risk factors (see methodology in the paper). Men older than 45 years and woman older than 55 years, mean age 67 years. Previous MI: 66%, previous CABG: 23%, previous PTCA: 15%, previous angiogram: 60%, Previous stroke: 5%. History of PVD: 12%, History of LVD: 9%, diabetes: 9%, hypertension: 47%, current smokers: 17%. Hospital admission for transient ischaemic attack: 2%.				disease, death or non-fatal MI. Others: Acute coronary syndromes, all CV events (CV mortality, non-fatal MI).		heart disease death or non-fatal MI: nicorandil 107/2565 (4.2%) versus placebo 134/2561 (5.2%), HR of 0.79 (95% CI 0.61 to 1.02), P = 0.068. Others: Coronary heart disease death: nicorandil 60/2565 (2.3%) versus placebo 73/2561 (2.9%). Non fatal MI: nicorandil 56/2565 (2.1%) versus placebo 72/2561 (2.8%). Unstable angina: nicorandil 56/2565 (2.1%) versus placebo 73/2561 (2.9%). Definite angina: nicorandil 115/2565 (4.5%) versus placebo 127/2561 (5.0%). Presumed angina: nicorandil 128/2565 (4.0%) versus placebo 153/2561 (6.0%). Stroke or hospital admission for transient ischaemic stroke: nicorandil 37/2565 (1.4%) versus placebo 40/2561 (1.6%). Coronary heart disease death or non-fatal MI or unstable angina: nicorandil 156/2565

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								(6.1%) versus placebo 195/2561 (7.6%), HR of 0.79 (95% CI 0.64 to 0.98), P = 0.028. All CV events: nicorandil 378/2565 (14.7%) versus placebo 436/2561 (17.0%), HR of 0.86 (95% CI 0.86 to 0.98), P = 0.027. All-cause mortality: nicorandil 111/2565 (4.3%) versus placebo 129/2561 (5.0%), HR of 0.85 (95% CI 0.66 to 1.10), P = 0.222.

Table 260: What is the effectiveness of adding omega-3 supplements versus placebo to improve outcomes in patients after MI?

Grading: 1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-	Randomised Controlled Trial	Inclusion criteria: Post MI (≤ 3 months), mean days since diagnosis ± SD = 25±21 days, male Characteristics and female (15%), no age	n-3 polyun-saturated fatty acids (PUFA) 1g gelatine capsule containing 850-882 mg eicosa-pentanoic acid (EPA)	No supplementation: 2828 patients.	42 months	Primary: Composite of death, non fatal MI, and non-fatal stroke. Composite of CV death, non-fatal MI, and non-fatal stroke. Secondary: All fatal events, CV	Bristol-Myers Squibb, Pharmacia-Upjohn, Soicetà Prodotti Antibiotici, Pfizer	Four-way analysis: Primary: Composite of death, non fatal MI, and non-fatal stroke: Treatment 356/2836 (12.3%) versus control 414/2828 (14.6%), RR = 0.85 (95% CI 0.74 to 0.98). Composite of CV death, non-fatal MI, and non-fatal stroke:

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Prevenzione trial. 1999 354 Lancet		limit (mean age ±SD = 59±10 years), mean ejection fraction ±SD = 53±11. Exclusion criteria: Contraindications to n-3 polyunsaturated fatty acids, known congenital defects in coagulation, unfavourable outlook (e.g., overt congestive heart failure,	and docisa-hexaenoic acid (DHA) as ethyl esters in the average ratio of EPA/DHA 1.2/1: 2836 patients.			deaths, Cardiac death, Coronary death, Sudden death, Other deaths, CHD death and non fatal MI Fatal and non-fatal stroke.		Treatment 262/2836 (9.2%) versus control 414/2828 (11.4%), RR = 0.80 (95% CI 0.68 to 0.95). Secondary: All fatal events:Treatment 236/2836 (8.3%) versus control 293/2828 (10.4%), RR = 0.80 (95% CI 0.67 to 0.95). CV deaths:Treatment 136/2836 (4.8%) versus control 193/2828 (6.8%), RR = 0.70 (95% CI 0.56 to 0.87). Cardiac death: Treatment 108/2836 (3.8%) versus control 165/2828 (5.8%), RR = 0.65 (95% CI 0.51 to 0.82). Coronary death: Treatment 100/2836 (3.5%) versus control 151/2828 (5.3%), RR = 0.65 (95% CI 0.51 to 0.84). Sudden death: Treatment 55/2836 (1.9%) versus control 99/2828 (3.5%), RR = 0.55 (95% CI 0.40 to 0.76). Other deaths: Treatment 100/2836 (3.5%) versus control 100/2828 (3.5%),

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								RR = 0.99 (95% CI 0.75 to 1.30). Non-fatal CV events: Treatment 140/2836 (4.9%) versus control 144/2828 (5.1%), RR = 0.96 (95% CI 0.76 to 1.21). CHD death and non fatal MI: Treatment 196/2836 (6.9%) versus control 259/2828 (9.2%), RR = 0.75 (95% CI 0.62 to 0.90). Fatal and non-fatal stroke: Treatment 54/2836 (1.9%) versus control 41/2828 (1.5%), RR = 1.30 (95% CI 0.87 to 1.96). Two-way analysis: Primary: Composite of death, non fatal MI, and non-fatal stroke: Treatment 715/5666 (12.6%) versus control 785/5668 (13.9%), RR = 0.90 (95% CI 0.82 to 0.99). Composite of CV death, non-fatal MI, and non-fatal stroke: Treatment 547/5666 (9.7%) versus control 608/5668 (10.8%), RR = 0.89 (95% CI 0.80 to 1.10). Secondary: All fatal events: Treatment

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								472/5666 (8.3%) versus control 545/5668 (10.4%), RR = 0.86 (95% CI 0.76 to 0.97). CV deaths: Treatment 291/5666 (5.1%) versus control 348/5668 (6.2%), RR = 0.83 (95% CI 0.71 to 0.97). Cardiac death: Treatment 228/5666 (4.0%) versus control 292/5668 (5.2%), RR = 0.78 (95% CI 0.65 to 0.92). Coronary death: Treatment 214/5666 (3.8%) versus control 265/5668 (4.7%), RR = 0.80 (95% CI 0.67 to 0.96). Sudden death: Treatment 122/5666 (2.2%) versus control 164/5668 (2.9%), RR = 0.74 (95% CI 0.58 to 0.93). Other deaths: Treatment 378/5666 (3.3%) versus control 197/5668 (2.9%), RR = 0.91 (95% CI 0.74 to 1.11). Non-fatal CV events: Treatment 287/5666 (5.1%) versus control 291/5668 (5.1%), RR = 0.98 (95% CI 0.83 to 1.15). CHD death

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								and non fatal MI: Treatment 196/5666 (6.9%) versus control 259/5668 (9.2%), RR = 0.75 (95% CI 0.62 to 0.90). Fatal and non-fatal stroke: Treatment 54/5666 (1.9%) versus control 41/5668 (1.5%), RR = 1.30 (95% CI 0.87 to 1.96). Side Effects: Nausea: treatment group 1.4%, GI disturbances: treatment group 4.9%. More than 70% of patients reported eating fish at least once a week at the start of the RCT in both the treatment and placebo groups (no difference between the groups). At 42 months, this had risen to 82% in both groups. The type of fish was not stipulated. At the start of the RCT, the percentage of patients prescribed cholesterol-lowering drug therapy in the treatment and control groups was 4.4% and 5.1%, respectively. At 42

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								months the percentage rose in the treatment and the control groups to 46.0% and 44.4%, respectively.

Table 261: What is the effectiveness of adding statins versus placebo to improve outcome in patients after MI?

Grading: 1+Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number: 1806 Ericsson CG;Hamsten A;Nilsson J;Grip L;Svane B;de FU; Angiographic assessment of effects of bezafibrate on progression of coronary artery disease in young male postinfarction patients 1996 347 Lancet	Randomised Controlled Trial	Inclusion criteria: Men aged below 45 years post MI (interval between acute event and study entry had to be 3 to 6 months). Whole serum cholesterol value of > 5.2 mmol/l and / or triglycerides values ≥ 1.6 mmol/l. Patients fulfilling the inclusion criteria were first treated	Bezafibrate, 200mg, three times a day: 47 patients.	Placebo: 45 patients.	5 years.	Coronary events (reinfarction, CABG, PTCA, sudden death, cardiovascular death). Plasma lipid concentration.	Boehringer, Mann-heim, GmbH, Karolinska Institue, Swedish Heart-Lung Found., Sera-firmer Found., Eirs Found.	Coronary events (reinfarction, CABG, PTCA, sudden death, cardiovascular death): Bezafibrate: 3/47 (one reinfarction then death, one sudden death, one reinfarction plus CABG) Placebo: 11/45 (three reinfarction, one reinfarction plus CABG, four CABF, three PTCA), P < 0.019 by log-rank test. Plasma lipid levels: Cholesterol at baseline (mmol/l): Bezafibrate: 6.87 (6.42 to 7.69) Placebo: 6.90 (6.21 to 7.27). HDL-C at baseline (mmol/l): Bezafibrate: 0.89 (0.82 to 0.96)

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
		with diet for 3 months (pre-treatment period). Patients were given a dietary instruction sheet and saw a nutritionist. Exclusion criteria: Severe hyperlipidemia (cholesterol > 10 mmol/l and or triglycerides ≥ 8 mmol/l), severe hypertension resistant to medication, diabetes mellitus, impaired renal function (creatinine ≥ 150 µmol/l) necessitating lowering of the benzafibrate dose, chronic liver disease, chronic alcoholism,						Placebo: 1.0 (0.91 to 1.10). LDL-C at baseline (mmol/l): Bezafibrate: 4.66 (3.99 to 5.19) Placebo: 4.62 (4.19 to 5.00)VLDL-C at baseline (mmol/l): Bezafibrate: 1.10 (0.93 to 1.47) Placebo: 0.86 (0.76 to 1.02). Total triglycerides at baseline (mmol/l): Bezafibrate: 2.44 (2.11 to 3.07) Placebo: 1.98 (1.84 to 1.69). VLDL triglycerides at baseline (mmol/l): Bezafibrate: 1.85 (1.30 to 2.22) Placebo: 1.43 (1.28 to 1.69). Mean % change during follow-up relative to baseline (95% CI) Cholesterol: Bezafibrate: -13.97 (-17.09 to -9.13) Placebo: -0.78 (-6.57 to 4.47), P < 0.001. HDL-C: Bezafibrate: 8.64 (1.02 to 16.37) Placebo: -0.78 (-6.57 to 4.47), P = 0.02. LDL-C: Bezafibrate: -3.49 (-9.71 to 2.88) Placebo: -2.19 (-7.05 to 2.61), P = 0.551. VLDL-C:

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
		symptomatic gallbladder disease, connective tissue disease or arthritis, psychiatric disease, any form of cancer, participation in other clinical trials. Concomitant drug therapy at baseline: Aspirin: 11%, Beta blockers: 99%, Diuretics: 19%, ACE inhibitors: 0%, Calcium channel blockers: 19%, Long acting nitrates: 27%. Concomitant drug therapy at end of study: Aspirin: 45%, ACE inhibitors: 5%.						Bezafibrate: -35.94 (-49.74 to 25.26) Placebo: 1.54 (-14.35 to 7.22), P < 0.001. Total triglycerides: Bezafibrate: -26.28 (-39.20 to -17.67) Placebo: 2.69 (-8.05 to 10.79), P < 0.001. VLDL triglycerides: Bezafibrate: -26.07 (-42.03 to -16.80) Placebo: 7.95 (-6.89 to 31.94). Discontinuation from study: One patient withdrew from the placebo group because of gastrointestinal complaints and one patient from the bezafibrate group who had pre-existing glomerulonephritis was withdrawn because of progression of renal dysfunction.

Table 262: What is the effectiveness of adding high dose statin (more potent cholesterol lowering) versus low dose statin (less potent cholesterol lowering) to improve outcome in patients after MI?

Grading: 1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number: 3806 de Lemos JA;Blazing MA;Wiviott SD;Lewis EF;Fox KA;White HD;Rouleau JL;Pedersen TR;Gardner LH;Mukherjee R;Ramsey KE;Palmisano J;Bilheimer DW;Pfeffer MA;Califf RM;Braunwald E; Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary	Randomised Controlled Trial	Inclusion criteria: Patients with acute coronary syndrome in preceding 10 days (median 7 days). Total cholesterol of level of 250 mg/dl or lower (6.48 mmol/l). Non ST-segment elevation acute coronary syndrome: 60% MI with ST-segment elevation: 40% Male and female (24%), between the ages of 21 to 80 years, mean (IQR) = 61(53-69) years. Other baseline characteristics:	Early intensive therapy: Simvastatin 40 mg once daily for 1 month followed by 80 mg once daily thereafter, 2265 patients.	Delayed conservative therapy: Placebo for 4 months followed by Simvastatin 20 mg once daily thereafter, 2232 patients.	At least 6 months and up to 24 months. Median follow up 721 days.	Primary: Composite of cardiovascular death, nonfatal MI, readmission for acute coronary syndrome and stroke. Secondary: All cause mortality, new onset CHF, revascularisation due to documented ischaemia.	Merck and Company.	Primary outcome: Composite of cardiovascular death, nonfatal MI, readmission for acute coronary syndrome and stroke: 309/2265 (14.4%) Simvastatin 40/80 mg versus 343/2232 (16.7%) Simvastatin placebo/20 mg, HR of 0.89 (95% CI 0.76 to 1.04, P = 0.14). Cardiovascular death: 83/2265 (5.4%) Simvastatin 40/80 mg versus 109/2232 (4.1%) Simvastatin placebo/20 mg, HR of 0.75 (95% CI 0.51 to 1.00, P = 0.05). Nonfatal MI: 151/2265 (7.1%) Simvastatin 40/80 mg versus 155/2232 (7.47%) Simvastatin placebo/20 mg, HR of 0.96 (95% CI 0.71 to 1.21, P = 0.74). Readmission for acute coronary syndrome:

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
syndromes: phase Z of the A to Z trial 2004 292JAMA		Diabetes Mellitus: 24%, Systemic Hypertension: 50%. Participation in Phase A: 58%. Exclusion criteria: On statin therapy at time of randomisation, participation in any other clinical trial, planned coronary revascularizatio n disease or cardiac transplantation, severe real or hepatic. Concomitant therapy at baseline: Aspirin: 98%, Beta blockers: 90%, ACE inhibitors: 72%.						309/2265 (14.4%) Simvastatin 40/80 mg versus 343/2232 (16.7%) Simvastatin placebo/20 mg, HR of 0.99 (95% CI 0.80 to 1.22, P = 0.90). Stroke: 103/2265 (5.0%) Simvastatin 40/80 mg versus 102/2232 (4.9%) Simvastatin placebo/20 mg, HR of 0.99 (95% CI 0.76 to 1.31, P = 0.97). Secondary outcomes: All cause mortality: 104/2265 (5.4%) Simvastatin 40/80 mg versus 130/2232 (6.7%) Simvastatin placebo/20 mg, HR of 0.79 (95% CI 0.61 to 1.02, P = 0.08). New onset CHF: 72/2265 (3.7%) Simvastatin 40/80 mg versus 98/2232 (5.0%) Simvastatin placebo/20 mg, HR of 0.72 (95% CI 0.53 to 0.98, P = 0.04). Revascularisation due to documented ischaemia: 119/2265 (5.9%) Simvastatin 40/80 mg versus 124/2232 (6.2%) Simvastatin placebo/20

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								mg, HR of 0.93 (95% CI 0.73 to 1.20, P = 0.60). Simvastatin placebo/20 mg: Median LDL-C levels increased 11% during the 4 month placebo period from 111 mg/dl (2.87 mmol/l) to 124 mg/dl (3.2 mmol/l), then decreased to 77 mg/dl (1.99 mmol/l at month 8 after the initiation of simvastatin 20 mg (31% change from baseline). Simvastatin 40/80 mg: Median LDL-C levels decreased by 39% to 68 mg/dl (1.61 mmol/l) over the first month of simvastatin 40 mg then decreased an additional 6% to 62 mg/dl (1.61 mmol/l) at month 4 following increase to 80 mg simvastatin. Safety Alanine aminotransferase or aspartate aminotransferase >3 x upper limit of normal at 2 Consecutive measurements:19/2232 (0.9%) Simvastatin 40/80 mg versus 8/2068 (0.4%)

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								Simvastatin placebo/20 mg (P = 0.05).Creatine kinas >10 x upper limit of normal at 2 consecutive measurements:9/2263 (0.4%) Simvastatin 40/80 mg versus 1/2230 (0.04%) Simvastatin placebo/20 mg (P = 0.02). Simvastatin 40/80 patient group: levels were high while taking 80 mg simvastatin. 3/9 with myopathy had creatine kinas levels > 10 000 units/l and met the criteria for rhabdomyolysis. Of these 3 patients, 1 had contrast media renal failure and 1 patient was receiving concomitant verapamil (inhibitor of CYP3A4). In addition, 1 patient receiving 80 mg simvastatin had a creatine kinase level 10 x the upper limit of normal without muscle symptoms, which was associated with alcohol abuse. Rates of

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								discontinuation due to adverse muscle-related events: Simvastatin 40/80 mg: 41/2263 (1.8%)Simvastatin placebo/20 mg: 34/2230 (1.5%) (P = 0.49).
Reference number: 74 LaRosa JC;Grundy SM;Waters DD;Shear C;Barter P;Fruchart JC;Gotto AM;Greten H;Kastelein JJ;Shepherd J;Wenger NK;Treating t; Intensive lipid lowering with atorvastatin in patients with stable coronary disease. 2005 352 New England	Randomised Controlled Trial	Inclusion criteria: Men and women (19%), age range 35 to 75 years (mean±SD = 61±9 years), with clinically evident coronary heart disease defined as one or more of the following: Previous MI: Atorvastatin 80 mg: 59.0%, Atorvastatin 10 mg: 57.7%, previous or current angina with objective evidence of atherosclerotic coronary heart	Atorvastatin: 10 mg once daily, 5006 patients.	Atorvastatin: 80 mg once daily, 4958 patients.	Median 4.9 years (up to 6 years).	Primary: Major cardiovascular event (death from CHD, nonfatal non-procedural MI, resuscitation after cardiac arrest or fatal or nonfatal stroke). Secondary: Major coronary event (death from CHD, nonfatal non-procedural MI, or resuscitation after cardiac arrest), cerebrovascular event, hospitalisation for CHF, PAD, death from any cause, any	Pfizer.	Primary outcome: Major cardiovascular event: 548/5006 (10.9%) Atorvastatin 10 mg versus 434/4995 (8.7%) Atorvastatin 80 mg, HR of 0.78 (95% CI 0.69 to 0.89, P < 0.001). Absolute RR= 2.2% (22% relative RR). Death from CHD: 127/5006 (2.5%) Atorvastatin 10 mg versus 101/4995 (2.0%) Atorvastatin 80 mg, HR of 0.80 (95% CI 0.61 to 1.03, P = 0.09). Nonfatal non-procedural MI: 308/5006 (6.2%) Atorvastatin 10 mg versus 243/4995 (4.9%) Atorvastatin 80 mg, HR of 0.78 (95% CI 0.66 to 0.93, P = 0.004). Resuscitation after cardiac arrest: 26/5006 (0.5%) Atorvastatin 10 mg versus

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Journal of Medicine		disease: Atorvastatin 80 mg: 81.8%, Atorvastatin 10 mg: 81.8%, History of coronary revascularisation: Angioplasty: Atorvastatin 80 mg: 53.8%, Atorvastatin 10 mg: 54.3%, Bypass Atorvastatin 80 mg: 46.4%, Atorvastatin 10 mg: 46.7%, Other baseline characteristics: Diabetes Mellitus: 15% Systemic Hypertension: 54%, PAD: 12%, CHF: 8%, Arrhythmia: 18%, Run in period: Patients with LDL-C between 130 and 250 mg/dl (3.4				cardiovascular event, any coronary		25/4995 (0.5%) Atorvastatin 80 mg, HR of 0.96 (95% CI 0.56 to 1.67, P = 0.89). Fatal or nonfatal stroke:155/5006 (3.1%) Atorvastatin 10 mg versus 117/4995 (2.3%) Atorvastatin 80 mg, HR of 0.75 (95% CI 0.59 to 0.96, P = 0.02). Secondary outcomes: Major coronary event: 418/5006 (8.3%) Atorvastatin 10 mg versus 334/4995 (6.7%) Atorvastatin 80 mg, HR of 0.80 (95% CI 0.69 to 0.92, P = 0.002). Cerebrovascular event (fatal or nonfatal stroke or transient ischemic attack): 250/5006 (5.0%) Atorvastatin 10 mg versus 196/4995 (3.9%) Atorvastatin 80 mg, HR of 0.77 (95% CI 0.64 to 0.93, P = 0.007). Hospitalisation for CHF:164/5006 (3.3%) Atorvastatin 10 mg versus 122/4995 (2.4%) Atorvastatin 80 mg, HR of 0.75 (95% CI 0.59 to 0.93, P = 0.01). PAD (as defined as any new diagnosis of

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
		mmol/l and 6.5 mmol) and triglycerides of 600 mg/dl or less (6.8 mol/l) entered an 8 week run in period of open label treatment with 10 mg atorvastatin. At the end of the run in phase patients with an LDL cholesterol of less than 130 mg/dl (3.4 mmol/l) were randomized to the study. Baseline lipids (mg/dl) mmol/lLDL cholesterol: Atorvastatin 80 mg: 97±18 (2.5±0.5 mmol/l), Atorvastatin 10 mg: 98±18 (2.5±0.5							PAD, any admission related to its treatment, or any incidental discovery of plaques or stenosis): 282/5006 (5.6%) Atorvastatin 10 mg versus 275/4995 (5.5%) Atorvastatin 80 mg, HR of 0.97 (95% CI 0.83 to 0.1.15, P = 0.76). Death from any cause: 282/5006 (5.6%) Atorvastatin 10 mg versus 284/4995 (5.7%) Atorvastatin 80 mg, HR of 1.02 (95% CI 0.75 to 1.17, P = 0.92). Any cardiovascular event: 1677/5006 (33.8%) Atorvastatin 10 mg versus 1405/4995 (28.1%) Atorvastatin 80 mg, HR of 0.81 (95% CI 0.75 to 0.87, P < 0.001). Any coronary event (as event. defined as a major coronary event, revascularization procedure, procedure-related MI, or documented angina): 1326/5006 (26.5%) Atorvastatin 10 mg versus 1078/4995 (21.6%)

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
		mmol/l), Total cholesterol: Atorvastatin 80 mg: 175±24 (4.5±0.6 mmol/l), Atorvastatin 10 mg: 175±24 (4.5±0.6 mmol/l), Triglycerides: Atorvastatin 80 mg: 151±70 (1.7±0.8 mmol/l), Atorvastatin 10 mg: 151±72 (1.7±0.8 mmol/l) HDL cholesterol, Atorvastatin 80 mg: 47±11 (1.2±0.3 mmol/l), Atorvastatin 10 mg: 47±11 (1.2±0.3 mmol/l). Exclusion criteria: Hypersensitivity to statins, acute						Atorvastatin 80 mg, HR of 0.79 (95% CI 0.73 to 0.86, P < 0.001). Plasma lipid levels Mean LDL-C levels during the study were 77mg/dl (2.0 mmol/l) for 80 mg atorvastatin patients and 101 mg/dl (2.6 mmol/l) for 10 mg atorvastatin. Total cholesterol levels and triglycerides levels decreased significantly to week 12 in the group given 80 mg atorvastatin (P < 0.001) for both comparisons, and levels remained stable during the treatment period. Both doses of atorvastatin produced non significant increases over baseline in HDL cholesterol, with no significant difference between the groups during the course of the study. Safety / Adverse events: 289/5006 (5.8%) Atorvastatin 10 mg versus 406/4995 (8.1%) Atorvastatin 80 mg (P <

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
		liver disease or hepatic dysfunction defined as aspartate aminotransferase > 1.5 times the upper limit of normal, women who were pregnant or breastfeeding, uncontrolled diabetes mellitus, uncontrolled hypothyroidism, uncontrolled hypertension, an MI, coronary revascularization or severe/unstable angina within 1 month of screening, any planned procedure for the treatment of atherosclerosis, ejection fraction						0.001), Myalgia:234/5006 (4.7%) Atorvastatin 10 mg versus 241/4995 (4.8%) Atorvastatin 80 mg (P = 0.72). Persistent elevation in alanine aminotransferase, aspartate aminotransferase, or both (defined as two consecutive measurements obtained 4 to 10 days apart that were more than three times the upper limit of normal range): 9/5006 (0.2%) Atorvastatin 10 mg versus 60/4995 (1.2%) Atorvastatin 80 mg (P < 0.001).There were no persistent elevations in creatine kinase. Five cases of rhabdomyolysis were reported (two in the group given 80 mg of atorvastatin and three in the group given 10 mg atorvastatin).

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
		< 30%, haemodynamically important valvular disease, GI disease limit drug absorption or partial ileal bypass, any nonskin malignancy, malignant melanoma or other survival limiting disease, unexplained creatine phosphokinase levels > 6 times upper limit of normal, concurrent therapy with lipid regulating drugs not in study protocol, history of alcohol abuse, participation in another trial concurrently or within 30 days before screening.						

Grading: 1+ Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number: 3802 Cannon CP;Braunwald E;McCabe CH;Rader DJ;Rouleau JL;Belder R;Joyal SV;Hill KA;Pfeffer MA;Skene AM; Intensive versus moderate lipid lowering with statins after acute coronary syndromes 2004 350 New England Journal of Medicine	Randomised Controlled Trial	Inclusion criteria: Patients hospitalized for acute coronary syndrome in preceding 10 days Characteristics(median 7 days). Unstable angina: 29%, MI without ST-segment elevation: 36%, MI with ST-segment elevation: 35%. Male and female (22%), at least 18 years (mean±SD = 58±11 years). Patients had to be in a stable condition, and were enrolled after percutaneous revascularizatio n	Pravastatin 40 mg once daily: 2063 patients.	Atorvastatin 80 mg once daily: 2099 patients.	Mean follow up 24 months (18 to 36 months).	Primary: Composite of death from any cause, MI, documented unstable angina requiring rehospitalisation, revascularisation with CABG or PCI (if these were performed at least 30 days after randomisation), or stroke. Secondary: Composite of death from coronary heart disease, nonfatal MI, or stroke.	Bristol Myers-Squibb, Sanko	Primary outcome: Composite of death from any cause, MI, documented unstable angina requiring rehospitalisation, revascularisation with CABG or PCI (if these were performed at least 30 days after randomisation), and stroke: 544/2063 (26.4%) Pravastatin versus 470/2099 (22.4%) Atorvastatin, HR of 0.84 (95% CI 0.74 to 0.95, P = 0.005). Death from any cause: non significant reduction (28%, P = 0.06) with intensive (atorvastatin) therapy. MI: Non significant reduction (13%, P = 0.07) with intensive (atorvastatin) therapy. Unstable angina requiring rehospitalisation:

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
		procedure if planned (69%). One quarter of patients were taking statins at index event. Patients had to have a total cholesterol level of 240 mg/dl or less (6.22 mmol/l) measured within first 24 hours after onset of acute coronary syndrome, or up to 6 months earlier if no sample had been obtained during first 24 hours. Patients receiving long term lipid-lowering therapy at the time of their index acute coronary syndrome had to have a total cholesterol level						Significant reduction (29%, P = 0.02) with intensive (atorvastatin) therapy. Revascularisation: Significant reduction (14%, P = 0.04) with intensive (atorvastatin) therapy. Secondary outcome: Composite of death from coronary heart disease, nonfatal MI, or stroke: Risk reduction of 14% (P = 0.029) in intensive (atorvastatin) treatment group compared with pravastatin group. Plasma lipid levels at randomization: median LDL-C levels were 106 (2.74 mmol/l) mg/dl before treatment. At follow-up: Pravastatin group: 95 mg/dl (IQR 79 to 113 mg/dl), (2.74 mmol/l IQR 2.04 to 2.92 mmol/l) Atorvastatin group: 62 mg/dl (IQR 50 to 79 mg/dl) (1.60 mmol/l IQR 1.29 to 2.04 mmol/l) (P < 0.001).LDL-C median

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
		of 200 mg/dl (5.18 mmol/l) or less at time of screening. Exclusion criteria: Coexisting condition that shortened expected survival to less than 2 years. On statin therapy at a dose of 80 mg per day at index event or fibrate therapy, or niacin therapy that could not be discontinued before randomization. Treatment with strong inhibitors of cytochrome P-450 3A4 within 1 month of randomization, or likelihood of requiring such						change among 2985 patients who had not previously received statin therapy: Note: absolute values not reported. Pravastatin group: 22% at 30 days post randomisation Atorvastatin group: 51% at 30 days post randomization (P < 0.001). Median HDL-C increases: Note: absolute values not reported. Pravastatin group: 8.1% at 30 days post randomisation Atorvastatin group: 6.5% at 30 days post randomization (P < 0.001). Rates of discontinuation Pravastatin discontinuation rate 21.4% versus Atorvastatin 22.8% at one year (P = 0.38), and 33% and 30.4%, respectively, at 2 years (P = 0.22). Dosage changes: Pravastatin group: 8% of patients had a dose increase to 80 mg. 1.4%

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
		therapy. Undergone PCI within previous 6 months, or CABG within previous 2 months before randomization. Having factors that may prolong QT interval. Obstructive haepatobilliary disease or other serious liver disease. Unexplained elevation in the creatine kinase level 3 times the upper limit of normal that was not related to MI. Creatinine level of more than 2.0 mg/dl. Concomittant therapy during RCT: Aspirin: To 93%, Warfarin To 8%, Beta							of patients had a dose decrease to 20 mg. Atorvastatin group: 1.9% of patients had a dose decrease to 20 mg (due to side effects or liver function abnormalities). Safety: Elevation in alanine aminotransferase levels: Pravastatin group: 1.1%Atovastatin group: 3.3% (P < 0.001). Investigator discontinuation of study medication due to myalgias, muscle aches or elevations in creatine kinase levels: Pravastatin group: 2.7%, Atovastatin group: 3.3% (P =0.23). No cases of rhabdomyolysis in either group.

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
		blockers: To 85%, antiplatelets (clopidogrel / ticlodipine): To 72% initially and 20% at one year, ACE inhibitors: 69%, Angiotensin II blockers: to 69% then 14% at one year.						

Table 263: What is the effectiveness of adding early statin therapy versus delayed statin therapy to improve outcomes in patients after MI?

Grading: 1+ Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number: 5146 Thompson PL;Meredith I;Amerena J;Campbell TJ;Sloman JG;Harris PJ;Pravastatin i; Effect of	Randomised Controlled Trial	Inclusion criteria: Patients were enrolled within 24 hours of symptoms of acute coronary syndrome (electro-cardiographic changes suggestive of unstable angina	Pravastatin 20 or 40 mg once daily: 1710 patients. Pravastatin 20 mg: 720 patients. Pravastatin 40 mg: 990 patients.	Placebo: 1698 patients.	4 weeks.	Primary: Composite of all cause mortality, nonfatal MI, readmission for unstable angina pectoris. Secondary: New unstable angina	Bristol-Myers Squibb.	Primary outcome: Composite of all cause mortality, nonfatal MI, readmission for unstable angina pectoris:199/1710 (11.6%) Pravastatin versus 211/1698 (12.4%) Placebo, RR of 0.94 (95% CI 0.72 to 1.13, P = 0.48). Absolute risk reduction of 0.8% (95% CI -1.4% to 3.0%). Fatal MI: 13/1710

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
pravastatin compared with placebo initiated within 24 hours of onset of acute myocardial infarction or unstable angina: the Pravastatin in Acute Coronary Treatment (PACT) trial 2004 148 American Heart Journal		pectoris or acute MI). Final diagnosis: Acute MI: 65%, Unstable angina pectoris: 30%, Other: 5%. Male and female (24%), between the ages of 21 to 85 years. Other baseline characteristics: Diabetes Mellitus: 14%, PAD: 43%. Concomittant therapy at baseline: Antiplatelet agent: 26%, Anticoagulant: 3%, Beta blockers: 16%, Calcium antagonists:16% , ACE inhibitors: 18%, Vasodilator including nitrates: 16%, Non statin lipid lowering agent:						(0.8%) Pravastatin versus 15/1698 (0.9%) Placebo, not significant. Nonfatal MI: 13/1710 (0.8%) Pravastatin versus 15/1698 (0.9%) Placebo, not significant. Death excluding fatal MI: 11/1710 (0.6%) Pravastatin versus 22/1698 (1.3%) Placebo, not significant. Readmission for unstable angina pectoris: 81/1710 (0.6%) Pravastatin versus 89/1698 (1.3%) Placebo, not significant. Secondary outcomes: New unstable angina: 81/1710 (0.6%) Pravastatin versus 89/1698 (1.3%) Placebo, not significant. Plasma lipid levels: Baseline serum lipids: Total cholesterol mean±SD: Pravastatin: 5.62±1.2 mmol/l Placebo: 5.69±1.1 mmol/l, not significant. Levels were not reported at end of study (4 weeks). Safety: Elevation in alanine

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
		2%.						aminotransferase or aspartate tramsaminase levels greater than 3 times the upper limit of normal: Pravastatin: 7/1710 (1.5%) Placebo: 5/1698 (1.1%), not significant. Elevation in creatine kinase levels greater than 10 times the upper limit of normal with suspected or diagnosed myopathy: Pravastatin: 0/1710, Placebo: 0/1698.

Table 264: What is the effectiveness of adding fibrates or niacin or ezetimibe versus placebo to improve outcome in patients after MI?

Grading: 1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number: 5160 Rubins HB;Robins SJ;Collins D;Fye CL;Anderson JW;Elam MB;Faas	Randomised Controlled Trial	Inclusion criteria: Men with documented coronary artery disease (defined as a history of MI, angina	Gemfibrozil slow release 1200 mg once daily, then Gembrozil 600 mg twice daily (when manufacturer ceased	Placebo: 1267 patients.	Median follow up 5.1 years (range 0 to 6.9 years).	Primary: Composite of nonfatal MI or death from coronary heart disease (fatal MI, sudden death, death due to CHF, death as a complication of	Co-operative Studies Program of Dept. Veterans Affaires Office Research and	Primary outcomes: Composite of nonfatal MI or death from coronary heart disease: 275/1264 (21.7%) Gemfibrozil versus 219/1267 (17.3%) placebo, RR of 0.78 (95% CI 0.65 to 0.93, P = 0.006). Composite of nonfatal MI or death from coronary

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
FH;Linares E;Schaefer EJ;Schectman G;Wilt TJ;Wittes J; Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group 1999 341 New England Journal of Medicine		corroborated by objective evidence of ischaemia, coronary revascularization, or angiogenic evidence of stenosis > 50% luminal diameter in one or major coronary arteries). Prior MI: 61%. Time since most recent MI mean±SD = 6±6 years. CABG or PCI: 57%. Other baseline characteristic. Hypertension: 57%. Diabetes: 25%. CHF: 8%. Aged less than 74 years, mean±SD = 64±7 years. An HDL-C level of 40 mg/dl (1.0 mmol/l) or less. LDL-C of 140	production): 1264 patients.			invasive cardiac procedures). Secondary: Composite of nonfatal MI, death from coronary heart disease or confirmed stroke. Stroke. Death from any cause. Transient ischaemic attack. Revascularisation. Hospitalisation for unstable angina. Hospitalisation for CHF. Carotid end-arterectomy.	Development, Parke-Davis.	heart disease (excluding silent MI): 195/1264 (15.4%) Gemfibrozil versus 241/1267 (19.0%) placebo, RR of 0.79 (95% CI 0.66 to 0.96, P = 0.02). Secondary outcomes: Composite of nonfatal MI, death from coronary heart disease or confirmed stroke: 258/1264 (20.4%) Gemfibrozil versus 330/1267 (26.0%) placebo, RR of 0.76 (95% CI 0.64 to 0.89, P <0.001). Nonfatal MI: 146/1264 (11.6%) Gemfibrozil versus 184/1267 (14.5%) placebo, RR of 0.77 (95% CI 0.62 to 0.96, P = 0.02). Death due to CHD: 93/1264 (7.4%) Gemfibrozil versus 118/1267 (9.3%) placebo, RR of 0.78 (95% CI 0.59 to 1.02, P = 0.07). Death from any cause: 198/1264 (15.7%) Gemfibrozil versus 207/1267 (17.4%) placebo, RR of

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
		mg/dl (3.6 mmol/l) or less. Triglyceride level of 300 mg/dl (3.4 mmol/l) or less). Exclusion criteria: Serious coexisting condition. Concomitant drug therapy at baseline: Aspirin: 82%, Beta blockers: 43%, Nitrates: 46%, ACE inhibitors: 21%, Calcium channel blockers: 53%.						0.89 (95% CI 0.73 to 1.08, P = 0.23). Investigator-designated stroke: 64/1264 (5.1%) Gemfibrozil versus 88/1267 (6.9%) placebo, RR of 0.81 (95% CI 0.52 to 0.98, P = 0.04). Confirmed stroke: 58/1264 (4.6%) Gemfibrozil versus 76/1267 (6.0%) placebo, RR of 0.75 (95% CI 0.53 to 1.06, P = 0.10). Transient ischaemic attack: 22/1264 (1.7%) Gemfibrozil versus 53/1267 (4.2%) placebo, RR of 0.61 (95% CI 0.25 to 0.67, P < 0.001). Revascularisation: 266/1264 (21.0%) Gemfibrozil versus 287/1267 (22.7%) placebo, RR of 0.91 (95% CI 0.77 to 1.08, P = 0.29). CABG: 164/1264 (13.0%) Gemfibrozil versus 173/1267 (13.7%) placebo, RR of 0.94 (95% CI 0.76 to 1.17, P = 0.60). PTCA: 120/1264 (9.5%) Gemfibrozil versus 241/1267 (19.0%) placebo, RR of 0.79 (95%

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								CI 0.68 to 1.01, P = 0.06). Peripheral vascular surgery: 19/1264 (1.5%) Gemfibrozil versus 28/1267 (2.2%) placebo, RR of 0.67 (95% CI 0.37 to 1.1.20, P = 0.18). Carotid endarterectomy: 16/1264 (1.3%) Gemfibrozil versus 44/1267 (3.5%) placebo, RR of 0.55 (95% CI 0.40 to 0.78, P < 0.001). Hospitalisation for unstable angina: 457/1264 (36.2%) Gemfibrozil versus 453/1267 (35.8%) placebo, RR of 1.04 (95% CI 0.88 to 1.14, P = 0.95). Hospitalisation for CHF: 134/1264 (10.6%) Gemfibrozil versus 168/1267 (13.3%) placebo, RR of 0.78 (95% CI 0.62 to 0.98, P = 0.04). Plasma lipid levels: One year after randomization: Mean HDL-C: Gemfibrozil: 34 mg/dl (0.9 mmol/l) Placebo: 32 mg/dl (0.8 mmol/l), P < 0.001. Mean cholesterol:

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								Gemfibrozil: 170 mg/dl (4.4 mmol/l) Placebo: 177 mg/dl (4.6 mmol/l), P <0.001. Mean triglyceriges: Gemfibrozil: 115 mg/dl (1.3 mmol/l) Placebo: 166 mg/dl (1.9 mmol/l), P < 0.001. Mean LDL-C: Gemfibrozil: 113 mg/dl (2.9 mmol/l) Placebo: 113 mg/dl (2.9 mmol/l), Not significant. Safety Dyspesia: Gemfibrozil: 506/1264 (40%) Placebo: 431/1267 (34%), P =0.002. Bilary disease: Gemfibrozil: 88/1264 (7%) Placebo: 89/1267 (7%), Not significant. Abdominal surgery: Gemfibrozil: 68/1264 (5.4%) Placebo: 54/1267 (4.3%), P =0.19. Discontinuation by physician due to concern about safety or adverse event: Gemfibrozil: 19/291 (7%) Placebo: 15/277 (5%), Not significant.

Grading: 1+ Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number: 5177 Clofibrate and niacin in coronary heart disease 1975 231 JAMA	Randomised Controlled Trial	Inclusion criteria: Post MI men aged 30 to 64 years (at least 3 months post infarction). Exclusion criteria: Patients with cardiac failure which required treatment with digoxin and / or diuretics. Patients with diabetes mellitus. Concomitant drug therapy: Not detailed.	Clofibrate, 1.8 g once daily, 1103 patients. Niacin, 3 g once daily, 1119 patients.	Placebo: 2789 patients.	5 years (all surviving patients in the study for at least 54 months).	Primary: All cause mortality. Secondary: Individual components of all cause mortality, nonfatal MI, coronary death or nonfatal MI, definite pulmonary embolism (fatal or nonfatal), definite or suspected fatal or nonfatal pulmonary embolism or thrombo-phlebitis, fatal or nonfatal stroke or intermittent cerebral ischaemic attack, any definite or suspected fatal or nonfatal cardiovascular event.	Nat. Heart and Lung Inst.	Results were analysed using the z test (comparison of 2 means of large groups). A z value of greater than 1.96 or less than -1.96 usually is considered significant ($P < 0.05$). However, the authors noted that for long term RCT it is more appropriate to consider z values > 2.58 or z < -2.58, ($P < 0.01$) or even z values > 2.81 or z < -2.81, ($P < 0.005$) as significant. A negative z value denotes an event rate in a drug group that is lower than the placebo group. Clofibrate versus placebo: Primary outcome: All cause mortality: 221/1103 (20.0%) Clofibrate versus 583/2789 (20.9%) placebo, z = 0.60, not significant. Secondary outcomes: All cardiovascular mortality: 191/1103 (17.3%) Clofibrate versus 528/2789 (18.8%)

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								placebo, z = -1.17, not significant. Mortality cause unknown: 7/1103 (0.6%) Clofibrate versus 13/2789 (0.5%) placebo, z = 1.27, not significant. Coronary heart disease mortality: 156/1103 (14.1%) Clofibrate versus 452/2789 (16.2%) placebo, z = -1.60, not significant. Sudden cardiovascular death: 93/1103 (8.4%) Clofibrate versus 269/2789 (9.6%) placebo, -1.17, not significant. All cancer deaths: 7/1103 (0.6%) Clofibrate versus 16/2789 (0.6%) placebo, z = 0.22, not significant. Other non cardiovascular death: 16/1103 (1.5%) Clofibrate versus 26/2789 (0.9%) placebo, z = 1.41, not significant. Non fatal MI: 128/1103 (11.6%) Clofibrate versus 339/2789 (12.2%) placebo, z = -0.48, not significant. Coronary death or nonfatal MI:

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								263/1103 (23.8%) Clofibrate versus 731/2789 (26.2%) placebo, z = -1.53, not significant. Definite pulmonary embolism (fatal or nonfatal): 20/1103 (1.8%) Clofibrate versus 30/2789 (1.1%) placebo, z = 1.84, not significant. Definite or suspected fatal or nonfatal pulmonary embolism or thrombophlebitis: 57/1103 (5.2%) Clofibrate versus 91/2789 (3.3%) placebo, z = 2.80, significant (P < 0.01). Fatal or nonfatal stroke or intermittent cerebral ischaemic attack: 117/1103 (10.6%) Clofibrate versus 271/2789 (9.7%) placebo, z = 0.84, not significant. Any definite or suspected fatal or nonfatal cardiovascular event: 929/1103 (84.2%) Clofibrate versus 2251/2789 (80.7%) placebo, z = 2.56,

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								significant (P < 0.01). Niacin versus placebo: Primary outcome: All cause mortality:237/1103 (21.2%) Clofibrate versus 583/2789 (20.9%) placebo, z = 0.19, not significant. Secondary outcomes: All cardiovascular mortality: 210/1103 (18.9%) Niacin versus 528/2789 (18.8%) placebo, z = -1.12, not significant. Mortality cause unknown: 3/1103 (0.3%) Niacin versus 13/2789 (0.5%) placebo, z = -0.88, not significant. Coronary heart disease mortality: 178/1103 (15.9%) Niacin versus 452/2789 (16.2%) placebo, z = -1.23, not significant. Sudden cardiovascular death: 118/1103 (10.5%) Niacin versus 269/2789 (9.6%) placebo, 0.85, not significant. All cancer deaths: 7/1103 (0.6%) Niacin versus 16/2789 (0.6%) placebo, z = 0.19, not significant. Other non

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								cardiovascular death: 17/1103 (1.5%) Niacin versus 26/2789 (0.9%) placebo, z = 1.59, not significant. Non fatal MI: 100/1103 (8.9%) Niacin versus 339/2789 (12.2%) placebo, z = -2.88, significant (P < 0.005). Coronary death or nonfatal MI: 255/1103 (22.8%) Niacin versus 731/2789 (26.2%) placebo, z = -2.23, significant (P < 0.01). Definite pulmonary embolism (fatal or nonfatal): 11/1103 (1.0%) Niacin versus 30/2789 (1.1%) placebo, z = -0.26, not significant. Definite or suspected fatal or nonfatal pulmonary embolism or thrombophlebitis: 44/1103 (3.9%) Niacin versus 91/2789 (3.3%) placebo, z = 1.04, not significant. Fatal or nonfatal stroke or intermittent cerebral ischaemic attack: 86/1103 (7.7%) Niacin versus 271/2789 (9.7%) placebo,

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								z = -1.99, not significant. Any definite or suspected fatal or nonfatal cardiovascular event: 875/1103 (78.2%) Niacin versus 2251/2789 (80.7%) placebo, z = -1.78, not significant. Plasma lipid values: Clofibrate: Mean decrease of cholesterol levels (after correcting for lipid changes in the placebo group) = 16.3 mg/100 ml, mean decrease of 6.5% from baseline level. Mean decrease of triglyceride levels (after correcting for lipid changes in the placebo group) = 1.5 mEq/100 ml, mean decrease of 22.3% from baseline level. Clofibrate: Mean decrease of cholesterol levels (after correcting for lipid changes in the placebo group) = 16.3 mg/dl (0.34 mmol/l), mean decrease of 6.5% from baseline level. Mean decrease of triglyceride

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								levels (after correcting for lipid changes in the placebo group) = 1.5 mEq/100 ml, mean decrease of 22.3% from baseline level. Niacin: Mean decrease of cholesterol levels (after correcting for lipid changes in the placebo group) = 26.2 mg/100 ml (0.67 mmol/l),, mean decrease of 9.9% from baseline level. Mean decrease of triglyceride levels (after correcting for lipid changes in the placebo group) = 1.8 mEq/l, mean decrease of 26.1% from baseline level. Side Effects Clofibrate: Decreased libido or potentia: 150/1065 (14.1%) Clofibrate versus 269/2695 (10.0%) placebo, z = 3.60, P < 0.005. Increase in appetite: 56/1065 (5.3%) Clofibrate versus 84/2695 (3.1%) placebo, z = 3.60, P < 0.005. Niacin: Combination of

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								diarrhoea, nausea, vomiting, black tarry stools, stomach pain: 230/1065 (21.4%) Niacin versus 385/2695 (14.3%) placebo, z = 5.36, P < 0.005. Flushing: 987/1065 (92.0%) Niacin versus 115/2695 (14.3%) placebo, z = 53.42, P < 0.005. Itching of skin: 525/1065 (48.9%) Niacin versus 167/2695 (6.2%) placebo, z = 30.53, P < 0.005. Urticaria: 77/1065 (7.2%) Niacin versus 40/2695 (1.5%) placebo, z = 9.09, P < 0.005. Other type of rash: 212/1065 (19.8%) Niacin versus 159/2695 (5.9%) placebo, z = 12.94, P < 0.005. Pain or burning when urinating: 103/1065 (9.6%) Niacin versus 32/2695 (1.2%) placebo, z = 3.68, P < 0.005. Decrease in appetite:44/1065 (4.1%) Niacin versus 40/2695 (1.5%) placebo, z = 4.81, P < 0.005. Unexpected

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								weight loss: 29/1065 (2.7%) Niacin versus 24/2695 (0.3%) placebo, z = 4.14, P < 0.005. Excessive sweating: 36/1065 (3.4%) Niacin versus 49/2695 (1.8%) placebo, z = 2.95, P < 0.005.
Reference number: 5167 Behar S;Brunner D;Kaplinsky E;Mandelzweig L;Benderly M; Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease: The bezafibrate infarction prevention (BIP) study 2000 102	Randomised Controlled Trial	Inclusion criteria: Men & women (8%) aged 45-74 yrs (mean±SD = 60±7 years, history of MI ≥ 6 months but < 5yrs before enrolment into the study and/or stable angina pectoris confirmed by coronary angiography, &/or radionuclear studies or standard exercise tests. Prior MI: 78%, Prior Angina: 57%, A	Bezafibrate retard 400 mg once daily: 1548 patients.	Placebo: 1542 patients.	Mean length of follow up was 6.2 years.	Primary: Composite of fatal MI, nonfatal MI or sudden death. Secondary: Composite of hospitalisation for unstable angina, percutaneous transluminal coronary angioplasty, coronary artery bypass graft. Cardiac Mortality. Noncardiac mortality. Stroke.	None listed.	Primary outcome: Composite of fatal MI, nonfatal MI or sudden death: 211/1548 (13.6%) Bezafibrate versus 232/1542 (15.0%) Placebo, RR= -9.4%, P = 0.26. Non fatal MI: 150/1548 (9.7%) Bezafibrate versus 172/1542 (15.0%) Placebo, RR= -12.8%, P = 0.18. Fatal MI:18/1548 (1.2%) Bezafibrate versus 17/1542 (1.1%) Placebo, P = 0.87. Sudden death: 43/1548 (2.8%) Bezafibrate versus 43/1542 (2.8%) Placebo, P = 0.98. Secondary outcomes: Composite of hospitalisation for unstable angina, percutaneous

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Circulation		serum lipid profile of: total cholesterol between 180 to 250 mg/dl (4.7 to 6.4 mmol/l), LDL-C ≤ 180 mg/dl (4.7 mmol/l) or (≤ 160 mg/dl (4.1 mmol/l), for patient < 50yrs) (HDL-C ≤ 45 mg/dl (1.16 mmol/l), triglycerides ≤ 300 mg/dl (3.4 mmol/l). Exclusion criteria: Insulin dependent diabetes mellitus, severe heart failure, unstable angina pectoris, hepatic or renal failure, known severity to bezafibrate, or current use of lipid modifying drugs.						transluminal coronary angioplasty, coronary artery bypass graft: 311/1548 (20.1%) Bezafibrate versus 327/1542 (21.2%) Placebo, P = 0.44. Hospitalisation for unstable angina: 76/1548 (4.9%) Bezafibrate versus 82/1542 (5.3%) Placebo, P = 0.61. Percutaneous transluminal coronary angioplasty: 91/1548 (5.9%) Bezafibrate versus 88/1542 (5.7%) Placebo, P = 0.84. Coronary artery bypass graft: 144/1548 (9.3%) Bezafibrate versus 157/1542 (10.2%) Placebo, P = 0.41. Mortality: 161/1548 (10.4%) Bezafibrate versus 152/1542 (9.9%) Placebo, P = 0.62. Cardiac mortality: 95/1548 (6.1%) Bezafibrate versus 157/1542 (5.7%) Placebo, P = 0.61 .Noncardiac mortality: 66/1548 (4.3%) Bezafibrate versus 64/1542 (4.2%) Placebo, P = 0.87. Stoke: 72/1548

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								(4.6%) Bezafibrate versus 77/1542 (5.0%) Placebo, P = 0.36. Ischemic stroke: 59/1548 (3.3%) Bezafibrate versus 69/1542 (4.5%) Placebo, P = 0.38. All outcomes: 522/1548 (33.7%) Bezafibrate versus 559/1542 (36.3%) Placebo, RR = -6.6%, P = 0.14. Plasma lipid levels: cumulative probability of primary endpoints at 6.2 years of follow up: Triglycerides:< 150 mg/dl (1.7 mmol/l) Bezafibrate: 938/1548 (12.6%) Placebo: 901/1542 (13.7%) RR = 7.9%, P = 0.43. ≥150 mg/dl (1.7 mmol/l) Bezafibrate: 603/1548 (16.3%) Placebo: 629/1542 (17.1%) RR = 4.6, P = 0.48. ≥ 175 mg/dl (2.0 mmol/l) Bezafibrate: 407/1548 (15.9%) Placebo: 385/1542 (20.3%) RR = 21.6%, P = 0.07. ≥ 200 mg/dl (2.26 mmol/l) Bezafibrate: 234/1548 (12.0%)

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								Placebo: 225/1542 (19.7%) RR = 39.5%, P = 0.02. HDL-C <35 mg/dl (0.9 mmol/l) & and triglycerides <150 mg/dl (1.7 mmol/l) Bezafibrate: 378/1548 (13.5%) Placebo: 382/1542 (15.5) RR = 12.4%, P = 0.46. ≥ 150 mg/dl (1.7 mmol/l) Bezafibrate: 420/1548 (18.5%) Placebo: 436/1542 (19.4%) RR = 4.5%, P = 0.56. ≥ 175 mg/dl (2.0 mmol/l) Bezafibrate: 294/1548 (17.2%) Placebo: 286/1542 (22.2%) RR = 22.6%, P = 0.09. ≥200 mg/dl (2.26 mmol/l) Bezafibrate: 184/1548 (13.0%) Placebo: 162/1542 (22.3%) RR = 41.8%, P = 0.02. HDL-C ≥35 mg/dl (0.9 mmol/l)& triglycerides < 150 mg/dl (1.7 mmol/l) Bezafibrate: 560/1548 (12.0%) Placebo: 518/1542 (12.2%) RR = 1.6%, P = 0.77. ≥ 150 mg/dl (1.7 mmol/l) Bezafibrate:

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								183/1548 (11.2%) Placebo: 193/1542 (12.2%) RR = 8.5%, P = 0.59. ≥ 175 mg/dl (2.0 mmol/l) Bezafibrate: 113/1548 (12.7%) Placebo: 99/1542 (15.2%) RR = 16.8%, P = 0.45. ≥ 200 mg/dl (2.26 mmol/l) Bezafibrate: 50/1548 (8.2%) Placebo: 63/1542 (17.8%) RR = 35.9%, P = 0.33. Safety: The overall incidence of any adverse event was 69% in both groups, and the frequency of each type adverse event was similar in both groups. 7 patients in the placebo group and 5 patients in the bezafibrate group complained of muscular pains during follow up. Creatine phosphokinase levels exceeding twice the upper normal limit was recorded in 4 patients in the benzafibrate group and 1 patients in the placebo group.

Table 265: What is the effectiveness of adding Vitamin K antagonist (warfarin) versus placebo to improve outcome in patients after an MI?

Grading: 1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number: 3746 Anand SS;Yusuf S; Oral anticoagulant therapy in patients with coronary artery disease: a meta-analysis 1999 282 JAMA	Systematic Review	Established coronary artery disease, MI, unstable angina, CABG surgery.			At least 3 months.		Medical Research Council Canada.	For studies that compared high intensity anticoagulant therapy (INR > 2.8) versus control, at total of 5044 patients received anticoagulants and 5012 were randomised to placebo or controls: Odds Reduction for anticoagulants versus control for total mortality = 22% (95%CI 13% to 31%, P < 0.001). Odds Reduction for anticoagulants versus control for fatal or non fatal MI = 42% (95%CI 34% to 48%, P < 0.001). Odds Reduction for anticoagulants versus control for stroke = 48% (95%CI 33% to 60%, P < 0.001). Major bleeding: relative increase with anticoagulants versus

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								control OR = 6.0 (95%CI 4.4 to 8.2, P < 0.001). For studies that compared moderate intensity anticoagulant therapy (INR > 2-3) versus control, at total of 1365 patients received anticoagulants: Odds Reduction for anticoagulants versus control for total mortality = 18% (95%CI -6% to 31%, P < 0.10). Odds Reduction for anticoagulants versus control for fatal or non-fatal MI = 52% (95%CI 37% to 64%, P < 0.001). Odds Reduction for anticoagulants versus control for stroke = 53% (95%CI 19% to 73%, P = 0.02). Major bleeding: relative increase with anticoagulants versus control OR = 7.0 (95%CI 3.3 to 18, P < 0.001). For studies that compared high / moderate intensity anticoagulant therapy versus aspirin, a total of 1431 patients received anticoagulants and 1440

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								were randomised to placebo or controls. Anticoagulation treatment: no reduction in the combination of death, fatal or non-fatal MI or stroke compared with aspirin. Major bleeding: increased 2.37 times with anticoagulants versus aspirin (95%CI 1.6 to 3.6, P < 0.001).

Grading: 1+ Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Smith P; Long-term anticoagulant treatment after acute myocardial infarction. The Warfarin Re-Infarction Study 1992 2 Annals of Epidemiology	Randomised Controlled Trial	Inclusion criteria: acute MI < 75 years, stratified for chronic beta blocker usage. Exclusion criteria: none listed.	Warfarin, set to a prothrombin time within range of 2.8 to 4.8 nternational Normalised Ratio (INR): 607 patients. Both treatment and control groups advised not	Placebo: 607 patients.	Mean follow-up 37 months.	Primary: Mortality, reinfarction. Secondary: Stroke, bleeding time.	Not listed.	Intention to treat analysis: Mortality: 94/607 treatment deaths (15%) versus 123/607 placebo deaths RR of 24% (95% CI 4% to 44%, P = 0.0267). Reinfarction: treatment 86/607 versus placebo 124/607 RR of 34% (95% CI 19% to 54%, P = 0.0007). Stroke: treatment 19/607 versus placebo 44/607 RR of 55% (95% CI 30% to 30 to 77%, P = 0.0015). Bleeding: major

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
			to take aspirin.					extracranial bleeding occurred in 8/607 treatment group (1.3% treatment versus 0% placebo, P = 0.005), 7/607 bleeding was associated with peptic ulcer, cancer or nonprotocol intake of antiplatelet drugs.
Reference number: 1277 Van Bergen PFMM;Jonker JJC;Van der Meer FJM;Azar AJ;Meeter K;Deckers JW;Colly LP;Tijssen JGP;Van Aken WG;Dunning AJ;Hofman A;Hugenholtz PG;Van der Kooij S;Loeliger EA;Lubsen J;Meade TW;van der Meer J;Miettinen	Randomised Controlled Trial	Inclusion criteria: Hospital survivors of MI within 6 weeks after hospital discharge, cardiac enzyme rises at least twice the normal upper limit, male and female (20%), mean age: 61 years. Exclusion criteria: indication for oral anticoagulant treatment.	Nicoumalone or phenpro-coumon decision made at discretion of cardiologist before randomization: 1700 patients. Prothrombin time in target range of 2.8-4.8 INR. Treatment and placebo group did not take aspirin.	Placebo: 1704 patients.	Mean follow-up: 37 months (range 6-76 months).	Primary: All cause mortality. Secondary: Recurrent MI, cerebro-vascular event, vascular event, major bleeding.	Ciba-Geigy V, Roche BV, Nycomed BV, Praeven-tiefonds NL, NL Thromb-osis Found.	Mortality: 170/1700 treatment deaths (10.0%) versus 189/1704 placebo deaths (11.1%) HR of 0.90 (95% CI 0.73 to 1.11, not significant). Reinfarction: treatment versus placebo: 114/1700 (6.7%) versus 242/1704 (14.2%) patients, HR of 0.47 (95% CI 0.38 to 0.59). Cerebrovascular event: treatment versus placebo: 37/1700 (2.2%) versus 62/1704 (3.6%) patients, HR of 0.60 (95% CI 0.40 to 0.90). Vascular event: treatment versus placebo: 82/1700 (4.8%) versus 135/1704 (7.9%) patients, HR of 0.65 (95% CI 0.55 to 0.76). Major bleeding: treatment versus placebo: 24/1700

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
OS;Mitchell JRA;et a; Effect of long-term oral anticoagulant treatment on mortality and cardiovascular after myocardial infarction 1994 343 Lancet								(1.4%) versus 7/1704 (0.4%) patients, HR of 3.87 (95% CI 2.33 to 6.41).

Table 266: What is the effectiveness of adding Vitamin K antagonist (warfarin) versus aspirin to improve outcome in patients after an MI?

Grading: 1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number: 3746 Anand SS;Yusuf S; Oral anticoagulant therapy in patients with coronary artery disease: a meta-	Systematic Review	Established coronary artery disease, MI, unstable angina, CABG surgery.			At least 3 months		Medical Res. Council Canada.	For studies that compared high intensity anticoagulant therapy (INR > 2.8) versus control, at total of 5044 patients received anticoagulants and 5012 were randomised to placebo or controls: Odds Reduction for anticoagulants versus control for total mortality

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
analysis 1999 282 JAMA								= 22% (95%CI 13% to 31%, P < 0.001). Odds Reduction for anticoagulants versus control for fatal or non fatal MI = 42% (95%CI 34% to 48%, P < 0.001). Odds Reduction for anticoagulants versus control for stroke = 48% (95%CI 33% to 60%, P < 0.001). Major bleeding: relative increase with anticoagulants versus control OR = 6.0 (95%CI 4.4 to 8.2, P < 0.001). For studies that compared moderate intensity anticoagulant therapy (INR > 2-3) versus control, at total of 1365 patients received anticoagulants: Odds Reduction for anticoagulants versus control for total mortality = 18% (95%CI -6% to 31%, P < 0.10). Odds Reduction for anticoagulants versus control for fatal or non-fatal MI = 52% (95%CI 37% to 64%, P < 0.001).

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								Odds Reduction for anticoagulants versus control for stroke = 53% (95%CI 19% to 73%, P = 0.02). Major bleeding: relative increase with anticoagulants versus control OR = 7.0 (95%CI 3.3 to 18, P < 0.001). For studies that compared high / moderate intensity anticoagulant therapy versus aspirin, a total of 1431 patients received anticoagulants and 1440 were randomised to placebo or controls. Anticoagulation treatment: no reduction in the combination of death, fatal or non-fatal MI or stroke compared with aspirin. Major bleeding: increased 2.37 times with anticoagulants versus aspirin (95%CI 1.6 to 3.6, P < 0.001).

Grading: 1+ Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number: 3749 van Es RF;Jonker JJ;Verheugt FW;Deckers JW;Grobbee DE;Antithrombotics i; Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study): a randomised controlled trial. 2002 360 Lancet	Randomised Controlled Trial	Inclusion criteria: acute MI (88%) or unstable angina within preceding 8 weeks, mean age 61years, male and women (23%). Exclusion criteria: planned revascularization, recent intracoronary stenting, thrombocytopenia, anaemia, history of stroke, established indications for treatment with oral anticoagulants, contraindications for the study drugs, serious comorbidity, increased risk of bleeding, inability to adhere to	Oral anti-coagulants (phenprocoumon or acenocoumon with a target INR of 3.0 to 4.0), 325 patients. Oral anti-coagulants (phenprocoumon or acenocoumon with a target INR of 2.0 to 2.5) plus aspirin 100 mg daily, 332 patients.	Aspirin 100 mg daily, 336 patients.	Mean follow-up ≤ 26 months.	Primary: Composite of death, nonfatal MI or stroke. Secondary: All-cause mortality, bleeding.	Praeventiefonds NL, NL National Health Ins. Fund Council, NL Heart Found.	Composite of death, nonfatal MI or stroke: Coumadin 17/325 (5%) versus aspirin 31/336 (9%), HR = 0.55 (95%CI 0.3 to 1.00) Coumadin plus aspirin 16/332 (5%) versus versus aspirin 31/336 (9%), HR = 0.50 (95%CI 0.27 to 0.92). All-cause mortality: Coumadin 4/325 (1%) versus aspirin 15/336 (4%), HR = 0.28 (95%CI 0.09 to 0.82) Coumadin plus aspirin 9/332 (3%) versus versus aspirin 15/336 (4%), HR = 0.60 (95%CI 0.26 to 1.36). Vascular death, MI or stroke: Coumadin 17/325 (5%) versus aspirin 28/336 (8%), HR = 0.61 (95%CI 0.33 to 1.12) Coumadin plus aspirin 15/325 (5%) versus aspirin 28/336 (8%), HR = 0.52 (95%CI 0.28 to 0.98). Vascular death: Coumadin 4/325 (1%) versus aspirin 12/336 (4%), HR = 0.34 (95%CI 0.11 to 1.06) Coumadin

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
		protocol or give written consent.						plus aspirin 15/325 (5%) versus aspirin 12/336 (4%), HR = 0.66 (95%CI 0.27 to 1.62). Myocardial infarction: Coumadin 13/325 (4%) versus aspirin 14/336 (4%), HR = 0.94 (95%CI 0.44 to 2.00) Coumadin plus aspirin 10/325 (3%) versus aspirin 14/336 (4%), HR = 0.70 (95%CI 0.31 to 1.58). Revascularization (CABG/PTCA): Coumadin 34/325 (10%) versus aspirin 39/336 (14%), HR = 0.90 (95%CI 0.58 to 1.39) Coumadin plus aspirin 32/325 (10%) versus aspirin 39/336 (14%), HR = 0.83 (95%CI 0.53 to 1.29). All stroke: Coumadin 0/325 versus aspirin 5/336 (1%), Coumadin plus aspirin 1/325 (0.3%) versus aspirin 5/336 (1%), HR = 0.20 (95%CI 0.02 to 1.7). Major bleeding (including intracranial): Coumadin 3/325 (1%) versus aspirin

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								3/336 (1%), HR = 1.03 (95%CI 0.21 to 5.08) Coumadin plus aspirin 7/332 (2%) versus versus aspirin 3/336 (1%), HR = 2.35 (95%CI 0.61 to 9.10). Minor bleeding: Coumadin 26/325 (8%) versus aspirin 16/336 (5%), HR = 1.68 (95%CI 0.92 to 3.07) Coumadin plus aspirin 50/332 (15%) versus versus aspirin 16/336 (5%), HR = 3.13 (95%CI 1.82 to 5.37).

Table 267: What is the effectiveness of adding vitamin K antagonist (warfarin) plus aspirin versus aspirin to improve outcome in patients after MI?

Grading: 1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number: 3842 Chen ZM;Pan HC;Chen YP;Peto R;Collins R; Early intravenous then oral metoprolol	Randomised Controlled Trial	Inclusion criteria: Post MI recruited within 24 h of suspected acute MI onset (ST elevation (87%), left bundle block (6%), or ST depression	Immediately: 5 mg metoprolol iv over 2-3 min, if heart rate was above 50 bpm and systolic blood pressure above 90 mm	Immediately: placebo iv over 2-3 min, then second and third iv. 15 min after these iv doses, placebo tablet. Subsequently: placebo once daily for up to 4 weeks (or, if earlier, until hospital discharge or death). 22 923 patients.	Up to 4 weeks.	Primary: Composite of death, reinfarction, or stroke. Death from any cause. Secondary: Re-infarction, ventricular fibrillation, cardiogenic	Sanofi-Aventis, Bristol-Myers Squibb, Astra-Zeneca, MRC UK, BHF, Cancer Research	Primary: Composite of death, reinfarction, or stroke: 2166/22929 (9.4%) treatment versus 2261/22923 (9.9%) placebo, OR of 0.96 (95% CI 0.90 to 1.01, P = 0.10). Death from any cause: 1774/22929 (7.7%) treatment versus 1797/22923 (7.8%)

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
45852 patients with acute myocardial infarction: randomised placebo-controlled trial 2005 366		(7%)). Mean age ± SD = 61 ± 11 years, male and female (28%). Patients with hypertension: 8%.	Hg, then second 5 mg metoprolol iv administered, and similarly for the third ampule. 15 min after these iv doses, 50 mg metoprolol tablet. Subsequently: 200 mg metoprolol slow release once daily for up to 4 weeks (or, if earlier, until hospital discharge or death). 22 929 patients.			shock, other cardiac arrest.	UK.	placebo, OR of 0.99 (95% CI 0.92 to 1.05, P = 0.69). Arrhythmia: 388/22929 (1.7%) treatment versus 498/22923 (2.2%) placebo, OR of 0.78 (95% CI 0.68 to 0.89, P = 0.0002). Shock: 496/22929 (2.0%) treatment versus 384/22923 (1.7%) placebo, OR of 1.29 (95% CI 1.13 to 1.47, P = 0.0002). Neither: 890/22929 (3.9%) treatment versus 915/22923 (4.0%) placebo, OR of 0.97 (95% CI 0.89 to 1.07, P = 0.55). Secondary: Reinfarction: Died, any cause: 206/22929 (0.9%) treatment versus 226/22923 (1.0%) placebo, OR of 0.91 (95% CI 0.75 to 1.10, P = 0.33). Survived: 258/22929 (1.1%) treatment versus 342/22923 (1.5%) placebo, OR of 0.75 (95% CI 0.64 to 0.88, P = 0.0005). Any: 464/22929

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								(2.0%) treatment versus 568/22923 (2.5%) placebo, OR of 0.82 (95% CI 0.72 to 0.89, P = 0.001). Ventricular fibrillation: Died, any cause: 492/22929 (2.1%) treatment versus 600/22923 (2.6%) placebo, OR of 0.82 (95% CI 0.73 to 0.92, P = 0.001). Survived: 89/22929 (0.4%) treatment versus 98/22923 (0.4%) placebo, OR of 0.91 (95% CI 0.68 to 1.12, P = 0.51). Any: 581/22929 (2.5%) treatment versus 698/22923 (3.0%) placebo, OR of 0.83 (95% CI 0.75 to 0.93, P = 0.001). Cardiogenic shock: Died, any cause: 755/22929 (3.3%) treatment versus 628/22923 (2.7%) placebo, OR of 1.20 (95% CI 1.08 to 1.34, P = 0.0006). Survived: 386/22929 (1.7%) treatment versus 257/22923 (1.1%) placebo, OR of 1.50 (95% CI 1.28 to 1.75, P <

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								0.0001). Any: 1141/22929 (5.0%) treatment versus 885/22923 (3.9%) placebo, OR of 1.30 (95% CI 1.19 to 1.41, P < 0.0001). Other cardiac arrest: Died, any cause: 624/22929 (2.7%) treatment versus 593/22923 (2.6%) placebo, OR of 1.05 (95% CI 0.94 to 1.18, P = 0.38). Survived: 61/22929 (0.3%) treatment versus 39/22923 (0.2%) placebo, OR of 1.55 (95% CI 0.1.05 to 2.30, P = 0.03). Any: 685/22929 (3.0%) treatment versus 632/22923 (2.8%) placebo, OR of 0.83 (95% CI 0.97 to 1.28, P = 0.11). Safety: Bradycardia: treatment 5.4% versus placebo 2.2%, OR = 2.41(95% CI 2.19 to 2.65, P = 0.0001).

Grading: 1+ Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number: 3728 CarsADD REFERENCE Randomised double-blind trial of fixed low-dose warfarin with aspirin after myocardial infarction. Coumadin Aspirin Reinfarction Study (CARS) Investigators. 1997 350 Lancet	Randomised Controlled Trial	Inclusion criteria 3-21 days post MI, men and women (approx 22%), aged 21 to 85 years, mean age 59 years. Exclusion criteria: CHF, circulatory shock, unresponsive angina, serious ventricular arrhythmias 24 h before randomization, history bleeding, stroke, previous intracranial haemorrhage, co morbidity with life expectancy < 4 years, liver disease, renal disease, anaemia, thrombocytope	Warfarin 3 mg plus aspirin 80 mg: 3382 patients. Warfarin 1 mg plus aspirin 80 mg: 2028	Aspirin 160 mg: 3393 patients.	Median follow-up 14 months, maximum 33 months.	Primary: Composite of reinfarction, nonfatal ischemic stroke or CV death. Secondary: All cause mortality, non fatal MI, ischemic stroke, CV death, spontaneous major haemorrhage.	Du Pont Merck Pharm. Co.	Primary endpoint: Aspirin 308/3393 versus 3 mg warfarin plus aspirin 295/3382., RR = 0.95 (95% CI 0.81 to 1.12, P = 0.57). At 6 months median (IQR) INR = 1.02 (0.98-1.06) for aspirin and INR = 1.19 (1.08-1.44) for 3 mg warfarin plus aspirin. Aspirin 308/3393 versus 1 mg warfarin plus aspirin 237/2028, RR = 1.03 (95% CI 0.87 to 1.11, P = 0.74). At 6 months median (IQR) INR = 1.04 (1.00-1.09) for 1 mg warfarin plus aspirin. Secondary endpoints: no significant difference in 3 treatment group except: Spontaneous major haemorrhage: Aspirin 30/3393 versus 3 mg warfarin plus aspirin 52/3382. I year life estimates 0.74% (95% CI 0.43 to 1.11) versus 3 mg warfarin plus aspirin 1.4% (95% CI 0.94 to 1.8, P = 0.014 log rank on follow-

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
		nia, haematuria, uncontrolled hypertension, scheduled CABG, patients requiring long term warfarin therapy for thromboembolism.						up) 1 mg warfarin plus aspirin 26/2028, not significant compared with aspirin group.
Reference number: 3727 Fiore LD;Ezekowitz MD;Brophy MT;Lu D;Sacco J;Peduzzi P;Combination H; Department of Veterans Affairs Cooperative Studies Program Clinical Trial comparing combined warfarin and aspirin with aspirin alone	Randomised Controlled Trial	Inclusion criteria: post MI within previous 14 days, male and female (2%), mean age 64 years. Exclusion criteria: comorbidity giving reduced life expectancy 2 years, ongoing bleeding / bleeding risk, entered into competing trial, refusal to compete, incompetent to give consent, died prior to	Aspirin 81 mg daily plus warfarin INR 1.5 to 2.5 IU: 2522 patients.	Aspirin 162 mg daily: 2537 patients.				

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
in survivors of acute myocardial infarction: primary results of the CHAMP study. 2002 105 Circulation		randomization, alcohol / drug dependency, hypersensitivity to aspirin / warfarin,						
Reference number: 2729 Hurlen M;Abdelnoor M;Smith P;Erikssen J;Arnesen H; Warfarin, aspirin, or both after myocardial infarction. 2002 347 New England Journal of Medicine	Randomised Controlled Trial	Inclusion criteria: hospitalized for acute MI, < 75 years, mean age 60 years, male and female (approx. 26%). Exclusion criteria: History of serious spontaneous bleeding on any of study drugs, heamorrhagic diathesis, any other contraindications.	Warfarin with a target INR 2.8 to 4.2, 1218 patients. Warfarin with a target INR 2.0 to 2.5 plus aspirin 75 mg daily, 1208 patients.	Aspirin, 160 mg daily, 1206 patients.	Mean follow-up: 1445 days (about 4 years).	Primary: Composite of death, nonfatal MI or thrombo-embolic stroke. Secondary: death, nonfatal MI, thrombo-embolic stroke, bleeding.	Norwegian Council on CV Disease.	Composite of death, nonfatal MI or thrombo-embolic stroke: Both warfarin groups (warfarin alone 16.7%, warfarin + aspirin 15.0%) lower rates of the first composite event compared with aspirin alone group 20%: aspirin 241/1206 (20.0%) warfarin 203/1216 (16.0%) warfarin + aspirin 81/1208 (15.0%). RR warfarin + aspirin (15%) versus aspirin (20%) = 0.71 (95%CI 0.60 to 0.83, P = 0.001). RR warfarin (16.7%) versus aspirin (20%) = 0.81 (95%CI 0.69 to 0.95, P = 0.03). RR warfarin plus aspirin (15%) versus warfarin (16.7%) = 0.87 (95%CI 0.73 to 1.03, P = 0.18).

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								For total cumulative events (death, nonfatal MI or thromboembolic stroke): aspirin 295/1206 (24.5%) warfarin 236/1216 (19.4%) warfarin + aspirin 210/1208 (17.4%) RR warfarin + aspirin versus aspirin = 0.65 (95%CI 0.53 to 0.80, P < 0.001). RR warfarin versus aspirin = 0.75 (95%CI 0.61 to 0.91, P = 0.003). RR warfarin plus aspirin versus warfarin = 0.87 (95%CI 0.71 to 1.08, P = 0.20). Reinfarction: aspirin 117/1206 (9.7%) warfarin 90/1216 (7.4%) warfarin + aspirin 69/1208 (5.7%). RR warfarin + aspirin versus aspirin = 0.56 (95%CI 0.41 to 0.78, P < 0.001). RR warfarin versus aspirin = 0.74 (95%CI 0.55 to 0.98, P = 0.03). Thromboembolic stroke: aspirin 32/1206 (2.7%) warfarin 17/1216 (1.4%) warfarin + aspirin 17/1208 (1.4%). RR

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								warfarin + aspirin versus aspirin = 0.52 (95%CI 0.28 to 098, P = 0.03). RR warfarin versus aspirin = 0.52 (95%CI 0.28 to 0.97, P = 0.03). Death: aspirin 92/1206 (24.5%) warfarin 96/1216 (19.4%) warfarin + aspirin 95/1208 (17.4%). The three groups did not differ for overall mortality. Bleeding: Both warfarin groups had higher rates for nonfatal bleeding compared with aspirin alone group Warfarin + aspirin 2% versus aspirin 0.7% Warfarin 3% versus aspirin 0.7%. Episodes of major, nonfatal bleeding were observed in 0.62% of patients per treatment year in both groups receiving warfarin compared with 0.17% patients receiving aspirin (P < 0.001).

Table 268: What is the effectiveness of adding eplerenone versus placebo to improve outcome in patients after MI?

Grading 1++ High quality meta analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number: 3804 Pitt B;Remme W;Zannad F;Neaton J;Martinez F;Roniker B;Bittman R;Hurley S;Kleiman J;Gatlin M; Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial 2003 348 New England Journal of Medicine pgs 1309 1321	Randomised Controlled Trial	Inclusion criteria: Post MI with LV dysfunction and heart failure. LV dysfunction documented as LV ejection fraction ≤ 40% on echocardiography, radionuclide angiography, or angiography of the left ventricle after the index acute MI, mean ejection fraction; 33%. Heart failure as documented by the presence of pulmonary rates, chest radiography showing pulmonary venous congestion, or the presence of	Initially 25 mg per day for four weeks, then titrated up to 50 mg. Mean dose equivalent of study medication was 42.6 mg. If serum potassium concentration was > 5.5 mmol per litre, dose of study drug was reduced or temporarily discontinued until serum potassium concentration fell below 5.5 mmol per litre. Randomised 3-14 days	Placebo: 3313 patients.	Mean follow-up 16 months (range 0 to 33).	Primary: Death from any cause. Death from CV causes or first hospitalisation for a CV event, including heart failure, recurrent acute MI, stroke, or ventricular arrhythmia. Secondary: Death from any cause or any hospitalisation (number of patients). Death from CV causes (number of patients). Sudden death from cardiac causes. Acute MI death. Heart failure death. Stroke death. Other death. Any hospitalisation (no. of patients). Hospitalisation	Pharmacia.	Primary: Death from any cause: 478/3319 treatment deaths versus 554/3313 placebo deaths, RR of 0.85 (95% CI 0.75 to 0.96, P = 0.008). Death from CV causes or first hospitalisation for a CV event: 885/3319 treatment deaths or events versus 554/3313 placebo deaths or events, RR of 0.87 (95% CI 0.79 to 0.95, P = 0.002). Secondary: Death from any cause or any hospitalisation (number of patients): 1730/3319 treatment versus 1829/3313 placebo, RR of 0.92 (95% CI 0.86 to 0.98, P = 0.02). Death from CV causes: (number of patients): 407/3319 treatment versus 483/3313 placebo, RR of 0.83 (95% CI 0.72 to 0.94, P = 0.005). Sudden death from cardiac causes: 162/3319 treatment

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Apr 3		a third heart sound (90%). Diabetic Patients: Documented LV dysfunction, however, symptoms did not have to be demonstrated, since diabetics have increased risk of CV events similar to non-diabetic patients with symptoms of heart failure (32%). Patients with hypertension: 61%. Mean age 64 years, male and female (29%). Patients received optimal medical therapy, which could include ACE inhibitors or ARBs (87%), diuretics	post infarction: 3319 patients.			for CV events (no. of patients). Acute MI hospitalisations (no. of patients). Heart failure hospitalisations (no. of patients). Stroke hospitalisations (no. of patients). Ventricular arrhythmia hospitalisations (no. of patients). Any hospitalisation (no. of episodes). Hospitalisation for CV events (no. of episodes). Acute MI (no. of episodes). Heart failure (no. of episodes). Stroke (no. of episodes). Ventricular arrhythmia (no. of episodes).		versus 201/3313 placebo, RR of 0.79 (95% CI 0.64 to 0.97, P = 0.03). Acute MI death: 78/3319 treatment versus 94/3313 placebo, RR of 0.82 (95% CI 0.61 to 1.10, P = 0.19). Heart failure death: 104/3319 treatment versus 127/3313 placebo, RR of 0.80 (95% CI 0.62 to 1.04, P = 0.10). Stroke death: 26/3319 treatment versus 28/3313 placebo, RR of 0.91 (95% CI 0.53 to 1.55, P = 0.73). Other death: 37/3319 treatment versus 33/3313 placebo, RR of 0.91 (95% CI 0.81 to 1.01, P = 0.99). Any hospitalisation (no. of patients): 1493/3319 treatment versus 1526/3313 placebo, RR of 0.95 (95% CI 0.89 to 1.02, P = 0.20). Hospitalisation for CV events (no. of patients): 606/3319 treatment versus 649/3313 placebo, RR of 0.91 (95% CI 0.81 to 1.01, P = 0.09). Acute MI hospitalisations

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
		(60%) and β blockers (75%), aspirin (88%) as well as coronary reperfusion. Exclusion criteria: Use of potassium-sparing diuretics, serum creatinine concentration ≥ 2.5 mg per decilitre (220 µmol per litre), and a serum potassium concentration was > 5.0 mmol per litre before randomization.						(no. of patients): 224/3319 treatment versus 229/3313 placebo, RR of 0.97 (95% CI 0.85 to 0.99, P = 0.71). Heart failure hospitalisations (no. of patients): 345/3319 treatment versus 391/3313 placebo, RR of 0.85 (95% CI 0.74 to 0.99, P = 0.03). Stroke hospitalisations (no. of patients): 70/3319 treatment versus 51/3313 placebo, RR of 0.95 (95% CI 0.65 to 1.39, P = 0.79). Ventricular arrhythmia hospitalisations (no. of patients): 52/3319 treatment versus 54/3313 placebo, RR of 0.95 (95% CI 0.65 to 1.39, P = 0.79). Any hospitalisation (no. of episodes): 2815/3319 treatment versus 29843/3313 placebo, ratio of 0.94 (P = 0.12). Hospitalisation for CV events (no. of episodes): 876/3319 treatment versus 1004/3313 placebo, RR of 0.87 (P =

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								0.12). Acute MI (no. of episodes): 268/3319 treatment versus 269/3313 placebo, ratio of 0.99 (P = 0.96). Heart failure (no. of episodes): 477/3319 treatment versus 618/3313 placebo, ratio of 0.77 (P = 0.002). Stroke (no. of episodes): 73/3319 treatment versus 54/3313 placebo, ratio of 0.92 (P = 0.11). Ventricular arrhythmia (no. of episodes): 58/3319 treatment versus 63/3313 placebo, ratio of 0.92 (P = 0.69). Safety: Blood pressure: After week 1, the mean systolic and diastolic blood pressure increased in both groups from baseline to each time point throughout the remainder of trial. The magnitude in these increases in the eplerenone group was

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								significantly smaller than in placebo group. At 1 year, mean BP increased by 8/4 mm Hg in the placebo group and by 5/3mm Hg in the eplerenone (P < 0.01). Serum creatinine concentration: At 1 year: serum creatinine concentration increased by 0.02 mg per decilitre (1.8 µmol per litre) in the placebo group and by 0.06 mg per decilitre (5.3 µmol per litre) in the eplerenone group (P < 0.001). Potassium levels: At 1 year: potassium levels increased by 0.2 mmol per litre in the placebo group and by 0.3 mmol per litre (5.3 µmol per litre) in the eplerenone group (P < 0.001). Serious hyperkalemia (serum potassium concentrations ≥ 6.0 mmol per litre) occurred in 5.5% of patients in eplerenone group, as compared with 3.9% in

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								placebo group (P < 0.002). For those patients with serious hyperkalemia, the incidence of greater elevation in potassium level was similar in the eplerenone group (0.6% with concentrations ≥ 7 µmol per litre and 0.2% with concentrations ≥ 8 µmol per litre) and in the placebo group (0.5% with concentrations ≥ 7 µmol per litre and 0.1% with concentrations ≥ 8 µmol per litre).15 patients in the eplerenone group and 3 patients in placebo group were hospitalized for condition, 1 death in placebo group was attributed to it. For patients with baseline creatinine clearance < 50 ml per minute, the incidence of serious hyperkalemia was 10.1% in eplerenone group versus 5.9% in placebo group (P = 0.006). For patients with baseline

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								creatinine clearance > 50 ml per minute, the incidence of serious hyperkalemia was 4.6% in eplerenone group versus 3.5% in placebo group (P = 0.04). Significant averse events: eplerenone versus placebo: Dyspnoea: treatment 243/3307 (7.3%) versus placebo 307/3301 (9.3%) (P = 0.004). Hyperkalemia: treatment 113/3307 (3.4%) versus placebo 66/3301 (2.0%) (P < 0.001). Serious hyperkalemia (serum potassium ≥ 6 mmol per litre): treatment 180/3251 (5.5%) versus placebo 126/3251 (3.9%) (P = 0.002). Hypokalemia: treatment 15/3307 (0.5%) versus placebo 49/3301 (1.5%) (P < 0.001). Serious hypokalemia: (serum potassium < 3.5 mmol per litre): treatment 273/3251 (8.4%) versus placebo 424/3251 (2.0%) (P <

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								0.001). Hypoglycemia: treatment 20/3307 (0.6%) versus placebo 35/3301 (1.1%) (P = 0.04). Gastrointestinal disorder: treatment 659/3307 (19.9%) versus placebo 583/3301 (17.7%) (P = 0.02). No significant different between treatment and placebo reported for the following: ≥ 1 event, CV disorder, cough, pneumonia, metabolic or nutritional disorder, hyperuricemia, neoplasm, urinary tract disorder, disorder of skin or appendages, musculoskeletal disorder, nervous system disorder, psychiatric disorder, endocrine disorder, impotence and gynecomastia (men), breast pain (woman).

Grading 1+: Well conducted analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number: 5108 Barnes BJ;Howard PA; Eplerenone: a selective aldosterone receptor antagonist for patients with heart failure. 2005 39 Annals of Pharmacotherapy	Randomised Controlled Trial	Inclusion criteria: Post MI patients recruited during hospitalization for enzyme confirmed MI. CharacteristicsAged 25 to 75 years. Mean age ± SD = 58 ± 10 years. Male and female (20%). Exclusion criteria: Ongoing cardiogenic shock or symptomatic	Diltiazem, 60 mg four times daily, 1232 patients.	Placebo: 1234 patients.	Patients were for followed for a minimum of 12 months, mean follow-up 25 months, maximum of 54 months.	Mortality. Death from cardiac causes. Nonfatal MI.	Tanabe Seiykaku Co Ltd, Marion Laboratories.	Total mortality: 166/1232 (13.5%) treatment versus 167/1234 (13.5%) placebo, HR of 1.02 (95% CI 0.82 to 1.27, not significant). Death from cardiac causes: 127/1232 (10.3%) treatment versus 124/1234 (10.0%) placebo. Nonfatal MI: 103/1232 (8.4%) treatment versus 110/1234 (8.9%) placebo. Combination of death from cardiac causes and nonfatal MI: 202/1232 (16.4%) treatment versus 226/1234 (18.3%) placebo, HR of 1.02 (95% CI 0.90 to 1.08, not significant). Interactions: The presence or absence of pulmonary congestion was found to have a significant interaction with (P < 0.01, two sided P value = 0.0042) with treatment assignment. A similar interaction was

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								noted between pulmonary congestion and diltiazem with death from cardiac causes as the endpoint (two sided P value = 0.0042). In 1909 patients without pulmonary congestion, diltiazem was associated with a reduced number of cardiac events (death from cardiac causes, or nonfatal MI): HR = 0.77 (95% CI 0.61 to 0.98). In 490 patients with pulmonary congestion, diltiazem was associated with an increased number of cardiac events: HR = 1.41 (95% CI 1.01 to 1.96).

Table 269: Are there stable patients after an MI who a) benefit prognostically from revascularisation b) those who do not benefit prognostically?

Grading 1++ High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number: 3081 National	Guideline							

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Institute for Clinical Excellence; Guidance on coronary artery stents in the treatment of ischaemic heart disease 2003 National Institute for Health and Clinical Excellence								
Reference number: 3083 Pignone M;Rihal C;Bazian Ltd.; Secondary prevention of ischaemic cardiac events: What are the effects of surgical treatments? 2002 Clinic	Systematic Review							CABG versus medical treatment alone: CABG reduced deaths at 5 and 10 years, death at 5 years: RR 0.61, 95% CI 0.48 to 0.77; death at 10 years: RR 0.83, 95% CI 0.70 to 0.98. Effects in people with reduced versus normal LV dysfunction: Relative benefits were similar in people with normal versus reduced LV dysfunction (normal LV dysfunction: death OR, 0.61, 95% CI 0.46 to 0.81

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
al Evidence 2005								versus reduced LV dysfunction: death OR 0.59, 95% CI 0.39 to 0.91). It was noted that the absolute benefit of CABG was greater in the LV dysfunction group because the baseline risk of death was greater. Effects in people with different numbers of diseased vessels: statistically lower mortality for CABG versus medical treatment in three vessel and left main stem disease (RR with single vessel disease 0.85, 95% CI 0.22 to 1.33, two vessel disease 0.84, 95% CI 0.54 to 1.32, three vessel disease 0.58, 95% CI 0.42 to 0.80, left main stem 0.32, 95% CI 0.15 to 1.70). PTCA versus medical treatment alone: PTCA versus medical treatment improved angina compared with medical treatment alone (RR 0.70, 95% CI 0.50 to 0.98), but was associated with a

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								higher rate of coronary artery bypass grafting (RR 1.59, 95% CI 1.09 to 2.32). CABG or PTCA versus medical treatment: Effects in asymptomatic people: Revascularisation versus medical treatment alone reduction of death or MI at 2 years was 4.7% with revascularization versus 8.8% with symptom guided treatment versus 12.1% with symptom plus electrocardiogram guided treatment.

Grading 1+ Well conducted meta-analyses, systematic reviews of RCTs or RCTs with a low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number: 3077 Joint Working Group on Coronary Angioplasty of the British Cardiac Society.;Britis	Randomised Controlled Trial	Post MI patients: 3 age groups: middle aged (45-65 years), old (66-75 years), very old (> 75 years).	Hospital-based cardiac rehabilita-tion (Hos-CR), home-based cardiac rehabilita-tion (Home-	3 interventions in each age group.	14 months.	Total work capacity (TWC), HRQoL.	National Research Council Florence Un. Reg. Gov. Tuscany Italy.	TWC improved in the Hosp-CR and Home-CR groups but not in the controls. Treatment-time interactions showed a greater effect of both interventions compared with controls in middle aged (P = 0.002) and old patients (P < 0.001) but

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
h Cardiovascular Intervention Society.; Coronary angioplasty : guidelines for good practice and training 2000 83 Heart			CR), no cardiac rehabilita-tion (no CR).					not in very old patients (P = 0.143). In middle aged and old patients, HRQoL improved significantly over the study period regardless of treatment assignment, whereas in very old patients, HRQoL improved with both Hosp-CR and Home-CR treatment (P = 0.013 and P < 0.035, respectively) but not with no CR (P = 0.079).

Grading 1- Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number: 3123 Eagle KA;Guyton RA;Davidoff R;Edwards FH;Ewy GA;Gardner TJ;Hart JC;Herrmann HC;Hillis LD;Hutter AM;Lytle	Systematic Review							

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
BW;Marlow RA;Nugent WC;Orszulak TA; ACC/AHA 2004 Guideline Update for Coronary Artery Bypass Graft Surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft S 2004 American College of Cardiology website								

Table 270: What is the effectiveness of comprehensive cardiac rehabilitation versus standard care with no cardiac rehabilitation to improve outcomes in patients after MI?

Grading 1++ High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number: 710 Beswick AD;Rees K;Griebsch I;Taylor FC;Burke M;West RR;Victory J;Brown J;Taylor RS;Ebrahim S; Provision, uptake and cost of cardiac rehabilitation programmes: Improving services to under-represented groups 2004 8 Health Technology Assessment (Winchester,	Systematic Review						DOH	All studies reported that there was benefit of intervention to improve uptake (healthcare led-professional interventions at the patient level, trained lay volunteers, coordination of referral post-discharge care at the service level, written or aural motivational communications). This may be indicative of publication bias. For adherence, the authors of the HTA stated that they found few studies of sufficient quality to make specific recommendations of methods to improve adherence to cardiac rehabilitation. Their opinion was that the most promising approach was the use of self management techniques based around individualised

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
England)								assessment, problem solving, goal setting and follow-up.
Reference number: 1358 Brown A;Taylor R;Noorani H;Stone J;Skidmore B; Exercise-based cardiac rehabilitation programs for coronary artery disease: a systematic clinical and economic review 2003 34 Ottawa	Systematic Review							Cardiac rehabilitation programs that include exercise, both exercise-only (EX CR) and comprehensive care programs (CCR), have beneficial effects on cardiac mortality (RR: 0.73, 95% CI 0.56 to 0.96 and 0.80, 95% CI 0.65 to 0.99, respectively). However, with respect to total mortality, exercise-only programs show a statistically significant reduction, whereas the comprehensive care programs showed a trend in that direction (RR: 0.76, 95% CI 0.59-0.98 and 0.87, 95% CI 0.74-1.04, respectively). There was no effect with either intervention on non-fatal MI, CABG, or PTCA. For HRQoL, few studies showed intervention improved HRQoL compared with usual

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								care.
Reference number: 1360 Joliffe JA; Exercise-based rehabilitation for coronary heart disease 2003 Cochrane Library	Systematic Review							For the exercise only intervention, the pooled effect estimate for total mortality showed a 27% reduction in all cause mortality (random effects model OR 0.73 (0.54-0.98)). Similarly, comprehensive cardiac rehabilitation reduced all cause mortality compared to usual care, but to a lesser, and non-significant, degree (13% OR 0.87 (0.71-1.05)). Total cardiac mortality was reduced by 31% (random effects model OR 0.69 (0.51-0.94)) and 26% (random effects model OR 0.74 (0.57-0.96)) in the exercise only and comprehensive cardiac rehabilitation intervention groups respectively when compared to usual care. There was no significant

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								effect of either intervention on sudden cardiac deaths, non-fatal reinfarctions, or revascularization. Overall for HRQoL, in the RCTs with an exercise only intervention, there were small changes or no change in HRQoL measures. In the RCTs examining comprehensive cardiac rehabilitation intervention, most showed small and variable effects in HRQoL measures.

Grading 1+ Well conducted meta-analyses, systematic reviews of RCTs or RCTs with a low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number: 2948 Reference number 2948 Holmback AM;Sawe U;Fagher B; Training after	Randomised Controlled Trial	All acute MI patients under 65 years and attending the Hospital Post-MI Clinic. Median age: 55 years. Total age range (years):	It started weeks post MI and patients trained over a 12 week period for at least 45 min (effective	Received regular medical care with no special emphasis on exercise.	1 year post MI.	Maximal Physical Capacity (MPC) (after 1 year testing). Mean exercise capacity. Return to work.	The research was supported by Malmohus county council.	MPC in intervention group: increased non significantly by an average of 10% or 12W (95% CI: 2 to 22W) over baseline. MPC in control group: increased non significantly by an average of 2% or 1W (CI: -

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
myocardial infarction: lack of long-term effects on physical capacity and psychological variables 1994 75 Arch Phys Med Rehabil		Intervention group: 38-65, Control group: 43-63. Gender: nearly all males.	time) twice a week with interval training involving large muscle groups.				No commercial party had a direct financial interest in the results of the research.	8 to 10W) over baseline. Intervention group difference: not significant. Mean exercise capacity: Interventon group: 172W (SD 33). Control group: 144W (SD 29). Return to work: After 1 year follow up median time of work return: not significant. Interventon group: 16 weeks (interquartile range 12 to 30 weeks). Control group: 12 weeks (interquartile range 9 to 23 weeks). Number of patients that resumed at least part-time work: Intervention group: 23/30 (77%), Control group: 27/32 (84%). There was a weak tendency of earlier return to work in those subjects who were least fit.

Grading 1- Meta-analyses, systematic reviews of RCTs or RCTs with a low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number: 2950	Randomised Controlled	Post MI patients ≥ 65 years.	Supervised outpatient	Exercise training versus usual care.	12 months.	Self-motivation, outcome	Nat. Asn. Heart &	No significant difference for: self-motivation,

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Stahle A;Lindquist I;Mattsson E; Important factors for physical activity among elderly patients one year after an acute myocardial infarction 2000 32 Scand J Rehabil Med	Trial		training program (50 min, 3x per week for 3 months).			expectation, efficacy expectation, physical activity.	Lung Foundn Swedish Heart & Lung Foundn Swedish Foundn Health Care Sciences Allergy Re-search King Gustaf V & Queen Victoria Foundn Swedish Nat. Center for Research in Sports.	outcome expectation, efficacy expectation. Reported physical activity at 12 months was significantly higher in the intervention group compared with controls (P < 0.0001). A multiple regression analysis between level of activity at 12 months and age, gender, BMI, support, SMI, activity level before admission, and group (intervention and controls) found that group and activity before admission were the only variables that predicted high activity at 12 months (RR = 0.74, P < 0.001).

Grading 2+ Well conducted case control or cohort studies with a low risk of confounding, bias or chance and a

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number: 1020	Cohort	Post MI patients 36 good	Exercise program: 3x	Exercise program for 12 months & no	12 month then follow	Cardiorespiratory fitness,	Not listed.	At 12 months, the treatment group had

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Dugmore LD;Tipson RJ;Phillips MH;Flint EJ;Stentiford NH;Bone MF;ittler WA; Changes in cardiorespiratory fitness, psychological wellbeing, quality of life, and vocational status following a 12 month cardiac exercise rehabilitation programme 1999 81 Heart (British Cardiac Society)		prognosis patients & their matched controls (ages 51.6±1.28 & 52.9±1.35 years, respectively). 26 poor prognosis patients & their matched controls (ages 59.6±1.4 & 59.5±1.36 years, respectively).	per week for a 12 month period- aerobic & local muscular endurance training. Each patient's training program was individually designed based on results of regular exercise tests.	exercise program.	up at 5 years.	psychoogical profiles, quality of life scores, mortality, full time employment return, non-fatal reinfarction.		significant improvements compared with matched controls in cardiorespiratory fitness (P < 0.01-0.001), psychological profiles (P < 0.05-0.001) & quality of life scores (P < 0.001) 5 years later by questionnaire and interview. The compliance rate was 95.6% (119 patients). There were 5 attributed deaths in the follow up period: 2 in the treatment group and 3 in the controls. The exercising groups suffered significantly fewer non-fatal reinfarctions (8%) compared with controls (22%) (P < 0.05). Compared with controls, the exercisers visited their general practitioners less frequently (P < 0.01), returned to work earlier (P < 0.05), and reported less angina (P < 0.001).

Table 271: Are there patients after an MI in whom the exercise component of cardiac rehabilitation is not safe?

Grading 1+ Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number: 631 Giannuzzi P;Temporelli PL;Corra U;Gattone M;Giordano A;Tavazzi L; Attenuation of unfavorable remodeling by exercise training in postinfarction patients with left ventricular dysfunction: results of the Exercise in Left Ventricular Dysfunction (ELVD) trial. 1997 96 Circulation	Randomised Controlled Trial	<40% ejection fraction after a first Q-wave myocardial infarction	6 month exercise training program 30-minute bicycle ergometry at least 3x per week for 2 months, thereafter continuation of exercise program (30 minute bicycle ergometry 3x per week	Exercise training vs usual care	6 months	Work capacity Left ventricular volumes Ejection fraction	Minist-ero della Sanità, Rome, Italy. S. Maug-eri Found-ation, Pavia, Italy	Significant increase in work capacity observed only in the training group (from 4.462±1.095 to 5.752±1.749 kilopond-meters [Kp-m], P < 0.01), not in the control group (from 4.375±1.143 to 4.388±1.199 Kp-m). Left ventricular volumes increased in the control group (end-diastolic volume, from 94±26 to 99±27 mL/m2, P < 0.01; end-systolic volume, from 62±20 to 67±23 mL/m2, P< 0.01) but not in the training group (end-diastolic volume, from 93±28 to 92±28 mL/m2, P = NS; end-systolic volume, from 61±22 to 57±23 mL/m2, P = NS). Ejection fraction improved in the training group (from 34±5% to 38±8%, P < 0.01) but not in the control group (from 34±5% to 33±7%, P = NS).

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number: 1350 Marchionni N;Fattirolli F;Fumagalli S;Oldridge N;Del LF;Morosi L;Burgisser C;Masotti G; Improved exercise tolerance and quality of life with cardiac rehabilitation of older patients after myocardial infarction: results of a randomized, controlled trial 2003 107 Circulation	Randomised Controlled Trial	Post MI patients: 3 age groups: middle aged (45-65 years), old (66-75 years), very old > 75	Hospital-based cardiac rehabilitation (Hos-CR), home-based cardiac rehabilitation (Home-CR), no cardiac rehabilitation (no CR).	3 interventions in each age group.	14 months.	Total work capacity (TWC), HRQoL.	National Research -Council Florence Un. Reg. Gov. Tuscany Italy.	TWC improved in the Hosp-CR and Home-CR groups but not in the controls. Treatment-time interactions showed a greater effect of both interventions compared with controls in middle aged (P = 0.002) and old patients (P < 0.001) but not in very old patients (P = 0.143). In middle aged and old patients, HRQoL improved significantly over the study period regardless of treatment assignment, whereas in very old patients, HRQoL improved with both Hosp-CR and Home-CR treatment (P = 0.013 and P < 0.035, respectively) but not with no CR (P = 0.079).
Scottish Intercollegiate Guidelines	Guideline							Contraindications to exercise training experienced a MI

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Network (SIGN).; Cardiac rehabilitation 2002 57								complicated by HF, cardiogenic shock and/or complex ventricular arrhythmias angina or breathlessness occurring at a low level of exercise, for example, inability to complete the first 4 minutes of the shuffle walking test. ST segment depression ≥ 1 mm on resting ECG. Undergone exercise testing with marked ST depression ≥ 2 mm or angina at < 5 METS (for example, 3 minutes of a Bruce protocol).

Grading 2+ well conducted case-control or cohort studies with a low risk of confounding , bias or chance

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number: 312 Otsuka Y;Takaki H;Okano Y;Satoh T;Aihara N;Matsumoto T;Yasumura	Cohort	74 patients with LVEF ≥ 45% (Group H), 35 patients with 35% ≤ LVEF < 45% (Group M), 17 patients with LVEF < 35% (Group L).	Exercise program consisting of walking, cycling on an ergometer and aerobic dance (50-90 min/session), 3-5 sessions	LVEF.	3 months.	Exercise capacity. Peak work rate. Rest heart rate. LV end-diastolic dimension.	Not listed.	After 3 months of exercise training, exercise capacity increased significantly in all 3 groups. Peak Vo2 increased from 1355±321 to 1575±336 ml/min (P < 0.01) in Group H, from 1278±332 to 1464±406 ml/min (P <

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Y;Morii I;Goto Y; Exercise training without ventricular remodeling in patients with moderate to severe left ventricular dysfunction early after acute myocardial infarction 2003 87 International Journal of Cardiology			per week for 3 months.					0.01) in Group M, and from 1248± 369 to 1454±424 ml/min in Group L (P < 0.01). Similarly, peak work rate increased from 122±35 to 144±34 W (P < 0.05) in group H, from 177±42 to 137±12 W in Group M (P < 0.05), and from 107±58 to 129±56 W (P < 0.01) in group L. Rest heart rate reduced from 75±13 to 72±11/ min (P < 0.05) in group H, from 76±13 to 72±12/min in Group M (P < 0.05), and from 80±15 to 75±10/min (NS) in group L. At 35±8 months follow-up there were no significant differences in the incidence of cardiac events among the 3 groups. There was also no significant change in LV end-diastolic dimension in each

Table 272: What is the effectiveness of an individualised cardiac rehabilitation programme versus a non-individualised cardiac rehabilitation programme to improve outcome in patients after an MI?

Grading 1+ Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number: 442 Mayou RA;Thompson DR;Clements A;Davies CH;Goodwin SJ;Normington K;Hicks N;Price J; Guideline-based early rehabilitation after myocardial infarction. A pragmatic randomised controlled trial 2002 52 Journal of Psychosomatic Research	Randomised Controlled Trial	Post MI < 70 years.	Intervention based on national guidelines. Patients seen 2-4 times in hospital, given information sheets (return to ADL and secondary prevention) and a relaxation tape. Following discharge, patients were telephoned to review goals and to discuss any problems.	Usual care, advice from medical and nursing staff. Access to standard booklets and medical outpatient clinic.	12 months.	HAD and Dartmouth COOP scales and questions about activities and belief.	British Heart Foundation.	Primary outcome: At 3 months: Significant improvement in the Dartmouth COOP score in intervention group (59% versus 33%: OR 0.34, 95% CI 0.16-0.73). Subsidiary outcomes: At 1 month: No significant differences between groups measured by HAD or COOP scores. Significantly less intervention patients had further treatment needs (25% versus 74%: OR 0.12, 95% CI 0.05-0.27). At 3 months: Significant improvement in the HAD score in intervention group (median score 5 (2.75-8.25) versus 8 (5-12), P = 0.002). At 1 year: No significant differences between groups measured by HAD or COOP scores. No significant further improvement seen in

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								intervention group, while control group improved.

Grading 4 Expert opinion

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number 45 Benzer W;Oldridge NB; Current concepts in cardiac rehabilitation medical considerations and outcomes evaluations 2001 4 Journal of Clinical & Basic Cardiology	Reviews and Reports						Not listed.	Cardiac rehabilitation should not be considered to be exercise training, but rather as a program based on the individual's requirements.
Reference number 2987 DeBusk RF;	Reviews and Reports						Not listed.	Determining functional capacity is useful in formulating individual guidelines for physical

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
How to individualize rehabilitation after myocardial infarction 1977 32 Geriatrics								activity within the hospital and during the early home phase of rehabilitation.

Table 273: What education and/or information best aids patients after an MI to i) reduce their risk of subsequent cardiac problems ii) return to a full and normal daily life (daily activities, driving, exercise, employment, leisure activities, sexual activities)

Grading 1++ High quality meta analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number 1289 Scottish Intercollegiate Guidelines Network (SIGN).; Cardiac rehabilitation 2002 57 SIGN	Guideline							Recommends that comprehensive cardiac rehabilitation should be delivered by healthcare staff using established principles of adult education and behavioural change.

Grading 1+ Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number 11 Lewin B;Robertson IH;Cay EL;Irving JB;Campbell M; Effects of self-help post-myocardial-infarction rehabilitation on psychological adjustment and use of health 1992 339 Lancet	Randomised Controlled Trial	Consecutive post MI patients, age < 80 years, speak / read English, no history of severe mental illness, dementia, uncontrolled arrhythmias or HF.	Edinburgh Heart Manual: Self-help rehabilitation program incorporating education, exercise and stress management components with follow-ups at 1, 3 and 6 weeks post MI by a trained	Standard care. Equal amount of facilitator's time and a package of educational leaflets (BHF, Scot Health Ed Group, Flora Project).	12 months.	Hospital Anxiety and Depression Scale (HAD) and the General Health Questionnaire (GHQ), Health Service Utilization.	Chief Scientist Office, Scot Office of Scot Home and health Dept, BHF.	Repeated measures analysis showed a significant effect of treatment between groups across time for anxiety (P < 0.04) and caseness (P < 0.01) but not for depression (P = 0.11). 'Distressed' post MI patients: Repeated measures analysis showed a significant effect of treatment between groups across time for anxiety (P < 0.001), caseness (P < 0.002) and for depression (P < 0.03). The intervention group made fewer visits to their GP at 6 month (P < 0.0001) and at 12 months (P < 0.05).
Reference number 442 Mayou RA;Thompson DR;Clements A;Davies	Randomised Controlled Trial	Post MI < 70 years.	Intervention based on national guidelines. Patients seen 2-4 times in hospital, given	Usual care, advice from medical and nursing staff. Access to standard booklets and medical outpatient clinic.	12 months.	HAD and Dartmouth COOP scales and questions about activities and belief.	British Heart Found.	Primary outcome: At 3 months: Significant improvement in the Dartmouth COOP score in intervention group (59% versus 33%: OR 0.34, 95% CI 0.16-0.73). Subsidiary outcomes: At 1 month:

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
CH;Goodwin SJ;Normington K;Hicks N;Price J; Guideline-based early rehabilitation after myocardial infarction. A pragmatic randomised controlled trial 2002 52 Journal of Psychosomatic Research			information sheets (return to ADL and secondary prevention) and a relaxation tape. Following discharge, patients were telephoned to review goals and to discuss any problems.					No significant differences between groups measured by HAD or COOP scores. Significantly less intervention patients had further treatment needs (25% versus 74%: OR 0.12, 95% CI 0.05-0.27). At 3 months: Significant improvement in the HAD score in intervention group (median score 5 (2.75-8.25) versus 8 (5-12), P = 0.002). At 1 year: No significant differences between groups measured by HAD or COOP scores. No significant further improvement seen in intervention group, while control group improved.
Reference number 1289 Scottish Intercollegiate Guidelines Network (SIGN).; Cardiac rehabilitation	Guideline							Contraindications to exercise training experienced a MI complicated by HF, cardiogenic shock and/or complex ventricular arrhythmias angina or breathlessness occurring at a low level of exercise, for

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
2002 57								example, inability to complete the first 4 minutes of the shuffle walking test. ST segment depression ≥ 1 mm on resting ECG. Undergone exercise testing with marked ST depression ≥ 2 mm or angina at < 5 METS (for example, 3 minutes of a Bruce protocol).
Reference number 2967 Van Horn E;Fleury J;Moore S; Family interventions during the trajectory of recovery from cardiac event: an integrative literature review 2002 31 Heart and Lung: Journal of Acute and Critical Care	Systematic Review							The majority of studies were conducted with family members of patients in the coronary care unit. Subjects were primarily wives or female family members of patients. Types of interventions included educationally oriented discussion, physical conditioning, or home visits or telephone calls made by registered nurses. Two studies (Dracup, Buls) found that family intervention decreased anxiety in the spouse. One study found that anxiety was also decreased in the

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								patient (Buls). One study showed that wives' perception of the husbands' cardiac efficacy improved when the wives' observed the husbands' treadmill test and also utilised it themselves (Taylor). Two studies found no positive effect of family intervention on the Family APGAR scale (Gortner, Gillis). A study measuring the effect of family intervention with a social network and social support scale showed no effect of family intervention (Fridlund). A study training spouses on CPR found that perceived control on the Family Control Attitudes Scale increased significantly (Moser).

Table 274: What are the information and support needs for patients at different points in the care pathway?

Grading 1++ High quality meta analyses, systematic reviews of RCTs, or RCTs with very low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number 2964 Dusseldorp E;Van ET;Maes S;Meulman J;Kraaij V; A meta-analysis of psychoeducational programs for coronary heart disease patients 1999 18 Health Psychology	Metaananalysis	MI, CABG, PTCA < 6 months	Psycho-educational and/or stress management.	Usual care.			Netherlands Organ. Scientific Res.	Cardiac mortality: For the long term, the odds of surviving were 1.52 times higher for the treatment group (34% reduction in mortality) than for the control group. For the partial success cluster, the odds of surviving were 1.44 times higher for the treatment group (31% reduction in mortality). MI recurrence: The odds ratios reflect a 20% (total term), 26% (medium term) and 29% (long term) reduction in recurrence of MI. Depression and anxiety: No significant

Grading 2+ Well conducted case control or cohort studies with a low risk of confounding, bias or chance

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number 2999 O'Rourke A;Hampson SE;	Cohort	Consecutive first time post MI patients, age < 76 years, speak / read English.	Hospital 1: Edinburgh Heart Manual. Self-help rehabilitation program	Hospital 2: Usual care.	6 months.	Significant Others Scale (SOS), Recovery Locus of Control Scale (RLOC), Generalised Self-Efficacy Scale	Not listed.	There was a significant interaction between group (hospital 1 versus hospital 2) and time (baseline versus 6 months) for perceptions of control over the illness

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Psychosocial outcomes after an MI: an evaluation of two approaches to rehabilitation 1999 4 Psychology Health & Medicine			incorporating education, exercise and stress management components with follow-ups at 1, 3 and 6 weeks post MI by a trained facilitator.			(GSES), Illness Percept-ion Questionnaire (IPQ), Hospital Anxiety and Depression Scale (HAD), Health Service Utilization		(F(1,45) = 4.14, P < 0.05, effect size 0.08) and depression (F(1,53) = 6.55, P < 0.01, effect size 0.11). Controlling for baseline differences, patients in hospital 1 had significantly higher perceptions of control over their illness and lower levels of depression compared with patients in hospital 2. No significant differences were found between groups for either hospital admissions or GP contact.

Table 275: What is the incidence of sexual dysfunction in patients after MI and how can patients be identified who would require referral to a specialist unit?

Grading 1+ Well conducted systematic reviews of RCTs, or RCTs with a low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number 3051 Conti, A.R. Pepine, C.J. Sweeney, M. Efficacy and safety of	Systematic Review	Male, IHD / ED.	Sildenafil (5-200 mg).	Placebo.	Up to 6 months	Sexual function, adverse events.	Not listed.	The mean end of treatment scores for achieving an erection and maintaining an erection were significantly higher in the sildenafil group than for the placebo group (P < 0.0001). On

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
sildenafil citrate in the treatment of erictile dysfunction in patients with ischemic heart 1999 83 Am J Cardiol								the 5 sexual function domains, scoring was significantly higher in the treatment group than the placebo group (P < 0.0001). At the end of treatment, improved erections were reported by 70% of patients with ischaemic heart disease who received sildenafil and by 20% of those in the placebo group (OR 10.3; 95% CI, 5.6-19.1; P < 0.0001 for treatment effect).
Reference number 220 DeBusk RF;Pepine CJ;Glasser DB;Shpilsky A;DeRiesthal H;Sweeney M; Efficacy and safety of sildenafil citrate in men with erectile dysfunction and stable	Randomised Controlled Trial	Male CAD / ED.	Sildenafil (25-100 mg).	Placebo.	12 weeks.	Sexual function. Adverse events.	Not listed.	After 12 weeks of treatment, the mean end of treatment scores for achieving an erection and maintaining an erection were significantly higher in the sildenafil group than for the placebo group (P < 0.01). Larger percentages of sildenafil treated patients reported improved erections (64%) and improved intercourse (65%) compared with placebo-treated patients (21% and

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
coronary artery disease 2004 93 American Journal of Cardiology								19%,

Grading 1- Meta analyses, systematic reviews of RCTs, or RCTs with a high risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number 59 Olsson AM;Persson CA;Swedish S; Efficacy and safety of sildenafil citrate for the treatment of erectile dysfunction in men with cardiovascular disease 2001 55 International Journal of Clinical Practice	Randomised Controlled Trial	CVD / ED, Male, 18% MI intervention, 20%. MI placebo.	Sildenafil (25-100 mg).	Placebo.	12 weeks.	Sexual function Adverse events.	Pfizer.	After 12 weeks of treatment, the mean end of treatment scores for achieving an erection and maintaining an erection were significantly higher in the sildenafil group than for the placebo group (P < 0.0001). The end of treatment responses to a global efficacy question found that the intervention group reported improved erections compared with the placebo group (P < 0.0001). The most frequent adverse events were flushing, headache and dyspepsia (sildenafil: 17%, 5%, and 2%,

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								respectively, placebo: 2%, 1%, 0%, respectively). Besides flushing, no treatment-related cardiovascular event was reported, and sildenafil did not produce any changes in blood pressure compared with either placebo or baseline values (data not shown).

Table 276: What approach to patient engagement best aids access to cardiac rehabilitation, particularly in reference to em, op, seg, women, those from rural communities, and those with mental and physical health co-morbidities?

Grading 1++ High quality meta analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference nuber 3058 Beswick AD;Rees K;Griebsch I;Taylor FC;Burke M;West RR; Provision, uptake and cost of cardiac rehabilitation programmes:	Systematic Review						DOH	All studies reported that there was benefit of intervention to improve uptake (healthcare led-professional interventions at the patient level, trained lay volunteers, coordination of referral post-discharge care at the service level, written or aural motivational communications). This may be indicative of publication bias. For

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
improving services to under-represented groups 2004 8 Health Technology Assessment								adherence, the authors of the HTA stated that they found few studies of sufficient quality to make specific recommendations of methods to improve adherence to cardiac rehabilitation. Their opinion was that the most promising approach was the use of self-management techniques based around individualised assessment, problem solving, goal setting and follow-up.

Grading 1- Meta analyses, systematic reviews of RCTs, or RCTs with a high risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number 3064 Hughes AR;Gillies F;Kirk AF;Mutrie N;Hillis WS;MacIntyre	Randomised Controlled Trial	Intervention MI/CABG: 12/4, Control MI/CABG: 8/7.	Exercise consultation plus exercise leaflet.	Exercise leaflet.	4 weeks.	Scottish Physical Activity Questionnaire. Measuring occupational and leisure physical activity.	Not listed.	Using Mann-Whitney tests, leisure activity at baseline was similar between intervention and control groups (95% CI -325, 105.1). In the intervention group, leisure physical activity increased by 29.5%

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
PD; Exercise consultation improves short-term adherence to exercise during phase IV cardiac rehabilitation: a randomized, controlled trial 2002 22 Journal of Cardiopulmonary Rehabilitation								(123/417.5) analysed by Wilcoxon signed rank test.

Table 277: What is the effectiveness of changing dietary regime from the pre-infarct diet?

Grading 1++ High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference 26 Shekelle P;Morton S;Hardy M;	Systematic Review							The available scientific studies offer little evidence that supplementation with vitamin C, vitamin E, or coenzyme Q10 has any

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Effect of supplemental antioxidants vitamin C, vitamin E, and coenzyme Q10 for the prevention and treatment of cardiovascular disease 2003								benefit on secondary prevention in secondary prevention of cardiovascular disease.

Grading 1+ Well conducted meta-analyses

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number 1482 de Lorgeril M;Salen P;Martin JL;Monjaud I;Delaye J;Mamelle N; Mediterranean diet, traditional risk factors, and the rate of cardiovascular	Randomised Controlled Trial	Post MI patients < 70 years.	The experimental group were advised to eat more bread, fruit and vegetables, fish, and less meat, and to replace butter and cheese with rapeseed margarine.	Diet change versus no diet change.	46 months.	All-cause mortality, cardio-vascular deaths.	Not listed.	Mean follow for survival in the control group was 44.9 month and 46.7 months in the experimental group. All-cause and cardiovascular (P = 0.01) mortality and the combination of recurrent MI and cardiac death were reduced in the treatment group (P = 0.0001).

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
complications after myocardial infarction: final report of the Lyon Diet Heart Study.[see comment] 1999 99 Circulation			Controls: no advice.					
Reference number 2070 Liem A;Reynierse-Buitenwerf GH;Zwinderman AH;Jukema JW;van V; Secondary prevention with folic acid: Effects on clinical outcomes 2003 41 Journal of the American College of Cardiology	Randomised Controlled Trial	Stable CAD, MI, coronary artery lesions, PCI, CABG. Age: Treatment: 64.9±9.9 years, Control:65.5±9.7 years. Male gender Treatment: 76%, Control: 80%.	Folic acid (0.5 mg/day).	No treatment.	24 months.	All-cause mortality and a composite of vascular events.	Not listed.	All-cause mortality and a composite of vascular events was found to be in 31 (10.3%) patients in the folic acid group, and in 28 (9.6%) patients in the control group (relative risk 1.05; 95% CI: 0.63 to 1.75).

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number 5198 Bonaa KH;Njolstad I;Ueland PM;Schirmer H;Tverdal A;Steigen T;Wang H;Nordrehaug JE;Arnesen E;Rasmussen Homocysteine lowering and cardiovascular events after acute Myocardial Infarction 2006 354 New England Journal of Medicine	Randomised Controlled Trial	Inclusion criteria: Men and women (26%), aged 30 to 85 years of age (mean 63 years) with acute MI within 7 days before randomisation. Concomitant therapy: Aspirin: 89%, Diuretics: 18%, Beta blockers: 91%, ACEs: 32%, ARBs: 5%, Statins: 81%, Warfarin: 12%. Exclusion criteria: Coexisting disease associated with a life expectancy of less than 4 years, prescribed treatment with B vitamins or	Folic acid 0.8 plus 0.4 mg vitamin B12 mg plus 40 mg vitamin B6 once daily: 937 patients.	Placebo: 943 patients. 40 mg vitamin B6 once daily: 934 patients. Folic acid 0.8 mg plus 0.4 mg vitamin B12 once daily: 953 patients.	Median follow-up 40 months (mean 36 months).	Primary: Composite of new nonfatal myocardial infarction and fatal myocardial infarction, fatal and nonfatal stroke or sudden death attributed to CHD. Secondary: Myocardial infarction, unstable angina pectoris requiring hospitalizatio n, stroke, CABG, PCI, death from any cause.	Norwegian Res Counc. Counc. Health and Rehab., Norwegian Concil CV disease, Northern Norway Reg health Authority, Norwegian Red Cross, Found. Promote Res. Into Functional Vitamin B12 Deficiency.	Results presented for the folate combination versus placebo. Primary: Composite of new nonfatal myocardial infarction and fatal myocardial infarction, fatal and nonfatal stroke or sudden death attributed to CHD: 201/937 (21.5%) folic acid plus vitamin B12 mg plus B6 versus 172/943 (18.2%) placebo RR of 1.22 (95% CI 1.00 to 1.50, P = 0.05). Secondary: Myocardial infarction: 182/937 (19.4%) folic acid plus vitamin B12 mg plus B6 versus 153/943 (16.2%) placebo RR of 1.23 (95% CI 0.99 to 1.52, P = 0.06). Fatal myocardial infarction: 68/937 (7.3%) folic acid plus vitamin B12 mg plus B6 versus 59/943 (6.3%) placebo RR of 1.19 (95% CI 0.84 to 1.69, P = 0.34). Nonfatal myocardial infarction: 132/937 (14.1%) folic acid

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
		untreated B vitamin deficiency or inability to follow the protocol, as judged by the investigator.						plus vitamin B12 mg plus B6 versus 104/943 (11.0%) placebo RR of 1.30 (95% CI 1.00 to 1.68, P = 0.05). Stroke: 21/937 (2.2%) folic acid plus vitamin B12 mg plus B6 versus 27/943 (2.9%) placebo RR of 0.87 (95% CI 0.47 to 1.47, P = 0.52). Death from any cause: 104/937 (11.1%) folic acid plus vitamin B12 mg plus B6 versus 89/943 (9.4%) placebo RR of 1.21 (95% CI 0.91 to 1.61, P = 0.19). Unstable angina pectoris requiring hospitalization: 125/937 (13.3%) folic acid plus vitamin B12 mg plus B6 versus 132/943 (14.0%) placebo RR of 0.93 (95% CI 0.73 to 1.19, P = 0.57). CABG: 138/937 (14.7%) folic acid plus vitamin B12 mg plus B6 versus 157/943 (16.6%) placebo RR of 0.89 (95% CI 0.71 to 1.13, P = 0.34). PCI: 257/937 (27.4%) folic acid plus vitamin B12 mg plus B6 versus 290/943

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								(30.8%) placebo RR of 0.86 (95% CI 0.72 to 1.02, P = 0.08).
Reference number 179 Morris CD;Carson S; Routine vitamin supplementation to prevent cardiovascular disease: a summary of the evidence for the U.S. Preventive Services Task Force.[see comment]. [Review] [65 refs] 2001 139 Annals of Internal Medicine	Systematic Review							Randomised controlled trials of specific supplements failed to demonstrate a consistent or significant effect on incidence of, or death from, cardiovascular disease.

Grading 1- Meta analyses, systematic reviews of RCTs or RCTs with a high risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number 1771 Burr ML;Fehily AM;Gilbert JF;Rogers S;Holliday RM;Sweetnam PM;Elwood PC;Deadman NM; Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART).[see comment] 1989 2 Lancet	Randomised Controlled Trial	Recent male post MI patients > 70.	Three dietary regimes were compared: fat advice, fibre advice and fish advice. Patients were advised to eat at least two weekly portions (220 to 400 g) of oily fish (mackerel, herring, kipper, pilchard, sardine, salmon or trout). Fat advice was to reduce fat intake to 30% of total energy and to increase the polyunsaturated fat / saturated fat ratio to 1.0. Fibre advice	No dietary advice	2 years.	Mortality, ischaemic heart disease events.	Not listed	Advice to eat oily fish was associated with a reduction in all cause mortality compared with no dietary advice after adjustment for confounders (RR = 0.71, 95%CI 0.54 to 0.92). There was no reduction in ischaemic heart disease events in the oily fish advice group compared with the group given no advice (RR 0.84, 95% CI 0.67 to 1.07). There was no reduction in ischaemic heart disease events in the oily fish advice group compared with the group given no advice (RR 0.84, 95% CI 0.67 to 1.07). Patients given oily fish advice had a lower mortality than patients within other dietary groups although these were not statistically significant. Advice to eat less fat as well as advice to eat more fibre was not associated with any reduction in mortality or ischaemic hear disease compared with no diet

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
			(to eat more cereal fibre). Patients in the oily fish advice group who could not tolerate oily fish were given omega-3- acid ethyl esters capsules; 3 x 0.5 g per day supplying 2.5 g of eicosapentaenoic acid per week.					advice.

Table 278: What is the effectiveness of regular physical activity versus a sedantry lifestyle to improve outcome in patients after MI?

Grading 1+ Well conducted meta-analyses, systematic reviews of RCTs and RCTs with a low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number 367 Naughton J;Dorn J;Imamura D; Outcomes measurement	Randomised Controlled Trial	Male (age range 35-64 years), post MI (≥ 8 weeks but < 2 years). Ability to exercise to minimum of 3 METS and	Exercise: 8 weeks brisk activity (1 hour per day, 3 times per week) then 34 months of exercise for	Controls.	3, 5, 10, 15, 19 years.	Mortality.	NIHR NHLBI.	At 3 years follow up, the exercise group's cumulative mortality = 15 (4.6%) compared with control's = 24 (7.3%). Observed effectiveness = 37% (95% CI -15, 68; p = 0.22). Cardiovascular

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
in cardiac rehabilitation: the National Exercise and Heart Disease Project 2000 4 Journal of Rehabilitation Outcomes Measurement		resting diastolic BP < 100 mm Hg. Exclusions: uncontrolled diabetes, coexisting CVD, terminal disease, heart block, emotional or physical impairment. Mean age: Exercise group: 51.5±7.4 years, Control group: 52.1±7.4 years	40 minutes 3 times per week.					deaths in exercise group = 14 (4.3%) compared with 20 (6.1%) in control group. Observed effectiveness = 29% (95% CI -33, 66; p < 0.40). MI deaths in exercise group = 1 (0.3%) compared with 8 (2.4%) in control group. Observed effectiveness = 87% (95% CI 22, 98; p < 0.047). Long term follow up: all cause mortality relative risk (95% CI) at 3, 5, 10, 15 and 19 years were 0.69 (0.39, 1.25), 0.84 (0.55, 1.28), 0.95 (0.71, 1.29), 1.02 (0.79, 1.32) and 1.09
Reference number 801 Shaw LW; Effects of a prescribed supervised exercise program on mortality and cardiovascular morbidity in patients after	Randomised Controlled Trial	Patients from 5 centres were recruited for this study. Patients had documented AMI within 1-3yrs of admission to the study. Subjects were all men. Mean age (yrs ± SEM):	During the first 8wks, the participants attended to exercise laboratory 1hr/day, 3days/week. They exercised for a total of 24min, by	Not reported.	3 yrs.	Mortality, nonfatal infarction, suspected infarctions, other events. all, recurrent MI. Total hospitalisations for reasons other than MI.	Grant from the Rehab. Services Admin of the Dept of Health, Education & Welfare. US.	All deaths: Intervention group: 15/323 (4.6%), Control group: 24/328 (7.3%), P=NS. Subtotal of all: Cardiovascular deaths (including AMI & other definite): Intervention group: 6/323 (1.9%), Control group: 14/328 (4.3%), P=0.13. Of which AMI deaths: intervention group: 1/323 (0.3%),

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
myocardial infarction. The National Exercise and Heart Disease Project 1981 48 American Journal of Cardiology		Intervention group: 51.5 ± 0.4, Control group: 52.0 ± 0.4.	exercising for 4min on each of the 6 stationary devices & resting for 2min after use of each device. The workload on each device was set to yield the target heart rate early in each 4min exercise period. Thereafter the exercise program was conducted in a gym without ECG monitoring. It consisted of supervised physical activities designed to yield the prescribed target heart					Control group: 8/328 (2.4%), P=0.05. Other definite (6 from arrhythmias, 2 from congestive cardiac failure, 1 from cardiogenic shock & 2 from cerebrovascular accidents) Intervention group: 5/323, Control group: 6/328. Sudden death: Intervention group: 8/323, Control group: 6/328. Indeterminate cause: Intervention group: 1/323, Control group: 4/328. Difference in mortality between smokers/non-smokers: Smokers: 9.4%, Non-smokers: 2.1%, P=NS. Nonfatal infarction: Intervention group: 15/323, Control group: 11/328. Suspected infarctions: Intervention group: 3/323, Control group: 2/328. Other events: Intervention group:

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
			rate. The activities included 15min of continuous jogging, cycling or swimming followed by 25min of games.					25/323, Control group: 25/328. All recurrent MI: Intervention group: 17/323 (5.3%), Control group: 23/328 (7.0%), P=0.4. Total hospitalisations for reasons other than MI: Intervention group: 92/323 (28.5%), Control group: 90/328 (27.4), P=0.04.

Grading 2+ Well conducted case control or cohort studies with a low risk of confounding, bias or chance

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number 469 Blumenthal JA;Babyak MA;Carney RM;Huber M;Saab PG;Burg MM;Sheps D;Powell L;Taylor CB;Kaufmann PG;	Cohort	Recent MI patients with perceived lack of social support and/or symptoms depression. Age: No exercise group: 61.1±12.7 years, Exercise group: 59.5±11.8 years.	Self reported exercise	Self reported exercising group and non-exercising group.	6 month after enrolment and each year up to 4 years.	Mortality, probability of survival.	NHLBI.	At 6 months, 982 (47.2%) patients reported that they had exercised regularly since their acute MI. During up to 4 years follow-up, 187 patients had died, 5.7 % of exercisers compared with 12.0% of non-exercisers. After statistical adjustment for medical and demographics, regular exercise was found to be significantly

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Exercise, depression, and mortality after myocardial infarction in the ENRICHD trial 2004 36 Medicine & Science in Sports & Exercise								associated with increased probability of survival (hazard ratio = 0.62, 95% CI = 0.44-0.86, P < 0.004). After adjustment for modification of diet, counselling sessions, smoking and participation in cardiac rehabilitation, regular exercise remained statistically associated with survival (hazard ratio = 0.69, 95% CI = 0.49-0.98, P = 0.037). The rate of non-fatal MI amongst the exercisers was 6.5% compared with 10.5% for non-exercisers. Exercise was significantly associated with reduced likelihood of non-fatal MI (hazard ratio = 0.72, 95% CI = 0.52-0.99, P = 0.044).

Grading 2- Case control or cohort studies with a high risk of confounding bias, or chance and a significant risk

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number 2908	Cohort	Post MI patients. Age: not reported.	3 months after an MI, patients in	Exercise program versus no exercise.	1 year, 4 year follow up.	All-cause mortality, cardiovascula	Not listed.	Patients in the treatment group were advised about the benefit of regular

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Wilhelmsen L;Sanne H;Elmfeldt D;Grimby G;Tibblin G;Wedel H; A controlled trial of physical training after myocardial infarction. Effects on risk factors, nonfatal reinfarction, and death 1975 4 Preventive Medicine			the treatment group were advised about the benefit of regular exercise and were encouraged to attend an exercise programme (3 half hour supervised training sessions per week)			r deaths.		exercise and were encouraged to attend an exercise programme. This consisted of 3 half hour supervised training sessions a week. However, at four year follow up, there were no significant differences found in all-cause mortality or cardiovascular deaths.

Table 279: What is the effectiveness of low/moderate alcohol consumption versus high alcohol consumption to improve outcomes in patients after MI?

Grading 2+ Well conducted case control or cohort studies with a low risk of confounding, bias or chase

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number 224	Case-Control	Sudden cardiac arrest (SCA). Cases (n= 117), controls (n=	Alcohol (glasses per week), 0, 1-6, 7-21, >21.	Retrospective.		SCA.	Wijnand M. Pon Foundation Leusden	Multiple logistic regression analysis, with SCA as the dependent variable, and two sets of

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
de Vreede Swagemakers JJ;Gorgels AP;Weijenberg MP;Dubois-Arbouw WI;Golombeck B;van R;Knottnerus A;Wellens HJ; Risk indicators for out-of-hospital cardiac arrest in patients with coronary artery disease 1999 52 Journal of Clinical Epidemiology		144).					Research Cardiol Foundation Maasrict NL.	independent variables found that alcohol consumption of 1-21 glasses per week (1-26 units/week) was negatively associated with SCA. Thus, alcohol consumption (1-21 glasses per week) (1-26 units/week) seems to protect patients with CAD from SCA (OR 0.05, 95% CI 0.2-
Muntwyler J;Hennekens CH;Buring JE;Gaziano JM; Mortality and light to moderate alcohol consumption after	Cohort	Subjects recruited into the Physicians' Health Study, male, post MI.	Number of alcoholic drinks: Rarely/never (n= 1125), 1-4/month (n= 1227), 2-6/week (n= 1390), 1/day (n= 1424), >		5 years.	Total mortality. Cardiovascular death.	NHLBI USA, Theodor und Ida Herzog-Egli Foundn Switzerland.	After multivariate adjustment, the total mortality risk in men who drank two to six drinks per week (4-13 units/wk) was significantly lower by 28% (95% CI 11-42) compared with men who never or rarely drank. Patients who reported drinking

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
myocardial infarction 1998 352 Lancet			2/day (n= 192).					one alcoholic drink per day (17 units/wk) had a significantly decreased risk (21%, 95% CI 4-36). For death due to cardiovascular diseases, the risk reduced up to an alcohol intake of two to six drinks per week.
Reference number 611 Shaper AG;Wannamethee SG; Alcohol intake and mortality in middle aged men with diagnosed coronary heart disease 2000 83 Heart (British Cardiac Society)	Cohort	455 post MI patients and 200 angina patients.	Alcohol consumption lifelong teetotallers (n= 43), ex-drinkers (n= 59), occasional drinkers (< 1 drink per month, n= 199) light drinkers (1-15 units per week, n= 230) moderate drinkers (16-42 units per week, n= 104), heavy drinkers (> 42 units per		Mean follow-up: 12.8 years.	All cause mortality. CVD mortality. Non CVD mortality.	Not listed.	There was little difference in risk of CHD, cardiovascular, non-cardiovascular, and all cause mortality between lifelong teetotallers, occasional drinkers (1-2 units/month), and light drinkers (1-15 units/wk). In the patients with previous MI, there was no difference in outcome between lifelong teetotallers, occasional drinkers, and light drinkers. Ex-drinkers showed a significant increase in cardiovascular mortality (marginal) and all cause mortality compared with

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
			week, n= 20). Men in the heavy drinking group were combined with the moderate drinking group because of the small numbers.					

Grading 2- Case control or cohort studies with a high risk of confounding bias, or chance and a significant risk

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number: 46 Aguilar D;Skali H;Moye LA;Lewis EF;Gaziano JM;Rutherford JD;Hartley LH;Randall OS;Geltman EM;Lamas GA;Rouleau JL;Pfeffer MA;Solomon	Cohort	Left ventricular dysfunction after MI, with a LV ejection fraction of 40% or less, 21-80 years of	Non drinkers (0 drinks/ week) (1276 patients), light-to-moderate drinkers (1 to 10 drinks/ week) (717 patients), and heavy drinkers (>10 drinks/ week) (235		2 years.	Development of symptomatic heart failure (HF), need for hospitalization for HF, endpoints that only occurred 90 days after enrolment	Not listed.	Compared with non drinkers, the unadjusted HR for the development of HF was lower in the light-to-moderate drinkers (2-22 units/wk) (HR 0.70, 95% CI 0.53-0.91). After adjustment for baseline characteristics, the difference was no longer statistically different (HR 0.93, 95% CI

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
SD; Alcohol consumption and prognosis in patients with left ventricular systolic dysfunction after a myocardial 2002 43 Journal of the American College of Cardiology			patients).					
Reference number 2944 De Lorgeril, M.; Salen, P.; martin, J.L.; Boucher, F.; Paillard, F.; De Leiris, J. Wine drinking and risks of cardiovascular complications after recent myocardial	Cohort	Participants of Lyon Diet Heart Study post MI, <70 years of age, male.	Quartiles of ethanol consumption . Zero percent of energy intake per day derived from ethanol (non-drinkers) was quartile 1 (44 patients), <5.4% of total energy intake per		4 years.	Clinical complications.	Not listed.	There were 36, 34, 18 and 16 complications in the quartiles 1, 2, 3, and 4, respectively. Multivariate risk ratios of CVD complications according to wine ethanol intake: Quartile 1: 0, 0 units/wk, Quartile 2: 0.74 (CI 95% 0.40-1.38) 8 units/wk, Quartile 3: 0.41 (0.20-0.83) 19 units/wk, Quartile 4: 0.48 (0.24-0.96) 53 units/wk.

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
infarction 2002 106 Circulation			day was quartile 2 (37 patients), >5.41% but <9.84% of total energy intake per day was quartile 3 (44 patients), and >9.84% of energy was quartile 4 (38 patients).					

Table 280: What is the level of physical activity which increases physical work capacity versus physical activity which does not increase physical work capacity

Grading 1+ Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference number 596 Dorn J;Naughton J;Imamura D;Trevisan M; Results of a multicenter randomized	Randomised Controlled Trial	Subjects were men aged between 30 to 64 yrs. Enrolled at 1 of 5 centres in the US during 1976. Age (yrs ± SD): Intervention	An exercise prescription was developed on the basis of each patient's MSET (multistage graded	Patients were encouraged to maintain normal routines but not to participate in any regular exercise program.	The original clinical trial was terminated on 1st Dec 1995, with morbidity & mortality follow-up	Secondary analysis of the NEHDP. Long term follow up: age adjusted all-cause mortality (95% CI) at 3, 5, 10, 15 and	Supported by a National Heart, Lung & Blood Institute First Independent Research Support in Transition award.	

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
clinical trial of exercise and long-term survival in myocardial infarction patients: the National Exercise and Heart Disease Project (NEHDP) 1999 100 Circulation		group: 51.5 ± 7.4, Control group: 52.1 ± 7.2. Work capacity (metabolic equivalents (METs) ±SD): Intervention group: 7.8 ± 2.1, Control group: 7.8 ±2.2. Men with documented MI after 8 weeks but before 3 years I before enrollment. Subjects with the ability to exercise at an intensity level of 3 METs and a surprine resting diastolic blood pressure of 100mm Hg. Excluded: Patients with other significant coexisting CVD or other disease likely to be fatal	exercise test) results. An exercise target heart rate guided the prescription & was determined as 85% of the peak heart rate achieved on the test (see comments).		completed on 31st May 1979.	19 years were 0.86 (0.76-0.98), 0.91 (0.82-1.00), 0.88 (0.83-0.95), 0.89 (0.84-0.95) and 0.92 (0.87-0.97), respectively. Long term follow up: age adjusted CVD mortality (95% CI) at 3, 5, 10, 15 and 19 years were 0.87 (0.74-1.02), 0.91 (0.81-1.03), 0.89 (0.82-0.96), 0.89 (0.82-0.96) and 0.93 (0.87-0.99), respectively.		

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
		in the						
Reference number 596 Dorn J;Naughton J;Imamura D;Trevisan M; Results of a multicenter randomized clinical trial of exercise and long-term survival in myocardial infarction patients: the National Exercise and Heart Disease Project (NEHDP) 1999 100 Circulation	Randomised Controlled Trial	As above.	As above	As above.	3, 5, 10, 15, 19 years.	Mortality.	NHLBI.	Secondary analysis of the NEHDP. Long term follow up: age adjusted all-cause mortality (95% CI) at 3, 5, 10, 15 and 19 years were 0.86 (0.76-0.98), 0.91 (0.82-1.00), 0.88 (0.83-0.95), 0.89 (0.84-0.95) and 0.92 (0.87-0.97), respectively. Long term follow up: age adjusted CVD mortality (95% CI) at 3, 5, 10, 15 and 19 years were 0.87 (0.74-1.02), 0.91 (0.81-1.03), 0.89 (0.82-0.96), 0.89 (0.82-0.96) and 0.93 (0.87-0.99), respectively.
Reference number 2948 Holmback AM;Sawe U;Fagher B;	Randomised Controlled Trial	All acute MI patients under 65 years and attending the Hospital Post-MI Clinic.	Program was designed and supervised by a physiotherapist. It started	Received regular medical care with no special emphasis on exercise.	1 year post MI.	Maximal Physical Capacity (MPC) (after 1 year testing).	Malmohus county council. No commercial party had a direct	MPC in intervention group: increased non significantly, average of 10% or 12 W (95% CI: 2 to 22W) over baseline. MPC in control

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Training after myocardial infarction: lack of long-term effects on physical capacity and psychological variables 1994 75 Arch Phys Med Rehabil		Median age: 55 years. Total age range (years): Intervention group: 38-65, Control group: 43-63. Gender: nearly all males.	weeks post MI and patients trained over a 12 week period for at least 45 min (effective time) twice a week with interval training involving large muscle groups.			Mean exercise capacity. Return to work	financial interest in the results of the research.	group: increased nonsignificantly, average of 2% or 1W (CI: -8 to 10W) over baseline. Intergroup difference: not significant. Mean exercise capacity: intervention group: 172W (SD 33) control group 144W (SD 29). Return to work: After 1 year follow up median time of work return: not significant, intervention group: 16 weeks (interquartile range 12 to 30 weeks), control group: 12 weeks (interquartile range 9 to 23 weeks).
Reference number 1350 Marchionni N; Fattirolli F; Fumagalli S; Oldridge N; Del Lungo F; Morosi L; Burgisser C; Masotti G; Improved exercise tolerance and	Randomised Controlled Trial	Patients older than 45yrs referred to CR unit by 4 of the 6 intensive care units in the Florence area for functional evaluation 4 to 6wks after MI over a 48mth period. Baseline characteristics	The American College of Sports Medicine guidelines were used for exercise prescription. Hosp CR programme consisted of 40 exercise	No CR patients attended a single structured education session on cardiovascular risk factor management with no exercise prescription & were referred back to their family physicians.	14 months.	Total Work Capacity (TWC), Sickness Impact Profile (SIP) & Health Related Quality of Life	National Research Council (CNR), the University of Florence & the Regional Government of Tuscany, Italy.	Baseline TWC was lower in older patients in each study arm but similar within each age group by treatment assignment. Baseline SIP scores were similar across age groups, but in middle-aged and very old patients they were higher (i.e., worse) in the Hosp CR than in the other study arms. TWC improved in Hosp CR & Home CR

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
quality of life with cardiac rehabilitation of older patients after myocardial 2003 107 Circulation		were different between the 3 age groups therefore these groups are examined separately in this trial. Age (yrs): 45-65 groups: 57 ± 0.6. 66-75 groups: 70 ± 0.3. >75 groups: 80 ± 0.3. Males (%): 45-65 groups: 85.6. 66-75 groups: 66.7. >75 groups: 60. 3 age groups predefined as middle age (45-65yrs), old (66 to 75 yrs) and very old (>75yrs). Excluded: Patients with severe cognitive	sessions: 24 sessions (3/wk) of endurance training on a cycle ergometer (5min warm-up, 20min training at constant workload, 5min cool down & 5min post-exercise monitoring) plus 16 (2/wk) 1hr sessions of stretching & flexibility exercises. Exercise intensity was set at 70% to 85% of heart rate attained during baseline symptom-limited exercise test. Patients					groups but not in controls with no significant difference between Hosp CR & Home CR. Significant treatment-time interactions confirmed a greater effect of both active interventions compared with control middle aged & old patients but not in very old patients, which suggests a lower enhancement in TWC at older age. No significant age-treatment interaction was found for changes in TWC, which suggests that the 2 active interventions were equally less effective in older patients. Despite this, at 2mths, TWC had improved significantly in very old patients with both interventions. Complications were similar across treatment & age groups. In middle aged & old patients, HRQL improved significantly over the

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
		impairment or physical disability, left ventricular ejection fraction <35%,	received cardiovascular risk factor management counselling twice per week & were invited to join a monthly support group with family members. Home CR patients participated in 4 to 8 supervised instruction sessions in the CR unit, where they were taught necessary precautions & how to perform their training at home. Patients received cardiovascula					entire study duration regardless of treatment assignment, whereas in very old patients, HRQL improved significantly with active treatment but not with no CR.

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
			r risk factor management counselling at each in hospital session & were invited to join a mthly family oriented support group. After the instruction phase, patients received an exercise prescription similar to that of the Hosp CR group, a wrist-watch digital pulse monitor, a cycle ergometer & a log book to record the heart rate					

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
			attained during each exercise session & reasons for not finishing or missing a session. A physical therapist made home visits every week to adjust if necessary the exercise prescription, to enhance adherence with intervention & to record the number of completed sessions & distance cycled.					
Reference number 664 Oberman	Randomised Controlled Trial	Subjects were men aged between 30 to 64 yrs. Enrolled	An exercise prescription was developed	Patients were encouraged to maintain normal routines but not to	The original clinical trial was	As of 31st Dec 1995. No of patients deceased:	Supported by a National Heart, Lung & Blood	As of 31st Dec 1995. No of patients deceased: Int gp: 162/315 (51.4%) Cont gp: 150/319 (47%)

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
A;Fletcher GF;Lee J;Nanda N;Fletcher BJ;Jensen B;Caldwell ES; Efficacy of high-intensity exercise training on left ventricular ejection fraction in men with coronary artery disease (the Training Level Comparison Study) 1995 76 American Journal of Cardiology		at 1 of 5 centers in the US during1976. Age (yrs ± SD): Intervention group: 51.5 ± 7.4 Cont gp: 52.1 ± 7.2 Work capacity equivalents (METs) ± SD): Intervention gp: 7.8 ± 2.1 Cont gp: 7.8 ± 2.2 Men with documented MI ³8wks but <3yrs before being enrolled. Subjects with the ability to exercise at an intensity level ³3 METs & a surprine resting diastolic blood pressure <100mm Hg. Excluded: Patients with other sig	on the basis of each patient's MSET (multistage graded exercise test) results. An exercise target heart rate guided the prescription & was determined as 85% of the peak heart rate achieved on the test. This gp performed brisk physical activity in the laboratory for 8wks, exercising 1hr per day, 3 days per week. Patients were supervised & underwent	participate in any regular exercise program.	terminated on 1st Dec 1995, with morbidity & mortality follow-up completed on 31st May 1979.	Risk of all-cause mortality in int gp compared with cont gp at average 3, 5, 10, 15 & 19 yrs follow up periods: Risk of CVD mortality in int gp compared with cont gp at average 3, 5, 10, 15 & 19 yrs follow up periods: RR of all-cause mortality according to PWC change at various follow up period: The NEHDP -	Institute First Independent Research Support in Transition award.	Deaths due to CVD: Int gp: 64.2% Cont gp: 72.7% Of which are stroke deaths: Int gp: 2 Cont gp: 7 RR: 0.32 CI: 0.07-1.56 P=0.16 Cause of death unknown: n=29 Risk of all-cause mortality in int gp compared with cont gp: 3 Years – RR: 0.69 CI: 0.39-1.25 5 Years – RR: 0.84 CI: 0.55-1.28 10 Years – RR: 0.95 CI: 0.71-1.29 15 Years – RR: 1.02 CI: 0.79-1.32 19 Years – RR: 1.09 CI: 0.87-1.36 Risk of CVD mortality in int gp compared with cont gp: 3 Years – RR: 0.73 CI: 0.37-1.43 5 Years – RR: 0.98 CI: 0.60-1.61 10 Years – RR: 1.21 CI: 0.79-1.60 15 Years – RR: 1.14 CI: 0.84-1.54 19 Years – RR: 1.16 CI: 0.88-1.52 Younger men, cigarette smokers & those with a low initial PWC (<7METs) generally derived more benefits from the exercise program than men who were older, non-smokers

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
		coexisting CVD or other disease likely to be fatal in the near future.	continuous ECG monitoring. Each individual exercised for 4min on each of 6 stationary machines with a 2min rest interval between machines. Attainment of the target heart rate was the goal for every 4min exercise period. Exercise was stopped if patients experienced any adverse signs or symptoms or ECG abnormalities. After 8wks,					or had a high PWC. Only stat sig difference in effectiveness of the program were between smokers & nonsmokers at the 10yr follow up period. Non Smokers- Int gp: 64/220 (29.7%) Cont gp: 57/238 (24%) Diff: 17.5% P<0.01 Secondary analysis found that each single-stage (1 MET) increase in PWC of the MSET was associated with a reduction in all-cause mortality risk in the range of 8% to 14% depending on the time period examined. The age-adjusted RRs were sig at every follow up period except 5yr. CVD mortality risks were similar to those observed for all-cause mortality. Patients were evaluated at 2 & 5mths after randomisation and semi-annually thereafter. This study focuses on long-term mortality follow up of patients in the original trial,

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
			subjects exercised in a gym or swimming pool without ECG monitoring, although exercise heart rates were periodically checked. Activities consisted of 15min of continuous jogging, cycling or swimming, followed by 25min of recreational games. The activities were performed at an intensity level enabling each participant to reach his					National Exercise & Heart Disease Project (NEHDP). After 19yrs of follow up 7cont & 2 exercise gp subjects died of stoke, resulting in RR in favour of the exercise program subjects. Initially, enrolment in the int gp appeared to offer survival benefits compared with cont gp assignment although none of the RR were stat. sig. At 3yrs of follow up, exercisers were at an ~30% lover risk of death than men in the cont gp. Death due to CVD, there was a benefit in favour of the int gp was detected only in the earliest yrs of the study. A nonsig elevated risk for CVD death associated with intgo assignment became evident at yr 10 & levelled off thereafter.

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
			individual prescribed target heart rate. The men were encouraged to attend 3 sessions per week but in some situations were allowed to exercise on their own. There was no formal education/targeting provided regarding other lifestyle habits.					
Reference 801 Shaw LW; Effects of a prescribed supervised exercise program on	Randomised Controlled Trial	Patients from 5 centres were recruited for this study. Patients had documented AMI within 1-3 years of	During the first 8 weeks, the participants attended to exercise laboratory 1hr/day,	Not reported	3 yrs	Primary outcome: mortality. Nonfatal infarction. Total hospitalisations for	Grant from the Rehab. Services Admin of the Dept of Health, Education & Welfare. US.	All deaths: Intervention group: 15/323 (4.6%) Control group: 24/328 (7.3%) P = not significant. Subtotal of all Cardiovascular deaths (including AMI & other definite) Intervention

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
mortality and cardiovascular morbidity in patients after myocardial infarction. The National Exercise and Heart Disease Project 1981 48 American Journal of Cardiology pgs 39- 46		admission to the study. Subjects were all men. Mean age (yrs 1± SEM): Intervention group: 51.51±0.4 Control group: 52.01±0.4	3days/week. They exercised for a total of 24min, by exercising for 4min on each of the 6 stationary devices & resting for 2min after use of each device.			reasons other than MI.		group: 6/323 (1.9%) Control group: 14/328 (4.3%) P = 0.13 of which AMI deaths Intervention group: 1/323 (0.3%) Control group: 8/328 (2.4%) P = 0.05. Other definite 6 from arrhythmias, 2 from congestive cardiac failure, 1 from cardiogenic shock and 2 from cerebrovascular accidents) Intervention group: 5/323 Control group: 6/328 Sudden death Intervention group: 8/323 Control group: 6/328 Indeterminate cause Intervention group: 1/323 Control group: 4/328. Difference in mortality between smokers/non-smokers Smokers: 9.4% Non-smokers: 2.1% P= not significant. Nonfatal infarction: Intervention group: 15/323 Control group: 11/328 Suspected infarctions: Intervention group: 3/323 Control group: 2/328. Other

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
								events: Intervention group: 25/323 Control group: 25/328. All recurrent MI: Intervention group: 17/323 (5.3%) Control group: 23/328 (7.0%) P=0.4 Total hospitalisations for reasons other than MI: Intervention group: 92/323 (28.5%) Control

Grading 1- Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
Reference 2910 Dubach P;Myers J;Dziekan G;Goebbels U;Reinhart W;Vogt P;Ratti R;Muller P;Miettunen R;Buser P; Effect of exercise	Randomised Controlled Trial	Recent MI, and heart failure.	Rehabilitation center for 2 months, training program consisting of two 1 hour sessions of walking daily, along with 4 monitored 45 minute sessions of stationary	Exercise training vs usual care.	2 months.	Maximal exercise oxygen uptake. Ejection fraction. Diastolic, systolic volume. Myocardial wall thickness.	Schweizerische Herzstiftung Switzerland Roche Research Foundation.	Oxygen uptake increased 26% at maximal exercise (19.7±3 to 23.9±5, P < 0.05) and 39% at the lactate threshold (P < 0.01) in the exercise group, whereas control values did not change. No differences were observed within or between groups in MRI measures of end-diastolic (187±47 pre versus 196±35 mL post in the exercise group and

	Study type	Patient characteristics	Interventions	Comparisons	Study length	Outcomes	Funding	Effect
training on myocardial remodeling in patients with reduced left ventricular function after myocardial infarction: application of magnetic resonance imaging 1997 95 Circulation			cycling weekly.					179±52 pre versus 180±51 mL post in the control group), end-systolic volume (118±41 pre versus 121±33 mL post in the exercise group and 119±54 pre versus 116±56 mL post in the control group), or ejection fraction (38.0±9 pre versus 38.2±10% post in the exercise group and 37.0±10 pre versus 38.3±13% post in the control group). Myocardial wall thickness measurements at end diastole and end systole and their difference in 80 myocardial segments determined by MRI yielded no significant interactions

Q.4 Health Economic Extractions

Ref ID: 21	**Ades PA, Pashkow FJ, Nestor JR. Cost-effectiveness of cardiac rehabilitation after myocardial infarction. J Cardpulm Rehabil 1997; 17(4): 222-231.**
Economic study type	CEA, benefit measure was years of life saved (YLS)
Population, country & perspective	Males with a post acute MI below the age of 65 years patient or insurance payer
Intervention	Cardiac rehabilitation + usual care
Comparison(s)	No cardiac rehabilitation (usual care which consisted of thrombolytic therapy, coronary bypass surgery, cholesterol lowering drugs and smoking cessation).
Source of effectiveness data	Published review of RCTs
Method of eliciting health valuations (if applicable)	Not applicable
Cost components included	Direct medical costs
Currency and cost year	The net cost for MI was $430 in 1985 and $940 in 1995. The costs of other common interventions were not stated
Results – cost per patient per alternative	The net cost for MI was $430 in 1985 and $940 in 1995. The costs of other common interventions were not stated
Results – effectiveness per patient per alternative	Cumulative all-cause mortality in the rehabilitation group was reduced by 21.2% at the end of year 1, by 22.9% at the end of 2 years and 16.9% at the end of 3 years of follow-up
Results –incremental cost-effectiveness	The cost per year of life saved was $2,130 in 1985 and the cost per year of life saved (projected) was $4,950 in 1995 (at a 5% discount rate)
Results-uncertainty	Varying the survival rate, the survival probabilities and the rehospitalisation expenses averted
Time horizon & discount rate	3 years 5%
Source of funding	Not stated
Comments	Quantities and costs were reported separately, The authors based their analysis of effectiveness on studies with a randomised design, but it is not clear whether these were identified through a systematic search of the medical literature. It should be noted that estimated benefits are unlikely to be generalisable to females of the same age. As acknowledged by the authors, adjustment for quality of life could have been made

Ref ID: 2919	**Hall JP, Wiseman VL, King MT, Ross DL, Kovoor P, Zecchin RP et al. Economic evaluation of a randomised trial of early return to normal activities versus cardiac rehabilitation after acute myocardial infarction. Heart, Lung & Circulation 2002; 11(1): 10-18.**
Economic study type	Cost consequence analysis. Outcomes were Quality of life (QOL) measures and four measures of return to normal activities (paid and unpaid return to any work and to pre-AMI level of work).
Population, country & perspective	Low-risk patients after acute myocardial infarction (AMI),
Intervention Comparison(s)	6 weeks of standard rehabilitation (REHAB, n = 70) (exercise and counselling 4 times a week) No formal rehabilitation (ERNA, n = 72).

Ref ID: 2919	Hall JP, Wiseman VL, King MT, Ross DL, Kovoor P, Zecchin RP et al. Economic evaluation of a randomised trial of early return to normal activities versus cardiac rehabilitation after acute myocardial infarction. Heart, Lung & Circulation 2002; 11(1): 10-18.
Source of effectiveness data	RCT
Method of eliciting health valuations (if applicable)	Not applicable
Cost components included	Direct medical costs and indirect costs
Currency and cost year	$AUD, cost year not stated
Results – cost per patient per alternative	$21.57/Patient/session for 14 sessions on average direct costs excluding hospital overheads $28.12/Patient/session for 14 sessions on average total hospital costs. The net cost that could be saved by the health service by targeting rehabilitation to high-risk patients was approximately $300 (Australian, 1999) per low-risk patient
Results – effectiveness per patient per alternative	There were no statistically significant differences between the two groups in any of the outcomes measured or in the use of other health services
Results –incremental cost-effectiveness	Not done (cost minimisation)
Results-uncertainty	Not done
Time horizon & discount rate	12 months and discounting was not necessary
Source of funding	Public
Comments	Did not state the cost year. Good discussion

Ref ID: 297	Levin LA, Perk J, Hedback B. Cardiac rehabilitation--a cost analysis. Journal of Internal Medicine 1991; 230(5): 427-434.
Economic study type	Cost consequence analysis
Population, country & perspective	Non-selected post MI patients, societal perspective. Mortality (total & cardiac) Readmission, non-fatal and total cardiac events
Intervention Comparison(s)	Comprehensive cardiac rehabilitation programme 147 non-selected MI patients aged less than 65 years (124 men vs. 23 women) Standard care after myocardial infarction (MI) non-selected MI-population aged less than 65 years (n = 158) (134 men vs. 24 women)
Source of effectiveness data	Prospective non- RCT
Method of eliciting health valuations (if applicable)	Not applicable
Cost components included	Both direct and indirect costs (time costs of rehab and lost productivity)
Currency and cost year	SEK 1996
Results – cost per patient per alternative	Rehab group SEK 484260 vs. SEK 557770 usual care and difference was SEK 73,500 in favour of the rehabilitated group
Results – effectiveness per patient per alternative	Mortality (total & cardiac) did not differ between the groups Readmission was less in the rehab 13.7 days vs. 19.3 days in the control $p<0.05$ They differed in non-fatal reinfaction (17.3 vs. 33.3%), total cardiac events (39.5 vs. 53.2%) p=0.001
Results –incremental cost-effectiveness	Not calculated because it was a cost consequence analysis
Results-uncertainty	Remained robust

Ref ID: 297	Levin LA, Perk J, Hedback B. Cardiac rehabilitation--a cost analysis. Journal of Internal Medicine 1991; 230(5): 427-434.
Time horizon & discount rate	5 yrs, 0 &10%
Source of funding	Not stated
Comments	Even though the study was not controlled it looked at two real life clinical situations, which make the results more useful for the case for comprehensive rehabilitation.

Ref ID: 166	Taylor R, Kirby B. Cost implications of cardiac rehabilitation in older patients. Coronary Artery Disease 1999; 10(1): 53-56.
Economic study type	Review of economic evaluations including costs of the UK cardiac rehabilitation programme
Population, country & perspective	Post-MI patients, Societal cost data for UK and effectives data from a Canadian trial
Intervention Comparison(s)	Cardiac rehabilitation Usual care
Source of effectiveness data	RCT
Method of eliciting health valuations (if applicable)	N/A
Cost components included	Both direct and indirect patient costs
Currency and cost year	£, 1994/5
Results – cost per patient per alternative	£140.00 excluding the indirect costs £207 including indirect costs
Results – effectiveness per patient per alternative	Life year gained per patient 0.022 QALY gained 0.052
Results –incremental cost-effectiveness	£6400/life year gained £2700/QALY gained
Results-uncertainty	Not done
Time horizon & discount rate	12 weeks & 5%
Source of funding	Not stated
Comments	Did not state where they derived the cost data from, but gives insight into the UK situation

No:	993
Study quality:	1+ Cost-effectiveness of captopril therapy after myocardial infarction.[see comment]
Author:	Tsevat J;Duke D;Goldman L;Pfeffer MA;Lamas GA;Soukup JR;Kuntz KM;Lee TH; 1995
Intervention:	Captopril
Comparison:	Placebo
Population:	Post MI patients with LVD
Perspective:	NHS
Study type:	CUA
Methods:	RCT (SAVE study)
Health valuations:	TTO, interviewed 82 patients

No:	**993**		
Cost components:	direct medical		
Currency:	US$		
Cost year:	1991		
Time horizon:	Lifetime		
Discount rate:	5%		
Results- cost:	AGE	Limited benefit	Persistent benefit model
	50 years		
	Captopril	$ 3209	$32883
	Placebo	$30369	$ 30369
	60 years		
	Captopril	$26128	$27382
	Placebo	$24449	$24449
	70 years		
	Captopril	$ 20822	$ 22292
	Placebo	$ 19099	$ 19099
	80 years		
	Captopril	$16699	$ 18067
	Placebo	$ 14844	$ 14844
Results - effectiveness			
	Age	Limited benefit	Persistent benefit model
		QALYs	QALYs
	50 years		
	Captopril	8.13	8.34
	Placebo	8.10	8.10
	60 years		
	Captopril	6.51	6.85
	Placebo	6.33	6.33
	70 years		
	Captopril	5.07	5.47
	Placebo	4.72	4.72
	80 years		
	Captopril	3.96	4.33
	Placebo	3.44	3.44
Results - ICER			
	Age	Ltd benefit ($/QALY)	Persistent benefit model ($/QALY)
	50 years	60800	10400
	60 years	9000	5600
	70 years	4900	4300
	80 years	3600	3700
Results - uncertainty			
For 60-80 years the results are robust to changes in utilities, discount rate, and costs and sensitive in the 50			

No:	993
year olds for the limited benefit model. The persistent benefit model was stable but sensitive to mainly utility changes for the 50 year olds. Worst case analysis showed that the >60yrs results still favour Captopril and for less than 60 years results are	
Source of funding – not stated	
Comments:	
Analysed the results using two models. A) Limited benefit model: assumed mortality will be the same between the intervention post-trial periods. B) Persistent benefit model: assumed differences observed during the trial period will persist for the remaining life time. They also analysed their results by subgroups of age. Appropriate analytical methods were used, and sources of data documented. Data was incorporated as point estimates and parameters subjected to sensitivity analysis.	

No:	984		
Study quality:	1+ The cost and cardioprotective effects of enalapril in hypertensive patients with left ventricular dysfunction		
Author:	Cook JR;Glick HA;Gerth W;Kinosian B;Kostis JB; 1998		
Intervention:	Enalapril		
Comparison:	Placebo		
Population:	Patients with elevated blood pressure and LVD		
Perspective:	SOCIETAL (only direct medical costs were collected)		
Study type:	CEA & CUA		
Methods:	RCT (SOLVD study)		
Health valuations:	From literature		
Cost components:	Direct medical		
Currency:	US$		
Cost year:	1996		
Time horizon:	life time projection and the 3 year trial observational period		
Discount rate:	5%		
Results – cost	Enalapril	Placebo	
	$8499	$9156	
Results – effectiveness			
	Outcome	Enalapril	Placebo
	Years gained	2.84	2.68
	QALYs	1.74	1.62
Results - ICER	Not calculated. Enalapril dominated placebo i.e. it costs less and results in more health benefits		
Results - uncertainty	Results were very robust and the CEACs showed that there was a less than 10% chance that enalapril treatment will increase the costs compared to placebo. Lifetime projection showed that 94% of the cases enalapril will dominate		
Source of funding	Not stated		
Comments	Placebo reported results of the treatment trial and prevention trial. This report focuses on the prevention trial results. They used standard methodology in their modelling. Sources of effectiveness and cost data well referenced. Data was incorporated as point estimates and subjected to probabilistic sensitivity analysis as well as univariate.		

No:	984	
No:	998	
Study quality:	1+ Cost-effectiveness of ramipril in patients at high risk for cardiovascular events: a Swiss perspective	
Author:	Aurbach A;Russ W;Battegay E;Bucher HC;Brecht JG;Schadlich PK;Sendi P; 2004	
Intervention:	Ramipril	
Comparison:	Placebo	
Population:	Patients with increased risk of cardiovascular events	
Perspective:	NHS	
Study type:	CEA	
Methods:	RCT (HOPE study)	
Health valuations:	NOT APPLICABLE	
Cost components:	direct medical	
Currency:	OTHER (Swiss Franc) CHF	
Cost year:	2001	
Time horizon:	4.5 years	
Discount rate:	5%	
Results – cost	Hope study (all patients)	Hope study (diabetic subgroup)
	LYB 11.88	LYG 19.69
Results – ICER	Hope study (all patients)	Hope study (diabetic subgroup)
	ICER 6005/LYG	3790/LYG
Results - uncertainty	Did both deterministic and probabilistic sensitivity analysis. Results were sensitive to cost of drug	
Source of funding	Private (Aventis Pharma)	
Comments	Well reported using standard methodology. Data incorporated as point estimates and subjected to sensitivity analysis Used CEACs to quantify the uncertainty surrounding the ICER. Also did a best case and worst case analysis	

No:	965
Study quality:	1+ The cost-effectiveness of ramipril in the treatment of patients at high risk of cardiovascular events: a Swedish sub-study to the HOPE study
Author:	Bjorholt I;Andersson FL;Kahan T;Ostergren J; 2002
Intervention:	Ramipril
Comparison:	Placebo
Population:	Patients at high risk of cardiovascular events
Perspective:	NHS
Study type:	CEA
Methods:	RCT (HOPE study)
Health valuations:	base case results did not consider quality of life, but in sensitivity analysis they did using TTO
Cost components:	direct medical for base case and direct medical and non medical + indirect costs
Currency:	OTHER (SKr)

No:	**965**			
Cost year:	1999			
Time horizon:	4.5 years			
Discount rate:	3%			
Results – cost	Total category	Ramipril	Placebo	Difference (Mean SEK)
	Total direct medical costs	48957	46294	2663 (NS)
	Direct non medical costs	1450	1725	-275 (NS)
	Indirect costs	52525	46972	2582 (NS)
Results – effectiveness	Expected LYG at the end of the study 0.16			
	Cardiovascular events avoided 3.8%			
Results – ICER	BASE CASE RESULTS			
Costs related to cardiovascular risk only		Cost/LYG	Cost/CVE avoided	
	Direct medical	16600	76100	
	Direct medical + direct non-medical	16100	73800	
Costs related to all diseases		Cost/LYG	Cost/CVE avoided	
	Direct medical	5400	207300	
	Direct medical + direct non-medical	54600	249600	
Using QoL weights	SEK 26600/QALY			
	SEK 333300/QALY if future costs are included			
Results – uncertainty	the results were sensitive to life expectancy assumptions and QALYs. The primary analysis focused on the health service provider perspective. Additional analysis was done from societal perspective which included direct medical + direct non medical + indirect costs.			
Source of funding	Private (Astra Zeneca and Aventis)			
Comments	Base case used the health care perspective, but considered societal in further analysis. Data was incorporated as point estimates from the HOPE study appropriate modelling methods were used.			

No:	**987**
Study quality:	1+ Cost-effectiveness of the treatment of heart failure with ramipril: a Spanish analysis of the AIRE study
Author:	Hart WM;Rubio-Terres C;Pajuelo F;Juanatey JR; 2002
Intervention:	Ramipril
Comparison:	Placebo
Population:	Post MI with heart failure
Perspective:	NHS
Study type:	CEA
Methods:	RCT (AIRE study)
Health valuations:	NOT APPLICABLE
Cost components:	Direct medical

No:	**987**			
Currency:	EURO			
Cost year:	2000			
Time horizon:	4 years			
Discount rate:	6%			
Results - cost	Follow up		Add on cost of ramipril	
	1 year		euro 129.2	
	2 year		euro 197.6	
	3 year		euro 435.5	
	3.8 year		euro 399.2	
Results – effectiveness	Follow up		Incremental LYG	
	1 year		0.027	
	2 year		0.059	
	3 year		0.071	
	3.8 year		0.100	
Results – ICER	Follow up		Cost/LYG	
	1 year		euro 4784	
	2 year		euro 2286	
	3 year		euro 2763	
	3.8 year		euro 1550	
Results – uncertainty	Two-way sensitivity analysis varying the length of stay and discount rate was done. Results were robust.			
Source of funding	Private (Aventis Pharma)			
Comments	The study was well reported. Data sources well referenced and incorporated as point estimates. Appropriate methods were used.			
No:	959			
Study quality:	1+ A South African pharmaco-economic analysis of the acute infarction ramipril efficacy (AIRE) study			
Author:	Anderson AN; Moodley I; Kropman K; 2000			
Intervention:	Ramipril			
Comparison:	Placebo			
Population:	Post MI patients with heart failure			
Perspective:	NHS			
Study type:	CEA + CUA			
Methods:	RCT (AIRE study)			
Health valuations:	NOT stated (used data from literature)			
Cost components:	Direct medical			
Currency:	Other (South African Rand)			
Cost year:	1999			
Time horizon:	4 year			
Discount rate:	5%			
Results – cost	Follow up	Incremental mean costs	Lower limit	Upper limit
	1 year	1833	1340	2465
	2 year	1576	1147	2125

No:	987			
	3.8 year	1278	949	1702
Results - effectiveness	Follow up	LYG		
	1 year	0.027		
	2 year	0.090		
	3.8 year	0.289		
	QALYs for <65 years = 0.786			
	QALYs for >65 years =0.932			
Results - ICER	Follow up	Cost/LYG	Lower limit	Upper limit
	1 year	67907	49633	91290
	2 year	17516	12743	23615
	3.8 year	4423	3284	5888
Cost utility results	Age group	Cost/QALY	Lower limit	Upper limit
	<65 years	5627	4177	7490
	>65 years	4744	3522	6315
Results - uncertainty	Results were robust in sensitivity analysis as shown by the confidence intervals			
Source of funding	Private (Hoechst Marion Russell)			
Comments	Used QoL weights from the literature and referenced their sources. Data incorporated as point estimates and appropriate methodology was used. Stratified their results according to age and as expected the ICERs were favourable for the elderly than the younger patients.			

No:	953	
Study quality:	1+ Economic aspects of treatment with captopril for patients with asymptomatic left ventricular dysfunction in The Netherlands.	
Author:	Michel BC; Al MJ; Remme WJ; Kingma JH; Kragten JA; van Nieuwenhuizen R; van Hout AB; 1996	
Intervention:	Captopril	
Comparison:	Placebo	
Population:	Post MI with LVD	
Perspective:	Societal (but only direct medical costs are reported)	
Study type:	CEA	
Methods:	RCT (SAVE & SOLVD study)	
Health valuations:	Not applicable	
Cost components:	Direct medical	
Currency:	Other (DFI Netherlands)	
Cost year:	Not stated	
Time horizon:	4 year and 20 year extrapolation	
Discount rate:	5%	
Results - cost	Follow up	Additional cost
	4 years	2491
	20 years	8723
	Follow up	Additional cost/additional survivor
	4 years	69126

No:	953	
	20 years	68142
Results - effectiveness	Follow up	LYG
	4 years	0.11
	20 years	0.55
Results – ICER	Follow up	Cost/LYG
	4 years	22887
	20 years	15799
Results - uncertainty	both univariate and multivariate sensitivity analysis were done. Univariate showed that results were sensitive to cost of the drug and the occurrence and prevention of heart failure	
Source of funding	Not stated	
Comments	Data was incorporated as point estimates and appropriate methods of modelling were used. Sources of both effectiveness and cost data were described and referenced. Sensitivity analysis was done and caveats of the study well discussed.	

No:	948	
Study quality:	1+ Clinical and economic benefits of ramipril: an Australian analysis of the HOPE study. [see comment]	
Author:	Smith MG; Neville AM; Middleton JC; 2003	
Intervention:	Ramipril	
Comparison:	Placebo	
Population:	Patients at high risk of cardiovascular diseases	
Perspective:	NHS	
Study type:	CEA	
Methods:	RCT (HOPE study)	
Health valuations:	Not applicable	
Cost components:	Direct medical	
Currency:	AU$	
Cost year:	Not stated	
Time horizon:	5 years	
Discount rate:	5%	
Results – cost:	Not given	
Results – effectiveness:	Outcome	Number avoided (95% CI) over 5 years
	Stroke	9188 (4305 to 14317)
	MI	14658 (6765 to 22801)
	Revascularisation	14317 (4925 to 23678)
	Cardiovascular related mortality	12534 (6156 to 18655)
Results – ICER	Cost/LYS (95%CI) = $ 17214 (8338 to 39536)	
Results – uncertainty	Both a univariate and Monte Carlo sensitivity analysis was done. The results were sensitive to risk of cardiovascular death, cost and risk of revascularisation mainly. Structural assumption about the similarity between the Australian population to that used in the HOPE were similar were tested, so was the effect of blood pressure reduction and results remained robust	

No:	948
Source of funding	Not stated but the author worked for Aventis Pharma
Comments	Did not provide detailed costs data. Used appropriate methodology for incorporating data. They used probabilistic sensitivity analysis to quantify the confidence intervals around the ICER and their findings were robust.

No:	946		
Study quality:	1+ Cost effectiveness of ramipril treatment for cardiovascular risk reduction		
Author:	Malik IS; Bhatia VK; Kooner JS; 2001		
Intervention:	Ramipril		
Comparison:	Placebo		
Population:	Patients with different risks of mortality. Mortality risks are classified as low (1%), medium (2.44%) high (4.5%) and highest (7%)		
Perspective:	NHS		
Study type:	CEA		
Methods:	RCT (HOPE & AIRE studies)		
Health valuations:	Not applicable		
Cost components:	Direct medical		
Currency:	£		
Cost year:	1999-2000		
Time horizon:	5 years to lifetime		
Discount rate:	6%		
Results – cost:	Not given		
Results – effectiveness	Authors estimated number of lives gained per year for those on ramipril as well as those eligible for treatment using HOPE study results		
		Eligible population	Life year gained
	Total population	>3000000	12000
	Ischemic heart disease	1400000	5600
	Stroke	600000	2400
	Diabetes	1700000	6800
	Peripheral vascular disease	1000000	4000
Results – ICER	Results	5 years	20 years
	Base case	14700	2800
	Low risk	36600	5300
	High risk	4000	100
	Highest risk	1300	-900 (net saving)
Results – uncertainty	Results were sensitive to drug cost and cost savings (arising from reduction in events) using arbitrary figures of 50 to 200% of the baseline values.		
Source of funding	Charitable		
Comments	The study was well reported using standard methodology including a half year correction factor for the occurrence of events. Data was incorporated as point estimates and sources well referenced. A detailed sensitivity analysis was done.		

No:	**941**	
Study quality:	1+ Cost-effectiveness of ramipril therapy for patients with clinical evidence of heart failure after acute myocardial infarction	
Author:	Martinez C; Ball SG; 1995	
Intervention:	Ramipril	
Comparison:	Placebo	
Population:	Patients with heart failure after MI	
Perspective:	NHS	
Study type:	CEA	
Methods:	RCT (AIRE study)	
Health valuations:	Not applicable	
Cost components:	Direct medical	
Currency:	£	
Cost year:	1993	
Time horizon:	4 years	
Discount rate:	6%	
Results – cost:	Follow up	Cost/patient
	1 year	11.42
	2 year	12.79
	3.8 year	73.77
Results – effectiveness	Follow up	LYG
	1 year	0.027
	2 year	0.090
	3.8 year	0.289
Results - ICER	Follow up	Cost/LYG
	1 year	425.79
	2 year	147.90
	3.8 year	286.24
Results - uncertainty	did a two way sensitivity analysis and results were not sensitive to changes in LYG and hospitalisation costs	
Source of funding	Not stated	
Comments		

No:	**982**
Study quality:	1+ Economic evaluation of ramipril in the treatment of patients at high risk for cardiovascular events
Author:	Backhouse ME;Richter A;Gaffney L; 2000
Intervention:	Ramipri
Comparison:	Placebo
Population:	Patients at high risk of cardiovascular events
Perspective:	NHS
Study type:	CEA
Methods:	RCT (HOPE study)
Health valuations:	Not applicable

No:	982	
Cost components:	Direct medical	
Currency:	£	
Cost year:	1999	
Time horizon:	5 years	
Discount rate:	6%	
Results – cost	Cost/patient:	
	Ramipril: 1426	
	Placebo: 808	
Results - ICER	£5544/LYG	
Results - uncertainty	Results were not sensitive to assumptions about the timing of the occurrence of events (half cycle correction factor), but rather to assumptions about life expectancy beyond the 5 year trial period. This also dependant on age. (structural assumption being tested in patients stratified by age)	
Source of funding	not stated	
Comments	Did a sensitivity analysis focusing on structural assumptions and a subgroup stratified by age. Data incorporated as point estimates using appropriate methodology	

No:	991	
Study quality:	1+ Cost-effectiveness analysis of ramipril in heart failure after myocardial infarction: economic evaluation of the Acute Infarction Ramipril Efficacy (AIRE) Study for Germany from the perspective of statutory health insurance	
Author:	Schadlich PK;Huppertz E;Brecht JG; 1998	
Intervention:	Ramipril	
Comparison:	Placebo	
Population:	Post MI patients with heart failure	
Perspective:	NHS	
Study type:	CEA	
Methods:	RCT (AIRE study)	
Health valuations:	Not applicable	
Cost components:	Direct medical	
Currency:	Other (Deutschmarks)	
Cost year:	1993/1995	
Time horizon:	3.8 years	
Discount rate:	5%	
Results - cost	Incremental costs of adding ramipril	
	Follow up	Mean cost (DM)
	1 year	223
	2 year	361
	3 year	860
	3.8 year	710
Results – effectiveness	Follow up	LYG

No:	991			
	1 year		0.027	
	2 year		0.090	
	3 year		0.170	
	3.8 year		0.289	
Results -ICER	Cost/LYG			
	Follow up	Mean cost(DM)	Lower limit CI	Upper limit CI
	1 year	7	-3712	13624
	2 year	4012	-2402	6863
	3 year	5056	2203	6438
	3.8 year	2456	-102	3623
	Negative ICERS indicate savings from ramipril use			
Results – uncertainty	Tested for both methodological and parameter uncertainty. They used Weibull and Kaplan-Mier to quantify the LYG, and a Monte Carlo simulation. Ramipril was found to be cost effective, dominating the alternative in 5% of the cases. 99% of the cases the ICER ranged between -DM2500 to DM8500. Results are sensitive to hospitalisation too.			
Source of funding	Private (Hoechst Marion Russell Germany)			
Comments	gave detailed description of the methods including an appendix			

No:	989	
Study quality:	1++ The economics of TRACE: a cost-effectiveness analysis of trandolapril in post infarction patients with left ventricular dysfunction	
Author:	LePen C; Lilliu H;Keller T;Fiessinger S; 1998	
Intervention:	Trandolapril	
Comparison:	Placebo	
Population:	Post MI patients with LVD	
Perspective:	NHS	
Study type:	CEA	
Methods:	RCT (TRACE study)	
Health valuations:	Not applicable	
Cost components:	Direct medical	
Currency:	Other (French francs)	
Cost year:	1996	
Time horizon:	2 years	
Discount rate:	5%	
Results – cost	Trandolapril	22 080 500
	Placebo	20 317 300
	Difference	1 763 200
Results – effectiveness		All cause mortality
	Trandolapril	304
	Placebo	369
	Difference	65
	Mean life expectancy 5.52 years in each group.	
Results - ICER	Using raw data from the trial, Cost/life year saved was FF27100	

No:	989	
	Using the life expectancy at the end of trial discounting both benefits and costs , FF6950/LYS	
	BOOTHSTRAP results (95% CI), FF8410 (7990 to 8840)	
Results – uncertainty	the results are robust in sensitivity analysis. Bootstrap results showed that 7.4% of the cases trandolapril dominated placebo and 92.6% of the cases the ICER was positive but still within the acceptable ranges of cost/LYG.	
Source of funding	Private (Hoechst Marion)	
Comments	The study was well reported. They tested for methodological uncertainty using different methods to estimate the cost effectiveness (student's T distribution, bootstrap method). Appropriate modelling methods were used. Data sources were referenced, and data was incorporated as point estimates. Probabilistic and univariate sensitivity analysis were done and results were robust.	

No:	986	
Study quality:	1++ Cost effectiveness in the treatment of heart failure with ramipril: a Swedish sub study of the AIRE study.	
Author:	Erhardt C; Ball Sanderson F; Bergentoft P; Martinez C; 1997	
Intervention:	Ramipril	
Comparison:	Placebo	
Population:	Post MI patients with heart failure	
Perspective:	NHS	
Study type:	CEA	
Methods:	RCT (AIRE study)	
Health valuations:	Not applicable	
Cost components:	Direct medical	
Currency:	Other (SEK)	
Cost year:	1993	
Time horizon:	3.8 years	
Discount rate:	5%	
Results - cost	Follow	Cost/patient
	1 year	991
	2 years	1579
	3.8 years	2826
Results – effectiveness	Follow up	Life saved
	1 year	0.03
	2 year	0.09
	3.8 years	0.22
Results - ICER	Follow up	Cost/LYS
	1 year	33033
	2 year	18153
	3.8 years	14148
Results – uncertainty	findings were reported to be robust to many variables (which were not mentioned) including number of live years saved. The model was sensitive to hospital costs	

No:	986
Source of funding	Private (Astra hassle and Hoechst Marion Russell)
Comments	Tested methodological uncertainty by using both the Weibull method of estimating survival and the Kaplan-Mier method. Did a two-way sensitivity analysis to test parameter uncertainty. Results were reported in two parts. First with only cost discounted and secondly with both costs and effects discounted. In line with NICE recommendations only results reporting discounting for both cost and benefits have been abstracted.

What is the effectiveness of adding aspirin versus clopidogrel to improve outcome in patients after MI?

No:	1108	
Study quality:	1+Clopidogrel versus aspirin for secondary prophylaxis of vascular events: a cost- effectiveness analysis	
Author:	Schleinitz MD; Weiss JP; Owens DK; 2004	
Intervention:	Clopidogrel	
Comparison:	Aspirin	
Population:	Patients at Risk of Ischemic Events. These included three set of patients, those with prior peripheral vascular disease, prior stroke, prior MI	
Perspective:	Societal	
Study type:	CUA, using a markov decision model. Outcomes were stroke, reinfaction, mortality, hemorrhagic events	
Methods:	RCTs, CAPRIE trial for base case, European stroke prevention study, and observational studies	
Health valuations:	From literature	
Cost components:	direct medical costs derived from literature, Medicare DRGs, wholesale prices for medication	
Currency:	US$	
Cost year:	2002 (using GDP deflator)	
Time horizon:	Lifetime	
Discount rate:	3%	
Reuslts - cost	Lifetime costs	
	Aspirin	$91700
	Clopdigorel	$98500
Results - effectiveness	Life expectancy in QALYs	
	Aspirin	11.09
	Clopidogrel	10.83
Results – ICER	Not calculated	
Results – uncertainty	results were sensitive to the cost and effectiveness of clopidogrel. Even in probabilistic sensitivity analysis, aspirin remained dominant in 88% of the cases.	
Source of funding	Charitable	
Comments	The study was well reported with details of how the data was obtained and used in the model. The authors stated they were considering a societal perspective; however, only direct medical costs were included. A detailed breakdown of the cost items was not provided since most of the data were obtained from published studies. This reduces the possibility of replicating	

No:	1108	
	the study.	
No:	1094	
Study quality:	1+ Cost-effectiveness analysis of clopidogrel versus aspirin in patients with atherothrombosis based on the CAPRIE trial	
Author:	Annemans L; LaMotte M; Levy E; Lenne X; 2003	
Intervention:	Clopidogrel	
Comparison:	Aspirin	
Population:	Patients with vascular disease with recent stroke, myocardial infarction (MI) or symptomatic peripheral arterial disease	
Perspective:	NHS, Belgium	
Study type:	CEA, markov model stroke, vascular and other death, reinfaction, costs, ICERs	
Methods:	RCT CAPRIE study, and Saskatchewan database	
Health valuations:	Not applicable	
Cost components:	Direct medical costs derived from literature and Diagnosis-related group (DRG)	
Currency:	Euro	
Cost year:	2002	
Time horizon:	2 years	
Discount rate:	3%	
Results – cost	Clopidogrel	Euro 12612 000
	Aspirin	Euro 11753 000
Results - effectiveness	Clopidogrel	12158 life years
	Aspirin	12084 life years
Results -ICER	Euro 13390/LYG using the deterministic model and 14320 euros/LYG 95%CI [6990-26470] using the probabilistic model. Using a willingness to pay threshold figure of 20000 euros/LYG clopidogrel is 86% cost effective.	
Results – Uncertainty	results were robust in both deterministic and probabilistic sensitivity analysis. They examined the impact of discount rate (0-6%), cost of adverse and ischemic events and assumptions about life expectancy plus or minus 50%. Monte Carlo probabilistic analysis was done using beta distribution for effects and triangular for costs.	
Source of funding	Private	
Comments	results were robust in both deterministic and probabilistic sensitivity analysis. They examined the impact of discount rate (0-6%), cost of adverse and ischemic events and assumptions about life expectancy plus or minus 50%. Monte Carlo probabilistic analysis was done using beta distribution for effects and triangular for costs.	

No:	1101
Study quality:	1++ Modeling the long term cost effectiveness of clopidogrel for the secondary prevention of occlusive vascular events in the UK
Author:	Karnon J; Brennan A; Pandor A; Fowkes G; Lee A; Gray D; Coshall C; Nicholls C; Akehurst R; 2005
Intervention:	Clopidogrel (75 mg/day) for 2 years followed by ASA (325 mg/day, average) for their remaining lifetime.

No:	1101		
Comparison:	ASA alone (325 mg/day, average) for life.		
Population:	Patients who were at risk of secondary occlusive vascular events OVEs (non-fatal myocardial infarction, non-fatal stroke or vascular death) who met the inclusion criteria of the CAPRIE study		
Perspective:	NHS		
Study type:	CUA, reinfaction, stroke, vascular death, ICERs,		
Methods:	RCT, CAPRIE study and data from the NHAR UK. London stroke register, Edinburgh Claudication study		
Health valuations:	Derived from literature		
Cost components:	direct medical costs of treatment and procedures. Costs were derived from the literature, and BNF.		
Currency:	£		
Cost year:	2002		
Time horizon:	Lifetime – 40 years		
Discount rate:	6%		
Results – cost	2 years of clopidogrel	£1359628	
	Lifetime costs of clopidogrel	£19199554	
	2 years of ASA	£1388494	
	Lifetime costs of ASA	£18380509	
Results – effectiveness		QALY gained	Life year gained
	Clopidogrel	12002	14242
	Aspirin	11964	14199
Results – ICER	Cost/QALY	£18888	
	Cost/LYG	£21489	
	Clopidogrel would be cost effective in 60% of the cases at £30000/QALY.		
Results - uncertainty	results were not sensitive to all input parameters except for the mean annual risk of vascular events and the relative risk of vascular death. Probabilistic sensitivity analysis showed that clopidogrel is cost effective in 60% of the cases at a threshold value of £30000/QALY.		
Source of funding	Private		
Comments	This study is well reported and the authors were very clear in the methodology used and the sources of their input parameters. The only problem however is that their results can not be generalized to the Post MI population per se as they did not report the three conditions separately, stroke, PAD and Post MI.		

No:	1100
Study quality:	1++ Clinical effectiveness and cost-effectiveness of clopidogrel and modified-release dipyridamole in the secondary prevention of occlusive vascular events: a systematic review and economic evaluation.
Author:	Jones L;Griffin C;Palmer S;Main C;Orton V;Sculpher M;Sudlow C;Henderson R; Hawkins, N; Riemsma R; 2004
Intervention:	Clopidogrel
Comparison:	ASA
Population:	Patients who experienced an MI
Perspective:	NHS

No:	1100
Study type:	CUA, reinfaction, stroke, cardiovascular and other death, ICERs
Methods:	CAPRIE and the NHAR
Health valuations:	From literature
Cost components:	direct medical costs hospitalisation, procedures, adverse events and drug costs. Cost data was derived from literature and DRGs, BNF
Currency:	£
Cost year:	
Time horizon:	40 years (lifetime)
Discount rate:	3.5%
Results – cost	Results were presented in four scenarios. Two of the scenario considered life treatment including or excluding treatment effect on vascular death. The other two considered 2 year treatment period including or excluding treatment effects on vascular death. Scenario 1. Life with non vascular death Clopidogrel: £25773 ASA: £18286 Scenario 2. Life with vascular death Clopidogrel: £25585 ASA: £18285 Scenario 3. 2 years with non vascular death Clopidogrel: £19202 ASA: £18284 Scenario 4.2 years with vascular death Clopidogrel: £19078 ASA: £18182
Results – effectiveness	Scenario 1. Life with non vascular death Clopidogrel: 9.10 QALYS ASA: 8.86 QALYS Scenario 2. Life with vascular death Clopidogrel: 8.94 QALYS ASA: 8.86 QALYS Scenario 3. 2 years with non vascular death Clopidogrel: 8.95 QALYS ASA: 9.90 QALYS Scenario 4.2 years with vascular death Clopidogrel: 8.91 QALYS ASA: 8.87 QALYS
Results – ICER	Scenario 1. Life with non vascular death £31400/QALY. Probability that clopidogrel is cost effective WTP was £10000/QALY is 0% and 48% at £30000/QALY

No:	1100
	Scenario 2. Life with vascular death £94446/QALY Probability that clopidogrel is cost effective WTP was £10000/qaly is 0% and 25% at £30000/QALY Scenario 3. 2 years with non vascular death £17081/QALY Probability that clopidogrel is cost effective WTP was £10000/qaly is 17% and 71% at £30000/QALY Scenario 4.2 years with vascular death £21448/QALY Probability that clopidogrel is cost effective WTP was £10000/qaly is 12% and 61% at £30000/QALY
Results – uncertainty	Results were sensitive to the efficacy of the treatment (if RR observed in CAPRIE were used, which showed increased risk of events with clopidogrel, aspirin would dominate clopidogrel. Results were also sensitive to the inclusion or exclusion of vascular death in the model.
Source of funding	Public
Comments	Two studies that are relevant for Post MI patients which were included in the HTA have been individually appraised. The authors did an extended economic model focusing on stroke, PAD, MI. Only results of the model reporting on Post MI patients have been reported. The model was well reported with references of the sources of data. The base case analysis included or excluded the effect of the treatment on vascular death in the short and long-term model.

What is the effectiveness of adding aspirin versus aspirin and clopidogrel to improve outcome in patients after MI?

No:	1102
Study quality:	1+ Using clopidogrel in non-ST-segment elevation acute coronary syndrome patients: A cost-utility analysis in Spain
Author:	Latour-Perez J; Navarro-Ruiz A; Ridao-Lopez M; Cervera-Montes M; 2004
Intervention:	Clopidogrel + aspirin
Comparison:	Aspirin alone
Population:	Patients with non-ST-segment elevation acute coronary syndrome
Perspective:	Societal
Study type:	CUA, stroke, reinfaction, death, refractory ischemia, bleeding, ICERs.
Methods:	RCT, CURE study, the Framingham study, and the Spanish age-sex-specific mortality rates
Health valuations:	NOT STATED, values derived from literature
Cost components:	direct medical cost, treatment and cost of procedures derived from DRGs and Spanish Ministry of Health
Currency:	EURO
Cost year:	1999
Time horizon:	Lifetime
Discount rate:	3%

No:	1102
Results – cost	Clopidogrel + ASA: euro 24806 Aspirin: euro 23962
Results – effectiveness	Clopidogrel + ASA: 8.77 QALYs ASA: 8.70 QALYs
Results – ICER	Euro 12221 95%CI (8392-28041) for men Euro 10299 for women Results were presented according to age and base baseline risk of events. The base case results shown above were of a 64 year old medium risk case. For 40 year old Low risk: 10846 euros/QALY Medium risk 7778 euros /QALY High risk 5272 euros/QALY 80 year old Low risk: 37726 euros/QALY Medium risk 23803 euros /QALY High risk 9831 euros/QALY
Results – uncertainty	a one way, two way and probabilistic sensitivity analysis was done. Main attention was given to the effect of age, sex and baseline risk. Results were sensitive to age of the patient, the base risk of cardiovascular events, and the precision of the estimated effectiveness of clopidogrel.
Source of funding	Not stated
Comments	The study was well reported used standard acceptable methodology. They did an elaborate sensitivity analysis and sub-group analysis which were helpful. The authors concluded that clopidogrel is cost effective in non-ST-segment elevation, however in the results section authors reported results stratified by men and women in the base case, but it's not clear in the paper which figures or results applied to men.

No:	1103
Study quality:	1+ The long-term cost-effectiveness of clopidogrel plus aspirin in patients undergoing percutaneous coronary intervention in Sweden
Author:	Lindgren P, Stenestrand U; Malmberg K; Jonsson B; 2005
Intervention:	Clopidogrel + aspirin
Comparison:	Aspirin
Population:	Patients with unstable coronary artery disease (CAD) undergoing PCI in Sweden
Perspective:	Societal
Study type:	CEA, reinfaction, cardiovascular and other death
Methods:	RCT, PCI-CURE study, Swedish Register of Heart and Intensive care Admissions (RIKS-HIA)
Health valuations:	NOT APPLICABLE
Cost components:	direct medical costs and indirect costs, Costs were derived from DRGs and literature
Currency:	Euro
Cost year:	2004. Converted using PCI

No:	**1103**
Time horizon:	Lifetime
Discount rate:	3%
Results – cost	Aspirin + Clopidogrel: Direct costs=2726 euros Indirect =282 euros Total=3132 euros Patients with Diabetes 50 year olds - -16 euros 60 year olds-72 euros 80 year olds-374 euros Patients without Diabetes 50 year olds -211 euros 60 year olds-261 euros 80 year olds-430 euros Aspirin Direct costs=2277 euros Indirect =523 euros Total=2799 euros
Results – effectiveness	Aspirin + Clopidogrel: 14.16 years Aspirin alone: 14.12 years Difference 0.04 years Patients with Diabetes 50 year olds -0.03 60 year olds-0.04 80 year olds-0.09 Patients without Diabetes 50 year olds -0.03 60 year olds-0.05 80 year olds-0.09
Results – ICER	Direct medical costs: 10993 euros/LYG Total costs: 8127 euros/LYG Cost utility was done in sensitivity analysis. 6506 euros/QALY Patients with Diabetes 50 year olds -dominance 60 year olds-1969 euros/LYG 80 year olds-3961 euros/LYG Patients without Diabetes 50 year olds -7243 euros/LYG

No:	1103
	60 year olds-6929 euros/LYG 80 year olds-4609 euros/LYG In sensitivity analysis they considered post MI patients that occurred 7 days after admission and combination therapy dominated aspirin alone.
Results – Uncertainty	the model was robust to changes in variables such as costs and discounting.
Source of funding	Private
Comments	Methodologically the paper was well reported. Sources of effectiveness and cost data were clearly reported and both deterministic and probabilistic sensitivity analysis was done. They also did a sub-group analysis in which the conclusions remained the same with either age or diabetes mellitus. ICERs were more favorable for the younger patients aged 50 years with diabetes mellitus and less favorable for the 70 year olds with or without diabetes. Their model predicted fewer/less events than the CURE study did making their estimates more conservative. Their results can not be generalized to the post MI population

No:	1111
Study quality:	1+Long-term cost-effectiveness of clopidogrel given for up to one year in patients with acute coronary syndromes without ST-segment elevation
Author:	Weintraub WS; Mahoney EM; Lamy A; Culler S; Yuan Y; Caro J; Gabriel S; Yusuf S; CURE S; 2005
Intervention:	Clopidogrel + ASA
Comparison:	ASA/placebo
Population:	Patients who had experienced an acute coronary syndrome (ACS) without ST-segment elevation
Perspective:	NHS
Study type:	CEA, outcomes were death, stroke, and myocardial infarction, ICERs
Methods:	RCT CURE study, observational data from the Saskatchewan and Framingham Heart study
Health valuations:	Not applicable
Cost components:	direct medical costs 9hospitalisations) and medication costs. These costs were derived from DRGs, Medicare and MEDSTAT data base.
Currency:	US $
Cost year:	2001
Time horizon:	12 months
Discount rate:	3%
Results – cost	Using Medicare DRG costs Clopidogrel: $13019 Placebo: $12578 Using MEDSTAT (private reimbursement) costs Clopidogrel: $17924 Placebo: $17586
Results - effectiveness	Total number of events using Framingham data Clopidogrel: 0.5327 Placebo: 0.6026

No:	1111
	LYG with clopidogrel: 0.0699 Total number of events using Saskatchewan data Clopidogrel: 0.3910 Placebo: 0.4592 LYG with clopidogrel: 0.0682
Results – ICER	Using Framingham data Medicare costs: $9144/LYG and 92.8% probability of being cost effective at $50000/LYG Using MEDISTAT costs: $ 7654/LYG and 93.4% probability of being cost effective at $50000/LYG Using Saskatchewan data Medicare costs: $9343/LYG and 97% probability of being cost effective at $50000/LYG Using MEDISTAT costs: $ 7833/LYG and 97.6% probability of being cost effective at $50000/LYG Sub-groups Using Framingham database <65 years $5022/LYG >65years $7569/LYG Male $2362/LYG Female $70396/LYG Diabetes $9857/LYG No diabetes $5583/LYG Prior MI $1404/LYG No prior MI $14171/LYG
Results - uncertainty	results remained robust in sensitivity analysis even when baseline data from the Saskatchewan database was used.
Source of funding	Not stated
Comments	The authors were very detailed in their reporting of the methods they used. For costing they used three different credible methods and for effectiveness data they used the CURE trial and two observational databases the Framingham and Saskatchewan to estimate life expectancy, which yielded comparable results.

No:	1109
Study quality:	1+ A cost-effectiveness analysis of combination antiplatelet therapy for high-risk acute coronary syndromes: clopidogrel plus aspirin versus aspirin alone.
Author:	Schleinitz MD, Heidenreich PA; 2005
Intervention:	Clopidogrel, 75 mg/d, plus Aspirin, 325 mg/d, for 1 year,
Comparison:	Aspirin
Population:	Patients with unstable angina and electrocardiographic changes or non-Q-wave myocardial infarction over a lifetime
Perspective:	Societal

No:	1109
Study type:	CUA, reinfaction, stroke, mortality, quality-adjusted life-years (QALYs), hemorrhagic events & ICERs
Methods:	RCT, CURE study
Health valuations:	derived the values from the literature
Cost components:	direct medical costs incurred during hospitalisation incusing nursing care and procedures, wholesale price for medications. Used a GDP deflator to update costs to 2002.
Currency:	US $
Cost year:	2002
Time horizon:	Lifetime
Discount rate:	3%
Results – cost	Patients treated with aspirin alone costs $127700 Addition of clopidogrel costs $129300
Results - effectiveness	Patients treated with aspirin alone lived 9.51 QALYs Addition of clopidogrel increased life expectancy to 9.61 QALYs
Results - ICER	The incremental cost-effectiveness ratio for clopidogrel plus aspirin compared with aspirin alone was 15,400 dollars per QALY. Duration of therapy The marginal costs of the second year of therapy was $31600/QALY, Third year $61300/QALY Fourth year $136500/QALY Fifth year $730000/QALY Before the end of the third year the efficacy of clopidogrel was reduced by about 25% in the model.
Results – uncertainty	results were not sensitive to changes in risk reduction and costs of clopidogrel in both deterministic and one way sensitivity analysis.
Source of funding	Public
Comments	This analysis may not apply to patients with severe heart failure, those undergoing long-term anticoagulant therapy or those recently managed with revascularization. The study did not focus on a particular ACS which might limit its applicability to the Post MI population. Otherwise the study was well reported, proving details of sources of data, how the data was incorporated as well as a clear model structure.

No:	1099
Study quality:	1+ Cost effectiveness of aspirin, clopidogrel, or both for secondary prevention of coronary heart disease
Author:	Gaspoz J; Coxson PG; Goldman PA; Williams LW; Kuntz KM; Hunnink M; Goldman L; 2002
Intervention:	Aspirin, clopidogrel,
Comparison:	Aspirin or aspirin + clopidogrel
Population:	Patients aged 35 to 84 years in which CHD developed and evaluated over a 25 year period.
Perspective:	Third payer
Study type:	Deterministic decision analysis, CUA. The outcomes were deaths from coronary/non coronary, MIs
Methods:	Framingham heart study, Scandinavian Simvastatin Survey, CURE study,

No:	1099
	CAPRIE and Antiplatelets T Collaborators
Health valuations:	Literature
Cost components:	direct medical costs including drug costs and costs of side effects like gastrointestinal. Costs were derived from literature (refs given) and National medical expenditure survey.
Currency:	US $
Cost year:	2000
Time horizon:	25 years
Discount rate:	3%
Results – cost	Incremental costs are estimated over the 30 year period in millions. Aspirin (ASA) for all eligible patients: $8000 000 Addition of Clopidogrel for those that are not eligible for ASA: $14 000 000 Clopidogrel alone for all patients: $156 000 000 Clopidogrel for all + Aspirin for all eligible: $182000 000
Results - effectiveness	Incremental QALYs Aspirin (ASA) for all eligible patients: 682000 QALYs Addition of Clopidogrel for those that are not eligible for ASA: 456000 QALYs Clopidogrel alone for all patients: 632 000 QALYs Clopidogrel for all + Aspirin for all eligible: 1437 000 QALYs
Results - ICER	Aspirin (ASA) for all eligible patients: $1100/QALY Addition of Clopidogrel for those that are not eligible for ASA: $31000/QALY Clopidogrel alone for all patients: $250000/QALY Clopidogrel for all + Aspirin for all eligible: $130000/QALY
Results - uncertainty	Results were sensitive to the effect of the intervention on revascularisation. Aspirin and clopidogrel will save money if they reduced the rate of revascularisation as much as they did on MI. The cost of clopidogrel was also assessed but the results were not reported as they did not change the conclusions.
Source of funding	Charitable
Comments	This is a detailed study but does not focus on a particular disease area of CHD, limiting its relevance to post MI patients. Baseline event rates and costs differ for subtypes of CHD which might alter cost effectiveness conclusions. Thus the generalisability of these results to the post MI patients is not clear.

No:	1104
Study quality:	++ Clopidogrel used in combination with aspirin compared with aspirin alone in the treatment of non-ST-segment-elevation acute coronary syndromes: a systematic review and economic evaluation
Author:	Main C; Palmer S; Griffin S; Jones L; Orton V; Sculpher M; 2004
Intervention:	Clopdigorel + ASA
Comparison:	ASA
Population:	Patienst with non-ST-elevation ACS
Perspective:	NHS
Study type:	CUA, death from cardiovascular causes, non-fatal myocardial infarction or stroke
Methods:	CURE study, PRAIS-UK and NHAR
Health valuations:	Quality of life weights were derived from the literature

No:	1104
Cost components:	Direct medical costs of treatment, procedures and side effects. Costs data was derived from the literature, BNF and NHS reference costs
Currency:	£
Cost year:	2002
Time horizon:	Lifetime
Discount rate:	6% for costs and 1.5% for benefits
Results – cost	Clopidogrel + ASA: £12695 ASA: £12225
Results – effectiveness	Clopdigrel + ASA: 8.2795 QALYS ASA: 8.2022 QALYS
Results - ICER	£6078/QALY Probability of being cost effective at £10000 and £30000 WTP is 32% and 21% respectively. Sub-groups For high risk group there was a reduction in the ICER to about £4939/QALY and low risk the ICER increased to £8734/QALY. The Assessment Group explored the cost effectiveness of using clopidogrel for periods shorter than 1 year. The ICER for 1 month of treatment with clopidogrel compared with standard care alone was calculated to be £824 per QALY with a 6% probability that clopidogrel is cost effective at £30000/QALY. The strategies of using clopidogrel for 3 or 6 months were ruled out by extended dominance, and the ICER for 12 months of treatment with clopidogrel compared with 1 month was £5159 per QALY, with a 83% probability that clopidogrel is cost effective at £30000/QALY. Results-Uncertainty: The results were most sensitive to the inclusion of additional strategies which assessed alternative treatment durations with clopidogrel for example reducing the treatment duration to 5 years more than doubled the ICERs to about £15000/QALY. Although treatment with clopidogrel for 12 months remained cost-effective for the overall cohort, provisional findings indicate that the shorter treatment durations may be more cost-effective in patients at low risk. Discount rate and impact of the cost of stroke did not affect the baseline ICER.
Source of funding	Public
Comments	One paper and a company submission met the inclusion criteria for this HTA. The results are in agreement and indicate that there is a benefit in the short term and the ICERs are favorable, the ICERs becomes less favorable in the long-term but remain within acceptable range of cost effectiveness. Authors did a sub-group analysis stratifying results according to low or high risk defined as patients with at least one of the following over 70years, those with an ST- depression on an ECG and diabetes.

What is the effectiveness of adding a beta blocker versus placebo to improve outcome in patients after MI?

No:	1224
Study quality:	Economic consequences of post infarction prophylaxis with beta blockers: cost effectiveness of Metoprolol
Author:	Olsson G; Levin L; Rehnqvist N; 1987

No:	1224
Intervention:	Metoprolol (Beta-blocker) 100mg. twice daily treatment started 2 weeks after acute onset of
Comparison:	Placebo
Population:	Post infarction patients <70 years of age
Perspective:	Swedish societal perspective
Study type:	CEA, mortality, reinfaction, readmissions, cerebrovascular events, and revascularisation
Methods:	Randomised Controlled Trial (RCT) of the Stockholm Metropolol study (66% post MI patients)
Health valuations:	N/A
Cost components:	Costs relates to the health service costs of medication, concomitant medication (digitalis, diuretics), inpatient care, and outpatient clinic & indirect costs sick leave or early retirement
Currency:	Swedish Kroner (SEK).
Cost year:	1985
Time horizon:	3 years
Discount rate:	5%
Results – cost	Metropolol Kr 118610 (approx £11981) inclusive of indirect costs
Results – effectiveness	Metropolol Kr 118610 (approx £11981) inclusive of indirect costs Excluding indirect costs Metropolol Kr 12310 (approx £1243) Placebo Kr 17120 (approx £1729)
Results	Significant differences were found on the reinfarction, cerebrovascular events, coronary bypass
Results – effectiveness	surgery and reduced hospitalisation in favor of metropolol. There were no significant differences between treatment groups in terms of mortality both total and cardiac, readmission for heart failure, arrhythmias, angina pectoris and leg amputations.
Results	Results were not synthesized. But metropolol was deemed cost effective on the basis of reduced
Incremental	Rates of adverse events and less cost over the three year follow up. Results only discounting was assessed and the results were robust.
Results – uncertainty	
Source	Funding not stated
Comments	There was no sensitivity analysis done except for discounting which did not affect the results. They used hospital billing data for costs of inpatient care, this may still be fine given that the healthcare system is state funded or "socialized medicine" They could have done better by synthesizing the results to estimate a cost/LYG or cost/QALY which is more informative to the decision maker.

No:	1220
Study quality:	1+ Costs and effectiveness of routine therapy with long-term beta-adrenergic antagonists after acute myocardial infarction
Author:	Goldman L; Sia ST; Cook EF; Rutherford JD; Weinstein MC; 1988
Intervention:	`Beta adrenegernic antagonist started at the end of hospitalisation and

No:	1220
	continued long-term thereafter
Comparison:	Placebo
Population:	Low-risk group, medium-risk group, and high-risk group men aged 45, 55 or 65 years Risk was defined by estimated cardiac mortality in the 15 year period after MI. First year mortality was estimated to be different from mortality of subsequent years High risk: first year mortality =13% and subsequent risk for 2-15 years =7.5% Medium risk: first year mortality =7.5% and subsequent risk for 2-15 years =5% Low risk: first year mortality =1.5% and subsequent risk for 2-15 years =1.5%
Perspective:	Third payer
Study type:	CEA, mortality, revascularisation, reinfaction, costs
Methods:	Pooled meta-analysis of trial data on beta-blockers and observational studies
Health valuations:	N/A
Cost components:	Costs of drugs excluding follow up outcome costs and costs of side effects.
Currency:	US$
Cost year:	1987
Time horizon:	Lifetime
Discount rate:	5%
Results – cost	Cost/patient not given
Results – effectiveness	Incremental life expectancy (% change) assuming the benefits observed in 6 years of treatment will be lost gradually Low 45yrs: 0.11 (0.4%) Low 55yrs: 0.10 (0.5%) Low 65yrs: 0.09 (0.7%) Medium 45yrs: 0.34 (2%) Medium 55yrs: 0.34 (2.6%) Medium 65y: 0.31 (3.1%) High 45yrs: 0.48 (3.8%) High 55yrs: 0.47 (4.6%) High 65yrs: 0.44 (5.5%) Results low-risk group 45yrs: $23457/LYG----------$12855/LYG Incremental: low-risk group 55yrs: $23446/LYG----------$13068/LYG Low-risk group 65yrs: $23417/LYG----------$13571/LYG Medium-risk group 45yrs: $5890/LYG----------$3567/LYG Medium-risk group 55yrs: $5884/LYG----------$3618/LYG Medium-risk group 65yrs: $5871/LYG----------$3737/LYG High-risk group 45yrs: $3623/LYG----------$2327/LYG High-risk group 55yrs: $3619/LYG----------$2357/LYG

No:	1220
	High-risk group 65yrs: $3609/LYG----------$2427/LYG NOTE: The first figures are for a conservative model which assumed that treatment benefits will persist for 6 years when treatment is being given. Once the treatment is stopped, the benefits are lost immediately. Figures after the dotted lines are for the best guess model which assumes that the benefits observed during the 6 years will be lost gradually once the treatment is stopped.
Results - uncertainty	Univariate sensitivity analysis was done and results were robust to assumptions about the baseline mortality despite a tendency of less favorable ICERs when mortality risk was reduced. Costs of beta Blockers was almost doubled and made ICERs less favorable but they remained cost effective.
Source of funding	Not stated
Comments	Authors did not include the outcome costs/savings as a result of the intervention and costs of treating side-effects of therapy. The assumption they made that these will cancel out each other was too strong. However it is more likely that the cost savings from reduced adverse outcomes may outweigh the cost of treating adverse events. They also applied the same magnitude of relative mortality reduction to the various age and mortality groups. They stated that they did a meta-analysis but the study inclusion criteria for the pooled estimates of efficacy are not fully known making the validity of the pooled estimates uncertain. Overall this study needs to be interpreted with caution.

What is the effectiveness of adding calcium channel blocker versus placebo to improve outcome after MI?

No:	1265
Study quality:	+ A cost-effectiveness evaluation of amlodipine usage in patients with coronary artery disease in Sweden
Author:	Doyle JJ; McGuire A; Arocho R; Arikian S; Casciano J; Svangren P; Kim R; Kugel H; 2002
Intervention:	Amlodipine
Comparison:	Placebo
Population:	Patients with CAD in Sweden
Perspective:	Swedish health care system
Study type:	CEA, hospitalisation for angina, hospitalisation for MI, hospitalisation for CHF, PTCA, CABG, death
Methods:	PREVENT study and authors assumptions adjusted according to Swedish data
Health valuations:	N/A
Cost components:	Direct medical costs with resource consumption estimated by experts using Delphi techniques. Costs were derived from General Hospitals and Pharmaceuticals Specialties in Sweden
Currency:	Swedish Kroner (SEK)
Cost year:	2000
Time horizon:	3 years
Discount rate:	3%

No:	1265
Results – cost	estimated costs per patient over the 3-year period were SEK 26,600 in the intervention group and SEK 27,400 in the control group. Thus, amlodipine was associated with cost-savings of SEK 800. These results were robust to all variations carried out in the sensitivity analyses
Results - effectiveness	patients given amlodipine experienced 469 hospitalizations per 1000 patients while placebo had 647/1000. 18% fewer hospitalizations attributable to amlodipine.
Results - incremental	not calculated because the treatment was dominant over placebo, that is, it was more effective and less costly. Treatment with amlodipine was effective in reducing hospitalisation events. It also resulted in cost-savings from the perspective of the Swedish health care system. i.e. a cost saving of SEK 4300/hospitalisation avoided
Results - uncertainty	the model was robust in both univariate and multivariate sensitivity analysis
Source of funding	Private
Comments	The study was well reported using appropriate methodology. Key assumptions of the model were tested in sensitivity analyses. It appears that all the relevant categories of costs have been included in the analysis. The authors noted that hospitalisation costs used in the analysis were average estimates and great variation may exist due to the length of stay, type of treatment and type of hospital. However to better evaluate the benefits of amlodipine quality-of-life issues should have been addressed.

No:	1264
Study quality:	+ The economic efficiency of amlodipine in the treatment of coronary atherosclerosis: an analysis based on the PREVENT study
Author:	Cathomas G; Erne P; Schwenkglenks M; Szucs TD; 2002
Intervention:	Amlodipine
Comparison:	Placebo
Population:	Patients with angiographically documented coronary heart disease (CHD) in Switzerland
Perspective:	Health insurance companies
Study type:	CEA. Fatal myocardial infarction, stroke, vascular deaths and bleedings per 1,000 patients
Methods:	PREVENT study
Health valuations:	N/A
Cost components:	Direct medical costs
Currency:	Swiss francs (Sfr)
Cost year:	Not stated
Time horizon:	3 years
Discount rate:	5%
Results – cost	The total costs per 100 patients were Sfr 639,323 for amlodipine and Sfr 505,672 for placebo. The additional costs (Sfr) 133,651) observed in the amlodipine group mainly arose from the high initial drug costs
Results - effectiveness	The annual mortality rates were 4.5% in the amlodipine group and 6.2% in the placebo group, but this difference was not statistically significant, (p=0.57) The adjusted life expectancy calculated using the DEALE approach was 18.43 years. Thus, the discounted life-years gained due to amlodipine

No:	1264
	therapy over placebo was 0.083 years per patient
Results - incremental	cost per life-year gained was Sfr 14,650.
Results - uncertainty	there was little sensitivity analysis done which was robust
Source of funding	Not stated
Comments	PREVENT study showed that there was no statistically significant difference in terms of survival between the amlodipine and placebo groups. A sensitivity analysis to investigate the effects of varying the difference in fatal events between the treatment groups would have been useful. Quality of life issues were not discussed. It appears that all the relevant categories of cost have been included in the analysis. The unit costs and the quantities of resources used were sometimes reported separately. The sources of the data for both costs and resource consumption were reported. The costs were treated deterministically, although sensitivity analyses were conducted on those categories of costs that appeared to be more subject to uncertainty. Appropriate discounting was performed. The price year was not mentioned, the economic analysis was conservative, as potential cost-savings due to lower hospitalisation episodes and fewer rehabilitation measures were not accounted for in the analysis.

What is the effectiveness of adding eplerenone versus placebo to improve outcome in patients?

No:	1354
Study quality:	1+ Scottish medicines Consortium new product assessment form submission:
Author:	Pfizer Ltd
Intervention:	Eplerenone
Comparison:	Placebo
Population:	Post MI patients with left ventricular dysfunction and heart failure (LVDF)
Perspective:	NHS
Study type:	CUA
Methods:	RCT EPHESUS study
Health valuations:	Not stated
Cost components:	Direct medical costs (DRG related)
Currency:	£
Cost year:	2002
Time horizon:	16 months
Discount rate:	6%
Results – cost	Eplerenone: £3400 Placebo: 2768 Difference: £632
Results - effectiveness	QALY lost Eplernone: 0.41 Placebo: 0.48 Difference: 0.07
Results - incremental	£9048/QALY gained
Results - uncertainty	Results were stable in sensitivity analysis. There is a 92% chance that Eplerenone is cost effective using a willingness to pay threshold of £20000/QALY.
Source of funding	Private (stakeholder submission)

No:	1354
Comments	This was a stakeholder submission by Pfizer. The submission document had a checklist at the end. The document does not show disaggregated resource use, but it appears the original documents had the information and is referred to on the checklist. In the absence of any other published economic evaluation from the UK perspective, these results can be relied upon as they compare favorably with other drug interventions used for patients post MI.

No:	1339
Study quality:	1+ Cost-effectiveness of eplerenone compared with placebo in patients with myocardial infarction complicated by left ventricular dysfunction and heart failure.
Author:	Author: Weintraub WS Zhang Z; Mahoney EM ;Kolm P; Spertus JA; Caro J;I shak J;Goldberg 2005 R; Tooley J; Willke R; Pitt B;
Intervention:	Eplerenone
Comparison:	Placebo
Population:	Post MI patients with LDV and HF
Perspective:	Third payer
Study type:	CEA
Methods:	RCT and observational data from Framingham, Saskatchewan database and Worcester Heart Attack Registry
Health valuations:	Not applicable
Cost components:	Direct medical costs using DRG as used in the Medicare Program
Currency:	US$
Cost year:	2001
Time horizon:	16 monhs and lifetime
Discount rate:	3%
Results – cost	Eplerenone $13494 Placebo$12104 Difference $1391 (95% CI 695 – 2165)
Results - effectiveness	QALYs lost Framingham 0.3940 compared to placebo 0.4616 Saskatchewan 0.2253 compared to placebo 0.2682 Worcester 0.4528 compared to placebo 0.5435
Results - incremental	Assuming no added costs from life years saved Framingham $21072/QALY Saskatchewan $30349/QALY Worcester $17374/QALY Assuming added costs from life years saved are included Framingham $29469/QALY Saskatchewan $43301/QALY Worcester $23724/QALY Subgroups using Framingham data. Cost per life year gained Base case $13718 and 96.6% probability that eplerenone is cost

No:	1339
	effective Age <65 years $13709 (92.1%) Age >65 years $15409 (87.3%) Male $16903 (89.6%) Female $11873 (91.7%) Diabetes $42160 (55.2%) Non-Diabetics $10999 (99%) Prior MI $21279 (78.4%) No previous MI $10818 (97.3%)
Results - uncertainty	Results were robust in probabilistic sensitivity analysis for the different sources of data used. The results also remained cost effective for different subgroups.
Source of funding	Private
Comments	This study was detailed and used three different data sources to estimate what would happen after the trial period.

What is the effectiveness of adding omega 3 supplements versus placebo to improve outcome in patients after MI?

No:	1315
Study quality:	1+ Cost-effectiveness Analysis of Omacor for Myocardial infarction Survivors in the UK, 2004
Author:	
Intervention:	N3_PUFA
Comparison:	No supplement
Population:	Post MI patients
Perspective:	NHS
Study type:	CUA
Methods:	RCT, GISSI-P trial
Health valuations:	taken from literature and references given
Cost components:	direct medical costs of drugs and events with assumptions spelt out clearly
Currency:	£
Cost year:	2003
Time horizon:	Four years and lifetime
Discount rate:	3.5%
Results – cost	4 year results: £1789148 vs £1140143 Lifetime model: £6471024 vs £5700588
Results - effectiveness	4 year results: 2839 vs 2797 QALYs Lifetime model: 9309 vs 9102 QALYs
Results - incremental	4 year results: 15189/QALY Lifetime model: 3717/QALY
Results - uncertainty	The results of the model were sensitive but remained robust to the assumptions about costs, discount rates and proportions of patients receiving post MI treatment.
Source of funding	Private

No:	1315
Comments	They provided results for other comparisons including Vitamin E, and a combination of Vitamin E with n3-PUFA. Results were presented using life years gained and death avoided. For the purpose of this review only the results which use the NICE reference case were considered, that is the cot utility results. Only results of n3-PUFA compared to placebo were used and other comparators were not included because they were not relevant. This study was appropriately reported using standard methods. However the sources of subsequent MI costs and those of stroke were not clear. They assessed these in sensitivity analysis but again failed to give specify the source of the ranges used (200% increase).

No:	1334
Study quality:	1+ Cost-effectiveness analysis of n-3 polyunsaturated fatty acids (PUFA) after myocardial infarction: results from Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto (GISSI)-Prevenzione Trial
Author:	Franzosi MG;Brunetti M;Marchioli R;Marfisi RM;Tognoni G;Valagussa F;GISSI- 2004 Prevenzione I;
Intervention:	n3-PUFA
Comparison:	No supplements
Population:	Post MI patients with no age restriction
Perspective:	THIRD PAYER
Study type:	CEA
Methods:	RCT, GISSI-P trial
Health valuations:	Not applicable
Cost components:	Direct medical costs using Italian reimbursement DRGs rates. They used resource consumption data from the trial reports.
Currency:	Euro
Cost year:	1999
Time horizon:	42 months (3.5 years)
Discount rate:	5%
Results - effectiveness	n-3-PUFA resulted in significant in the primary combined endpoint including mortality. See the clinical evidence report. This translated to 0.0332 (95% CI 0.0303-0.361) life years gained
Results - incremental	Base case results Euro 24603/LYG Best case scenario: euro 15721/LYG Worse case scenario: euro 52524/LYG
Results - uncertainty	Costs of n3-PUFA, best worst case scenarios were tested in sensitivity analysis. The results were most sensitive to cost of n3-PUFA but remained cost effective especially that they modelled an expected price fall. The worst case scenario will change the conclusion about cost effectiveness if the payer was willing to pay upto US$50000.
Source of funding	Private
Comments	This paper was well reported. They could have done better buy reporting the impact of the treatment on quality of life. The authors compared their results with those of other interventions.

What is the effectiveness of adding vitamin K antagonist versus placebo to improve outcome in patients after MI?

No:	1198
Study quality:	1+ Costs and effects of long-term oral anticoagulant treatment after myocardial infarction
Author:	Van Bergen PFMM;Jonker JJC;van Hot BA;van Domburg RT;Azar AJ;Hofman, 1995
Intervention:	Warfarin
Comparison:	Placebo
Population:	Non selected Post MI patients
Perspective:	Societal
Study type:	CEA
Methods:	REVIEW of the ASPECT trial data
Health valuations:	Not applicable
Cost components:	Stated societal perspective but only collected direct medical costs related to major cardiologic events, anticoagulation treatment, hospital readmissions obtained from the Dutch Hospitals
Currency:	Dutch DFI
Cost year:	1994
Time horizon:	3 years
Discount rate:	5%
Results	Anticoagulation: average Dfl 9878 and total costs are Dfl 17621613 Cost/patient: Placebo: average Dfl 10784 and total costs are Dfl 19222590 Warfarin treatment results in: Effectiveness: a 10% (95% CI: -11% to 27%) reduction of death 53% (95% CI: 41% to 62%) reduction of recurrent MI 40% (95% CI: 10% to 60%) reduction of cerebrovascular events and an increase in the relative risk of bleeding complications of 3.9 (95% CI: 2.3 to 6.4).
Results - incremental	Authors did not sythesise costs and benefits; therefore it is a cost minimisation study. The total costs of warfarin were $519.00 cheaper for the warfarin arm.
Results - uncertainty	Results of sensitivity analysis shows that changes in costs of the main variables will not affect the conclusions
Source funding	Public/private
Comments	Although the study showed cost savings as a result of warfarin treatment, there was a 400% increase in major bleeding events which was not incorporated in the model and thus weakens the model results.

What is the effectiveness of adding vitamin K antagonists versus aspirin to improve outcome in patients after MI?

No:	1197
Study quality:	1+ A cost-effectiveness analysis of aspirin versus oral anticoagulants after acute myocardial infarction in Italy: equivalence of costs as a possible case for oral anticoagulants
Author:	Gianetti J; Gensini G; De CR; 1998
Intervention:	Aspirin

No:	1197
Comparison:	Warfarin
Population:	Patients having had an acute myocardial infarction
Perspective:	NHS, Italy
Study type:	CEA, re-infarction, PCTA, CABG, major bleeding, cerebrovascular events, AV Thromboembolism
Methods:	RCT ASPECT study, APT collaboration
Health valuations:	Not applicable
Cost components:	Direct medical and treatment costs. Costs were derived from literature and DRGs Treatment costs were estimated for two DRG pricing schemes: the mean price and the daily price multiplied by mean length of stay
Currency:	OTHER (Italian Lira) and European currency
Cost year:	1994
Time horizon:	3 years
Discount rate:	No discounting was done
Results	The total cost of therapy per patient/year, was ECU277.56 (warfarin) and ECU62.53 (aspirin).The cost of morbidity per patient per year, using DRG mean total costs, was ECU1, 873.32 (warfarin) and ECU2,125.4 (aspirin). The cost of morbidity per patient per year, using the product of DRG mean cost per day and mean length of stay, was ECU1,848.06 (warfarin) and ECU2, 074.01 (aspirin)
Results - incremental	Results are presented graphically as aspirin/warfarin efficacy ratio.This was found to be close to 0.68 Results were not synthesized therefore it was a cost minimisation analysis. The total cost per patient per year, using DRG mean total costs, was ECU2, 150.8 or $2,731.4 (warfarin), and ECU2,187.9 or $2,778.9 (aspirin). The total cost per patient per year, using the product of DRG mean cost per day and mean length of stay, was ECU2,125.2 or $2,699.0 (warfarin), and ECU2,136.6 or $2,713.9 (aspirin).
Results - uncertainty	Two way sensitivity analyses was done on the efficacy of warfarin/aspirin and the cumulative costs of both drugs. Results were sensitive to variations in the aspirin-warfarin efficacy ratio. Warfarin is no longer the cost-effective strategy in Italy once an efficacy ratio of approximately
Source funding	Not stated
Comments	The study was well reported but had some weaknesses which were identified. The authors reported aspirin-warfarin efficacy ratio of about 0.68 which was based on indirect comparisons. This showed that warfarin was as cheap and effective as aspirin. Recent data WARIS 11 has shown an efficacy ratio of 0.81. Using this recent data it would appear cumulative costs of Aspirin are cheaper than those of Warfarin. The study did not report on the true variability of cost items and only an arbitrary value of 5% was imposed.

No:	1197
Study quality:	1+ A cost-effectiveness analysis of aspirin versus oral anticoagulants after acute myocardial infarction in Italy: equivalence of costs as a possible case for oral anticoagulants
Author:	Gianetti J; Gensini G; De CR; 1998
Intervention:	Aspirin
Comparison:	Warfarin

No:	1197
Population:	Patients having had an acute myocardial infarction
Perspective:	NHS, Italy
Study type:	CEA, re-infarction, PCTA, CABG, major bleeding, cerebrovascular events, AV Thromboembolism
Methods:	RCT ASPECT study, APT collaboration
Health valuations:	Not applicable
Cost components:	Direct medical and treatment costs. Costs were derived from literature and DRGs Treatment costs were estimated for two DRG pricing schemes: the mean price and the daily price multiplied by mean length of stay
Currency:	OTHER (Italian Lira) and European currency
Cost year:	1994
Time horizon:	3 years
Discount rate:	No discounting was done
Results	The total cost of therapy per patient/year, was ECU277.56 (warfarin) and ECU62.53 (aspirin).The cost of morbidity per patient per year, using DRG mean total costs, was ECU1, 873.32 (warfarin) and ECU2,125.4 (aspirin). The cost of morbidity per patient per year, using the product of DRG mean cost per day and mean length of stay, was ECU1,848.06 (warfarin) and ECU2, 074.01 (aspirin)
Results - incremental	Results are presented graphically as aspirin/warfarin efficacy ratio.This was found to be close to 0.68 Results were not synthesized therefore it was a cost minimisation analysis. The total cost per patient per year, using DRG mean total costs, was ECU2, 150.8 or $2,731.4 (warfarin), and ECU2,187.9 or $2,778.9 (aspirin). The total cost per patient per year, using the product of DRG mean cost per day and mean length of stay, was ECU2,125.2 or $2,699.0 (warfarin), and ECU2,136.6 or $2,713.9 (aspirin).
Results - uncertainty	Two way sensitivity analyses was done on the efficacy of warfarin/aspirin and the cumulative costs of both drugs. Results were sensitive to variations in the aspirin-warfarin efficacy ratio. Warfarin is no longer the cost-effective strategy in Italy once an efficacy ratio of approximately
Source funding	Not stated
Comments	The study was well reported but had some weaknesses which were identified. The authors reported aspirin-warfarin efficacy ratio of about 0.68 which was based on indirect comparisons. This showed that warfarin was as cheap and effective as aspirin. Recent data WARIS 11 has shown an efficacy ratio of 0.81. Using this recent data it would appear cumulative costs of Aspirin are cheaper than those of Warfarin. The study did not report on the true variability of cost items and only an arbitrary value of 5% was imposed.

Statins and fibrates

No:	1453
Study quality:	1+ Cost-effectiveness of gemfibrozil for coronary heart disease patients with low levels of high-density lipoprotein cholesterol: the Department of Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial
Author:	Nyman JA;Martinson MS;Nelson D;Nugent S;Collins D;Wittes J;Fye CL;Wilt TJ;Robins SJ;Bloomfield R;VA-HIT Study Group; 2002

No:	1453		
Intervention:	Gemfibrozil		
Comparison:	Placebo		
Population:	Patients with coronary heart disease, low HDL-C levels and low LDL-C levels		
Perspective:	Third payer		
Study type:	CUA/CEA		
Methods:	RCT, VA-HIT trial. A markov model was used		
Health valuations:	NOT STATED used values from time trade off (ref 8) from the paper		
Cost components:	Direct medical costs. Sources of costs were documented including DRGs		
Currency:	US $		
Cost year:	1998		
Time horizon:	Lifetime		
Discount rate:	Did not discount base case results but used 0%, 3% & 5% in sensitivity analysis		
Results	Results were reported for 55, 65 and 75 year old males reflecting the population of the trial. Also results were reported according to the price of gemfibrozil used. 1) Negotiated price by VA was $46.75/yr 2) Wholesale price $956.96/yr Using negotiated prices for all age groups treatment with gemfibrozil results in savings Placebo gemfibrozil Age 55: $13464 $17428 Age 65: $10462 $14434 Age 75: $8284 $12193		
Results - effectiveness	Life expectancy	Placebo	Gemfibrozil
	Age 55:	22.5	23.15
	Age 65:	17.45	18.07
	Age 75:	13.36	13.98
Results - ICER	Reported for both cost effectiveness and cost utility		
	Age 55	$6607/LYG	
	Age 65	$6403/LYG	
	Age 75	$6305/LYG	
	Cost utility results		
	Age 55	$7480/QALY	
	Agr 65	$7217/QALY	
	Age 75	$7239/QALY	
Results - uncertainty	Results remained robust to assumptions about discounting used 0-5% and age. Utility did not affect the results as well. When discounting was done at 5% ICERs ranged from about $12000/QALY for an 85 year old to about $17000 for a		
Source funding	Charitable		
Comments	this was a detailed study which used appropriate methodology. They showed that gemfibrozil was cost effective for men in the various age groups considered.		

Q.5 Clinical Questions and Search Strategy

Table 281: Guideline questions

	Question	Population	Interventions	Comparisons	Outcomes
1	What is the effectiveness of changing dietary regime from the pre-infarct diet?	patients after MI	fibre, low-saturated fat, low GI, low blood sugar, folate rich, fish oils, plant stenols, anti-oxidant diets,	no change	re-infarction, mortality, revascularisation, stroke, readmission,
2	What education and/or information best aids patients after MI to (i) reduce their risk of subsequent cardiac problems (ii) return to a full and normal life (daily activities, driving, exercise, employment, leisure activities, sexual activities	patients after MI	patient education/information		(i) reduce their risk of subsequent cardiac problems (ii) return to a full and normal life (daily activities, driving, exercise, employment, leisure activities, sexual activities)
3	What psychological and social (carers) support best aids people after MI to reduce their risk of subsequent cardiac problems and to promote their return to a full and normal life?	patients after MI	psychological/ social support		(i) reduce their risk of subsequent cardiac problems (ii) return to a full and normal life (daily activities, driving, exercise, employment, leisure activities, sexual activities)
4	What is the incidence of sexual dysfunction in patients after MI and how can patients be identified who would require referral to a specialist unit?	patients after MI	incidence and identification of sexual dysfunction		referral
5	What is the effectiveness of adding ACEI	(i) unselected patients after MI? (ii)	ACEI	Placebo	re-infarction, mortality, revascularisation, stroke, readmission

	Question	Population	Interventions	Comparisons	Outcomes
	versus placebo to improve outcome in...	patients after MI with LV dysfunction?			
6	What is the effectiveness of adding ARBs versus placebo to improve outcome in…..	(i) patients after MI without LV dysfunction? (ii) patients after MI with LV dysfunction?	ARB	Placebo	re-infarction, mortality, revascularisation, stroke, readmission
7	What is the effectiveness of adding ACEI versus ARBs to improve outcome in…	(i) unselected patients after MI? (ii) patients after MI with LV dysfunction?	ACEI	ARB	re-infarction, mortality, revascularisation, stroke, readmission
8	What is the effectiveness of adding ACEI plus ARBs versus ACEI to improve outcome in..	patients after MI with LV dysfunction?	ACEI plus ARB	ACEI	re-infarction, mortality, revascularisation, stroke, readmission
9	How frequently should renal function tests, including serum potassium, be monitored in patients treated with ACEI and/or ARBs after MI?	patients after MI treated with ACEI and/or ARB	frequency of renal function tests - serum potassium		
10	What is the effectiveness of adding aspirin versus placebo to improve outcome in patients after MI?	patients after MI	aspirin	placebo	re-infarction, mortality, revascularisation, stroke, readmission,
11	What is the effectiveness of adding aspirin versus clopidogrel to improve outcome in patients after MI?	patients after MI	aspirin	clopidogrel	re-infarction, mortality, revascularisation, stroke, readmission,
12	What is the most effective method of delivering dietary advice?	patients after MI			adherance, compliance, concordance
13	What is the	(i) patients	aspirin	aspirin and	re-infarction, mortality,

	Question	Population	Interventions	Comparisons	Outcomes
	effectiveness of adding aspirin versus aspirin and clopidogrel to improve outcome in…	after NSTEMI (ii) patients after STEMI		clopidogrel	revascularisation, stroke, readmission,
14	What is the effectiveness of adding a beta blocker versus placebo to improve outcome in...	(i) unselected patients after MI? (ii) patients after MI with LV dysfunction?	Beta blocker	Placebo	re-infarction, mortality, revascularisation, stroke, readmission,
15	What is the effectiveness of adding vitamin K antagonist (warfarin) versus placebo to improve outcome in patients after an MI?	patients after MI	Warfarin	Placebo	re-infarction, mortality, revascularisation, stroke, readmission,
16	What is the effectiveness of adding vitamin K antagonist (warfarin) versus aspirin to improve outcome in patients after an MI?	patients after MI	Warfarin	Placebo	re-infarction, mortality, revascularisation, stroke, readmission,
17	What is the effectiveness of adding vitamin K antagonist (warfarin) plus aspirin versus aspirin to improve outcome in patients after MI?	patients after MI	Warfarin and aspirin	Aspirin	re-infarction, mortality, revascularisation, stroke, readmission,
18	What is the effectiveness of adding vitamin K antagonist (warfarin) plus aspirin versus warfarin to improve outcome in patients after MI?	patients after MI	Warfarin and aspirin	Warfarin	re-infarction, mortality, revascularisation, stroke, readmission,

	Question	Population	Interventions	Comparisons	Outcomes
19	What is the effectiveness of adding calcium channel blocker versus placebo to improve outcome in…	(i) patients after MI without LV dysfunction? (ii) patients after MI with LV dysfunction?	Calcium channel blocker	placebo	re-infarction, mortality, revascularisation, stroke, readmission,
20	What is the effectiveness of adding potassium channel activators versus placebo to improve outcome in patients after MI?	patients after MI	Potassium channel activators	Placebo	re-infarction, mortality, revascularisation, stroke, readmission,
21	How frequently should renal function, including serum potassium, be monitored in patients post MI treated with eplerenone?	patients after MI treated with eplerenone	frequency of renal function tests - serum potassium		
22	What is the effectiveness of adding eplerenone versus placebo to improve outcome in patients after MI ?	patients after MI with heart failure and LV dysfunction	eplerenone	Placebo	infarction, mortality, revascularisation, stroke, readmission,
23	What is the effectiveness of adding Omega-3-acid ethyl esters versus placebo to improve outcome in patients after MI?	patients after MI	Omega-3-acid ethyl esters treatment	Placebo	re-infarction, mortality, revascularisation, stroke, readmission,
24	What is the effectiveness of low/ moderate alcohol consumption versus high alcohol consumption to improve	patients after MI	Low to moderate alcohol consumption	No alcohol	re-infarction, mortality, revascularisation, stroke, readmission,

	Question	Population	Interventions	Comparisons	Outcomes
	outcome in patients after MI?				
25	What is the effectiveness of no/ low/moderate alcohol consumption versus high alcohol consumption to improve outcome in patients after MI?	patients after MI	none to moderate alcohol consumption	high alcohol consumption	re-infarction, mortality, revascularisation, stroke, readmission,
26	What is the effectiveness of low/ moderate alcohol consumption versus high alcohol consumption to improve outcome in patients after MI?	patients after MI	low to moderature alcohol consumption	no alcohol	re-infarction, mortality, revascularisation, stroke, readmission,
27	What is the effectiveness of adding statins versus placebo to improve outcome in patients after MI?	patients after MI	statins	Placebo	re-infarction, mortality, revascularisation, stroke, readmission,
28	What is the effectiveness of adding high dose statin (more potent cholesterol lowering) versus low dose statin (less potent cholesterol lowering) to improve outcome in patients after MI?	patients after MI	high dose statin	low dose statin	re-infarction, mortality, revascularisation, stroke, readmission,
29	What is the effectiveness of adding early statin therapy	patients after MI	early statin	delayed statin	re-infarction, mortality, revascularisation, stroke, readmission,

	Question	Population	Interventions	Comparisons	Outcomes
	versus delayed statin therapy to improve outcome in patients after MI?				
30	What is the effectiveness of adding fibrates or niacin or ezetimibe versus placebo to improve outcome in patients after MI?	patients after MI	fibrates	placebo	re-infarction, mortality, revascularisation, stroke, readmission
31	Are there stable patients who don't benefit prognostically from revascularisation	patients after MI with reversible ischaemia without LV dysfunction	Revascularisation		re-infarction, mortality, revascularisation, stroke, readmission
32	Are there stable patients after MI who a) benefit prognostically from revascularisation b) those who don’t benefit prognostically	patients after MI with reversible ischaemia and LV dysfunction	Revascularisation		re-infarction, mortality, revascularisation, stroke, readmission
33	What is the optimal target blood pressure for patients after MI with hypertension? Assuming a patient is treated with ACEI and or ARB and a beta blocker already (and in LV dysfunction and HF eplerenone)	patients after MI with hypertension	optimal blood pressure		re-infarction, mortality, stroke, readmission,
34	Does determining LV function versus standard care improve (that is, affect) outcome of patients MI (summarising LV dysfunction effect on drugs/	patients after MI	determining (testing?) LV dysfunction	standard care	adverse effects

	Question	Population	Interventions	Comparisons	Outcomes
	ICD /rehab)?				
35	Is there any benefit in giving ACEI at a later stage of treatment in patients with previous MI (later than one year)		late treatment		re-infarction, mortality, revascularisation, stroke, readmission, safety, tolerance
36	Does a history of proven MI in the past (> 1 year) versus recent MI (< 1 year) change treatment / management / outcome?	i) proven MI in the past > 1 year	treatment for MI < 1 year	treatment for MI > 1 year	re-infarction, mortality, revascularisation, stroke, readmission,
37	What is the effectiveness of regular physical activity versus a sedantary lifestyle to improve outcome in patients after MI?	patients after MI	regular exercise (need to define this) structured exercise, unstructured exercise, frequency, duration, intensity	no exercise	re-infarction, mortality, revascularisation, stroke, readmission,
38	What is the level of physical activity which increases physical work capacity versus physical activity which does not increase physical work capacity		level of physical activity		physical work capacity, re-infarction, mortality
39	What is the effectiveness of comprehensive cardiac rehabilitation versus standard care with no cardiac rehabilitation to improve outcome in patients after MI ?	patients after MI	comprehensive cardiac rehab	standard care	re-infarction, mortality, stroke, readmission, resumption of daily activities, return to work, QoL, increased psychological wellbeing
40	What is the effectiveness of exercise only cardiac	patients after MI	exercise only rehab	standard care	re-infarction, mortality, stroke, readmission, resumption of daily activities, return to

	Question	Population	Interventions	Comparisons	Outcomes
	rehabilitation versus standard care with no cardiac rehabilitation to improve outcome in patients after MI?				work, QoL, increased psychological wellbeing
41	What is the effectiveness of comprehensive cardiac rehabilitation versus exercise only cardiac rehabilitation to improve outcome in patients after MI?	patients after MI	comprehensive cardiac rehab	exercise only rehab	re-infarction, mortality, stroke, readmission, resumption of daily activities, return to work, QoL, increased psychological wellbeing
42	What is the effectiveness of an individualised cardiac rehabilitation programme versus a non-individualised cardiac programme to improve outcome in patients after MI?	patients after MI	individualised cardiac rehab	non-individualised cardiac rehab	re-infarction, mortality, stroke, readmission, resumption of daily activities, return to work, QoL, increased psychological wellbeing, patient satisfaction
43	Are there any patients after MI in whom the exercise component of cardiac rehabilitation is not safe?	patients after MI	risk factors of cardiac rehab		re-infarction, mortality, stroke, readmission,
44	What approach to patient engagement best aids access to cardiac rehabilitation, particularly in reference to em, op, seg, women, those from rural communities, and those with	previous MI - women, ethnic minorities, older people, lower social economic groups, mental and physical health co-morbidities,	access to cardiac rehab		

	Question	Population	Interventions	Comparisons	Outcomes
	mental and physical health co-morbidities?	living in rural communities			
45	What is the effectiveness of regular physical activity versus a sedantary lifestyle to improve outcome in patients after MI?	patients after MI	regular exercise (need to define this) structured exercise, unstructured exercise, frequency, duration, intensity	no exercise	re-infarction, mortality, revascularisation, stroke, readmission
46	Does a history of proven MI in the past (> 1 year) versus recent MI (< 1 year) change treatment / management / outcome?	i) proven MI in the past > 1 year	treatment for MI < 1 year	treatment for MI > 1 year	re-infarction, mortality, revascularisation, stroke, readmission,
47	What is the effectiveness of adding fibrates versus placebo to improve outcome in patients with CHD		Fibrates	Placebo	total cholesterol, HDL-C, LDL-
48	What is the effectiveness of adding ezetimibe versus placebo to improve outcome in patients with CHD		ezetimibe	placebo	total cholesterol, HDL-C, LDL-
49	Is there an optimum time for ACEI to be administered in the nonacute phase?	(i) unselected patients after MI? (ii) patients after MI with LV dysfunction?	Early ACEI	Delayed ACEI	re-infarction, mortality, revascularisation, stroke, readmission,
50	Is there and optimum time for beta-blockers to be initiated in unselected patients after MI?	unselected patients after MI	timing of beta blocker		re-infarction, mortality, revascularisation, stroke, readmission
51	What is the potential harm of adding the following:	(i) patients after MI with LV dysfunction in	calcium channel blocker, thiazide	standard care	adverse effects

	Question	Population	Interventions	Comparisons	Outcomes
	calcium channel blocker or thiazide diuretic or alpha blocker versus placebo in…	whom further blood pressure lowering is warranted? (ii) patients after MI without LV dysfunction in whom further blood pressure lowering is warranted?	diuretic, alpha blocker		
52	What is the incidence of anxiety and depression in patients after MI and how can patients be identified? (can be cross-referenced to the Anxiety & Depression guidelines)				
53	What are the information and support needs for patients at different points in the care pathway?	patients after MI	patient information and support		
54	At what level of renal function do the risks of therapy with ACEIs outweigh the benefits in patients after MI with poor renal function		Whether to continue ACEI treatment. what are the risk factors?	Discontinue ACEI treatment	Chronic renal failure, mortality, re-infarction
55	Is there any benefit in initiating beta blockers at a later stage of treatment		beta blocker at later stage		re-infarction, mortality, revascularisation, stroke, readmission,

The following Guideline sources were searched for each question.

Guidelines sources searched

National electronic Library for Health (NeLH) Guidelines Finder

http://libraries.nelh.nhs.uk/guidelinesFinder/

National Guidelines Clearinghouse

http://www.guideline.gov/

National Institute for Clinical Excellence (NICE) guidelines & technology appraisals

http://www.nice.org.uk/page.aspx?o=ourguidance

Scottish Intercollegiate Guidelines Network (SIGN)

www.sign.ac.uk

Canadian Medical Association (CMA) Infobase

http://mdm.ca/cpgsnew/cpgs/index.asp

National Health and Medical Research Council (NHMRC) Australian guidelines

http://www7.health.gov.au/nhmrc/publications/subjects/clinical.htm

New Zealand Guidelines Group

http://www.nzgg.org.nz/index.cfm?screensize=800&ScreenResSet=yes

Guidelines International Network

http://www.g-i-n.net/index.cfm?fuseaction=homepage

BMJ Clinical Evidence

http://www.clinicalevidence.com/ceweb/conditions/index.jsp

The following databases were searched for all questions:

Medline, Embase, Cinahl, Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Heath Technology Assessment Database (HTA), CENTRAL, NHS Economic Evaluations Database (NHS EED), Social Science Citation Index. Where relevant to the question PsycINFO, Allied & complementary Medicine (AMED) and PEDro (Physiotherapy Evidence Database) and were also searched

For each question the Medline strategy is given below. This strategy was adapted to run on the other databases searched. Medline, Embase, NHS EED and the Social Science Citation Index (SCCI) were searched for economic literature using the following filters developed by ScHaRR, University of Sheffield. This filter was adapted to run on (SCCI).

Medline economics/quality of life filter

1. exp "costs and cost analysis"/

2. economics/

3. exp economics,hospital/

4. exp economics,medical/

5. economics,nursing/

6. economics,pharmaceutical/

7. exp "fees and charges"/

8. exp budgets/

9. budget$.tw.

10. cost$.tw.

11. (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ab.

12. (economic$ or pharmacoeconomic$ or pharmaco-economic$).ti.

13. (price or pricing).tw.

14. (financial or finance or finances or financed).tw.

15. (fee or fees).tw.

16. (value adj2 (money or monetary)).tw.

17. value of life/

18. quality adjusted life year/

19. quality adjusted life.tw.

20. (qaly$ or qald$ or qale$ or qtime$).tw.

21. disability adjusted life.tw.

22. daly$.tw.

23. health status indicators/

24. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.

25. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.

26. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sf twelve or shortform twelve or shortform twelve or short form twelve or short form twelve).tw.

27. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sf sixteen or shortform sixteen or shortform sixteen or short form sixteen or short form sixteen).tw.

28. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sf twenty or shortform twenty or shortform twenty or short form twenty or short form twenty).tw.

29. (euroqol or euro qol or eq5d or eq 5d).tw.

30. (hql or hqol or h qol or hrqol or hr qol).tw.

31. (hye or hyes).tw.

32. health$ year equivalent$.tw.

33. health utilit$.tw.

34. (hui or hui1 or hui2 or hui3).tw.

35. disutilit$.tw.

36. rosser.tw.

37. quality of wellbeing.tw.

38. quality of well being.tw.

39. qwb.tw.

40. willingness to pay.tw.

41. standard gamble$.tw.

42. (time trade off or time tradeoff).tw.

43. tto.tw.

44. exp models,economic/

45. *models, theoretical/

46. *models, organizational/

47. economic model$.tw.

48. markov chains/

49. markov$.tw.

50. monte carlo method/

51. monte carlo.tw.

52. exp decision theory/

53. (decision$ adj2 (tree$ or analy$ or model$)).tw.

54. or/1-53

55. (letter or editorial or comment).pt.

56. 54 not 55

Embase economics/quality of life filter

1. exp 'economic aspect'/

2. cost$.tw.

3. (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ab.

4. (economic$ or pharmacoeconomic$ or pharmaco-economic$).ti.

5. (price or pricing).tw.

6. (financial or finance or finances or financed).tw.

7. (fee or fees).tw.

8. (value adj2 (money or monetary)).tw.

9. quality adjusted life.tw.

10. (qaly$ or qald$ or qale$ or qtime$).tw.

11. disability adjusted life.tw.

12. daly$.tw.

13. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.

14. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.

15. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sf twelve or shortform twelve or shortform twelve or short form twelve or short form twelve).tw.

16. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sf sixteen or shortform sixteen or shortform sixteen or short form sixteen or short form sixteen).tw.

17. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sf twenty or shortform twenty or shortform twenty or short form twenty or short form twenty).tw.

18. (euroqol or euro qol or eq5d or eq 5d).tw.

19. (hql or hqol or h qol or hrqol or hr qol).tw.

20. (hye or hyes).tw.

21. health$ year equivalent$.tw.

22. health utilit$.tw.

23. (hui or hui1 or hui2 or hui3).tw.

24. disutilit$.tw.

25. rosser.tw.

26. quality of wellbeing.tw.

27. quality of well being.tw.

28. qwb.tw.

29. willingness to pay.tw.

30. standard gamble$.tw.

31. (time trade off or time tradeoff).tw.

32. tto.tw.

33. exp 'mathematical model'/

34. economic model$.tw.

35. markov$.tw.

36. monte carlo method/

37. monte carlo.tw.

38. exp decision theory/

39. (decision$ adj2 (tree$ or analy$ or model$)).tw.

40. or/1-39

41. (letter or editorial or comment).pt.

Full details of the search strategies are available on request from the National Collaborating Centre for Primary Care.

1.5 Drug therapy

Questions 1-4,6, 52-53. Angiotensin converting enzyme (ACE) & Angiotensin II receptor blockers (ARB)

Medline 1999-May Wk 3 2005 via Ovidweb

Search date: 01/06/05

Update search: May wk 3 2005-May wk 5 2006

Search date: 08/06/06

1. exp myocardial infarction/

2. (infarct$ or MI or heart attack$ or heart arrest$ or heart event$).ti,ab.

3. 1 or 2

4. Angiotensin-Converting Enzyme Inhibitors/

5. Captopril/ae, tu

6. lisinopril/ae, tu

7. ramipril/ae, tu

8. enalapril/ae, tu

9. perindopril/ae, tu

10. fosinopril/ae, tu

11. cilazapril/ae, tu

12. (captopril or lisinopril or ramipril or trandolapril or enalapril or quinapril or perindopril or moexipril or imadipril or fosinopril or cilazapril).ti,ab.

13. angiotensin converting enzyme inhibit$.ti,ab.

14. (aceI or ace inhibit$).ti,ab.

15. exp Receptors, Angiotensin/

16. losartan/ae, tu

17. (losartan or valsartan or candesartan or eprosartan or irbesartan or olmesartan or telmisartan).ti,ab.

18. (angiotensin adj2 antagonist$).ti,ab.

19. (angiotensin adj3 receptor$).ti,ab.

20. (angiotensin adj3 (blocker$ or blockade)).ti,ab.

21. (arb$1 or AIIA or AIIRA).ti,ab.

22. or/4-18

23. (systematic adj review$).tw.

24. (published adj studies).ab.

25. (data adj synthesis).tw.

26. (data adj extraction).ab.

27. meta-analysis/

28. meta-analysis.ti,ab.

29. meta-analysis.pt.

30. or/23-29

31. 3 and 22

32. 30 and 31

33. randomized controlled trial.pt.

34. controlled clinical trial.pt.

35. randomized controlled trials.sh.

36. random allocation.sh.

37. double blind method.sh.

38. single blind method.sh.

39. or/33-38

40. clinical trial.pt.

41. exp clinical trials/

42. (clin$ adj5 trial$).ti,ab.

43. ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).ti,ab.

44. placebos.sh.

45. placebo$.ti,ab.

46. random$.ti,ab.

47. or/40-46

48. 39 or 47

49. 31 and 48

50. 32 or 49

51. animals/

52. humans/

53. 51 not (51 and 52)

54. 50 not 53

55. (comment or letter or editorial).pt.

56. 54 not 55

Question 5. Renal function tests with ACE and/or ARBs

Medline 1966-June wk 2 2005 via Ovidweb

Search date: 16/06/05

Update search June wk 2 2005-may wk 5 2006

Search date: 08/06/06

1. exp myocardial infarction/

2. (infarct$ or MI or heart attack$ or heart arrest$ or heart event$).ti,ab.

3. 1 or 2

4. Angiotensin-Converting Enzyme Inhibitors/

5. Captopril/ae, tu

6. lisinopril/ae, tu

7. ramipril/ae, tu

8. enalapril/ae, tu

9. perindopril/ae, tu

10. fosinopril/ae, tu

11. cilazapril/ae, tu

12. (captopril or lisinopril or ramipril or trandolapril or enalapril or quinapril or perindopril or moexipril or imadipril or fosinopril or cilazapril).ti,ab.

13. angiotensin converting enzyme inhibit$.ti,ab.

14. (aceI or ace inhibit$).ti,ab.

15. exp Receptors, Angiotensin/

16. losartan/ae, tu

17. (losartan or valsartan or candesartan or eprosartan or irbesartan or olmesartan or telmisartan).ti,ab.

18. (angiotensin adj2 antagonist$).ti,ab.

19. (angiotensin adj3 receptor$).ti,ab.

20. (angiotensin adj3 (blocker$ or blockade)).ti,ab.

21. (arb$1 or AIIA or AIIRA).ti,ab.

22. or/4-18

23. 3 and 22

24. (serum potassium or creatinine).ti,ab.

25. Creatinine/

26. (glomerular filtration rate or gfr).ti,ab.

27. Kidney Function Tests/

28. GLOMERULAR FILTRATION RATE/

29. ((renal or kidney) adj2 (test$ or assess$ or evaluat$ or investigat$)).ti,ab.

30. or/24-29

31. 23 and 30

32. animal/

33. Humans/

34. 32 not (32 and 33)

35. 31 not 34

Questions 7-9. Antiplatelets

Medline 1999-Jul wk 1 2005 via Ovidweb

Search date: 20/07/05

Update search: Jul wk 1 2005-May wk 4 2006

Search date: 08/06/06

1. exp myocardial infarction/

2. (infarct$ or MI or heart attack$ or heart arrest$ or heart event$).ti,ab.

3. 1 or 2

4. Aspirin/

5. aspirin.tw.

6. 4 or 5

7. (clopidogrel or plavix).tw.

8. DIPYRIDAMOLE/

9. (dipyridamole or persantin).tw.

10. placebo/

11. placebo$.tw.

12. or/7-11

13. 3 and 6 and 12

14. (aspirin adj2 (intoleran$ or hypersensitiv$ or hyper-sensitiv$ or resistan$ or allerg$ or sensitiv$)).tw.

15. 3 and 14

16. (systematic adj review$).tw.

17. (published adj studies).ab.

18. (data adj synthesis).tw.

19. (data adj extraction).ab.

20. meta-analysis/

21. meta-analysis.ti,ab.

22. meta-analysis.pt.

23. or/16-22

24. 13 and 23

25. comment.pt.

26. letter.pt.

27. editorial.pt.

28. or/25-27

29. randomized controlled trial.pt.

30. controlled clinical trial.pt.

31. randomized controlled trials.sh.

32. random allocation.sh.

33. double blind method.sh.

34. single blind method.sh.

35. or/29-34

36. clinical trial.pt.

37. exp clinical trials/

38. (clin$ adj2 trial$).ti,ab.

39. ((singl$ or doubl$ or trebl$ or tripl$) adj2 (blind$ or mask$)).ti,ab.

40. placebos.sh.

41. placebo$.ti,ab.

42. random$.ti,ab.

43. or/36-42

44. 35 or 43

45. 13 and 44

46. 24 or 45

47. 46 or 15

48. Animals/

49. Humans/

50. 48 not (48 and 49)

51. 47 not 50

52. 51 not 28

Question 10. Betablockers

Medline 1999-Aug wk 1 2005 via Ovidweb

Search date: 17/08/05

Update search: Aug wk 1 2005-May wk 5 2006

Search date:12/06/06

1. exp myocardial infarction/

2. (infarct$ or MI or heart attack$ or heart arrest$ or heart event$).ti,ab.

3. 1 or 2

4. adrenergic beta-antagonists/ or acebutolol/ or atenolol/ or bisoprolol/ or celiprolol/ or labetalol/ or metoprolol/ or nadolol/ or oxprenolol/ or pindolol/ or propranolol/ or timolol/

5. (atenolol or metoprolol or acebutolol or propranolol or timolol or bisoprolol or carvedilol or nadolol or oxprenolol or pindolol or nebivolol or labetalol or celiprolol).ti,ab.

6. (beta adj3 block$).ti,ab.

7. (b adj3 block$).ti,ab.

8. (beta adj2 antagonist$).ti,ab.

9. or/4-8

10. 3 and 9

11. (systematic$ adj review$).ab.

12. review.pt.

13. meta-analysis.ab.

14. meta-analysis.pt.

15. meta-analysis.ti.

16. or/11-15

17. 10 and 16

18. randomized controlled trial.pt.

19. controlled clinical trial.pt.

20. randomized controlled trials.sh.

21. random allocation.sh.

22. double blind method.sh.

23. single blind method.sh.

24. or/18-23

25. clinical trial.pt.

26. exp clinical trials/

27. (clin$ adj5 trial$).ti,ab.

28. ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).ti,ab.

29. placebos.sh.

30. placebo$.ti,ab.

31. random$.ti,ab.

32. or/25-31

33. 24 or 32

34. 10 and 33

35. 17 or 34

36. animals/

37. humans/

38. 36 not (36 and 37)

39. 35 not 38

40. (comment or letter or editorial).pt.

41. 39 not 40

Question 11,54. Timing of initiating Betablockers

Medline 1966-Aug wk 2 2005 via Ovidweb

Search date: 24/08/05

Update search: Aug w2 2005-may wk 5 2006

Search date: 12/06/06

1. exp myocardial infarction/

2. (infarct$ or MI or heart attack$ or heart arrest$ or heart event$).ti,ab.

3. 1 or 2

4. (secondary or post or previous$ or prior or follow$ or former$ or earlier or history).ti,ab.

5. 3 and 4

6. adrenergic beta-antagonists/ or acebutolol/ or atenolol/ or bisoprolol/ or celiprolol/ or labetalol/ or metoprolol/ or nadolol/ or oxprenolol/ or pindolol/ or propranolol/ or timolol/

7. (atenolol or metoprolol or acebutolol or propranolol or timolol or bisoprolol or carvedilol or nadolol or oxprenolol or pindolol or nebivolol or labetalol or celiprolol).ti,ab.

8. (beta adj3 block$).ti,ab.

9. (b adj3 block$).ti,ab.

10. (beta adj2 antagonist$).ti,ab.

11. or/6-10

12. 5 and 11

13. time factors/

14. time factor$.ti,ab.

15. (later adj2 (time or stage)).ti,ab.

16. or/13-15

17. 12 and 16

18. animals/

19. humans/

20. 18 not (18 and 19)

21. 17 not 20

22. (letter or comment or editorial).pt.

23. 21 not 22

Question 12-13,29. Calcium Channel blocker & Potassium activators

Medline 1999-aug wk 5 2005 via Ovidweb

Search date: 14/09/05

Update search: Aug wk 5 2005-May wk 5 2006

Search date: 13/06/06

1. exp myocardial infarction/

2. (infarct$ or MI or heart attack$ or heart arrest$ or heart event$).ti,ab.

3. 1 or 2

4. calcium channel blockers/ or amlodipine/ or diltiazem/ or felodipine/ or isradipine/ or nicardipine/ or nifedipine/ or nimodipine/ or nisoldipine/ or verapamil/

5. (calcium channel adj (blocker$ or antagonist)).ti,ab.

6. (nifedipine or amlodipine or diltiazem or verapamil or felodipine or nicardipine or isradipine or lacidipine or lercanidipine or nisoldipine or nimodipine).ti,ab.

7. or/4-6

8. Nicorandil/

9. (potassium channel adj (activator$ or opener)).ti,ab.

10. (nicorandil or ikorel).ti,ab.

11. or/8-10

12. 7 or 11

13. 3 and 12

14. (systematic$ adj review$).ab.

15. review.pt.

16. meta-analysis.ab.

17. meta-analysis.pt.

18. meta-analysis.ti.

19. or/14-18

20. 13 and 19

21. randomized controlled trial.pt.

22. controlled clinical trial.pt.

23. randomized controlled trials.sh.

24. random allocation.sh.

25. double blind method.sh.

26. single blind method.sh.

27. or/21-26

28. clinical trial.pt.

29. exp clinical trials/

30. (clin$ adj5 trial$).ti,ab.

31. ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).ti,ab.

32. placebos.sh.

33. placebo$.ti,ab.

34. random$.ti,ab.

35. or/28-34

36. 27 or 35

37. 13 and 36

38. 20 or 37

39. animal/

40. humans/

41. 39 not (39 and 40)

42. 38 not 41

43. (letter or editorial or comment).pt.

44. 42 not 43

Question 14. Omega-3-acid ethyl esters treatment

Medline 1966- Oct wk 2 2005 via Ovidweb

Search date: 25/10/05

Update search Oct wk 2 2005-may wk 5 2006

Search date: 13/06/06

1. Fatty Acids, Omega-3/

2. omega-3.ti,ab.

3. n-3 fatty acid$.ti,ab.

4. n-3 polyunsaturated fatty acid$.ti,ab.

5. n-3 pufa.ti,ab.

6. n-3 polyunsaturated fa.ti,ab.

7. omacor.ti,ab.

8. maxepa.ti,ab.

9. fish oil$1.ti,ab.

10. or/1-9

11. (supplement$ or concentrate$ or dose$ or capsule$ or tablet$ or additive$ or treatment$ or therap$ or intervention$).ti,ab.

12. dietary supplementation/

13. 11 or 12

14. exp Myocardial Infarction/

15. (infarct$ or mi or heart attack$ or heart arrest$ or heart event$).ti,ab.

16. 14 or 15

17. 10 and 13 and 16

18. (systematic$ adj review$).ab.

19. review.pt.

20. meta-analysis.ab.

21. meta-analysis.pt.

22. meta-analysis.ti.

23. or/18-22

24. 17 and 23

25. randomized controlled trial.pt.

26. controlled clinical trial.pt.

27. randomized controlled trials.sh.

28. random allocation.sh.

29. double blind method.sh.

30. single blind method.sh.

31. or/25-30

32. clinical trial.pt.

33. exp clinical trials/

34. (clin$ adj5 trial$).ti,ab.

35. ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).ti,ab.

36. placebos.sh.

37. placebo$.ti,ab.

38. random$.ti,ab.

39. or/32-38

40. 31 or 39

41. 17 and 40

42. 24 or 41

43. (letter or editorial or comment).pt.

44. 42 not 43

45. animals/

46. humans/

47. 45 not (45 and 46)

48. 44 not 47

Question 19-22. Vitamin K antagonists

Medline 1966-July wk 2 2005 via Ovidweb

Search date: 27/05/05

Update search: Jul wk 2 2005-May wk 5 2006

Search date: 13/06/06

1. exp Myocardial Infarction/

2. (infarct$ or mi or heart attack$ or heart arrest$ or heart event$).ti,ab.

3. 1 or 2

4. Warfarin/

5. ACENOCOUMAROL/

6. warfarin.ti,ab.

7. acenocoumarol.ti,ab.

8. nicoumalone.ti,ab.

9. phenindione.ti,ab.

10. oral anticoagulant$.ti,ab.

11. oral anti-coagulant$.ti,ab.

12. or/4-11

13. 12 and 3

14. (systematic$ adj review$).ab.

15. review.pt.

16. meta-analysis.ab.

17. meta-analysis.pt.

18. meta-analysis.ti.

19. or/14-18

20. 13 and 19

21. randomized controlled trial.pt.

22. controlled clinical trial.pt.

23. randomized controlled trials.sh.

24. random allocation.sh.

25. double blind method.sh.

26. single blind method.sh.

27. or/21-26

28. clinical trial.pt.

29. exp clinical trials/

30. (clin$ adj5 trial$).ti,ab.

31. ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).ti,ab.

32. placebos.sh.

33. placebo$.ti,ab.

34. random$.ti,ab.

35. or/28-34

36. 27 or 35

37. 13 and 36

38. 20 or 37

39. animal/

40. human/

41. 39 not (39 and 40)

42. 38 not 41

43. (letter or editorial or comment).pt.

44. 42 not 43

Question 23-24. Eplerenone

Medline 1966-Nov wk 3 2005 via Ovidweb

Search date: 29/11/05

Update search: Nov wk 3 2005-May wk 5 2006

Search date: 13/06/06

1. exp MYOCARDIAL INFARCTION/

2. (infarct$ or MI or heart attack$ or heart arrest$ or heart event$).ti,ab.

3. 1 or 2

4. eplerenone.ti,ab.

5. inspra.ti,ab.

6. 4 or 5

7. 3 and 6

8. Animals/

9. Humans/

10. 8 not (8 and 9)

11. 7 not 10

12. (letter or comment or editorial).pt.

13. 11 not 12

Question 15-18. Lipid lowering agents

Medline 1966-Dec wk 4 2005 via Ovidweb

Search date: 10/01/06

Update search: Dec wk 4 2005-May wk 5 2006

Search date: 13/06/06

1. exp Myocardial Infarction/

2. (infarct$ or MI or heart attack$ or heart arrest$ or heart event$).ti,ab.

3. 1 or 2

4. Hydroxymethylglutaryl-CoA Reductase Inhibitors/

5. SIMVASTATIN/

6. PRAVASTATIN/

7. (simvastatin or pravastatin or rosuvastatin or fluvastatin or atorvastatin).ti,ab.

8. statin$1.ti,ab.

9. hmg-coa.ti,ab.

10. or/4-9

11. 3 and 10

12. (systematic adj review$).tw.

13. (published adj studies).ab.

14. (data adj synthesis).tw.

15. (data adj extraction).ab.

16. meta-analysis/

17. meta-analysis.ti,ab.

18. meta-analysis.pt.

19. or/12-18

20. comment.pt.

21. letter.pt.

22. editorial.pt.

23. or/20-22

24. 11 and 19

25. randomized controlled trial.pt.

26. controlled clinical trial.pt.

27. randomized controlled trials.sh.

28. random allocation.sh.

29. double blind method.sh.

30. single blind method.sh.

31. or/25-30

32. clinical trial.pt.

33. exp clinical trials/

34. (clin$ adj5 trial$).ti,ab.

35. ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).ti,ab.

36. placebos.sh.

37. placebo$.ti,ab.

38. random$.ti,ab.

39. or/32-38

40. 31 or 39

41. 11 and 40

42. 24 or 41

43. 42 not 24

44. animals/

45. humans/

46. 44 not (44 and 45)

47. 43 not 46

48. limit 47 to english language

49. limit 48 to yr="1999 - 2006"

50. Clofibric Acid/

51. Bezafibrate/

52. Procetofen/

53. Gemfibrozil/

54. (bezafibrate$ or ciprofibrate$ or fenofibrate$ or gemfibrozil$ or fibrate$).ti,ab.

55. Niacin/

56. (niacin or nicotinic acid or acipimox).ti,ab.

57. ezetimibe.ti,ab.

58. or/50-57

59. 3 and 58

60. 59 not 46

61. 59 not 23

62. limit 61 to english language

63. 49 or 62

64. 19 and 62

65. 40 and 62

66. 65 or 64

67. 49 or 66

1.5.1 Coronary revascularisation

Question 26-27. What is the prognostic benefit of coronary revascularisation

Medline 1966-Jun wk 2 2005 via Ovidweb

Search date: 21/06/05

1. exp myocardial infarction/

2. (acute coronary syndrome$ or acs).ti,ab.

3. (infarct$ or mi or heart attack$ or heart arrest$ or heart event$).ti,ab.

4. or/1-3

5. exp myocardial revascularization/

6. (revascularisation or revascularization).ti,ab.

7. exp angioplasty, balloon/

8. (balloon adj2 (dilation or catheter$ or transluminal)).ti,ab.

9. angioplasty.ti,ab.

10. (pci or ptca or ptcra).ti,ab.

11. coronary atherectomy/

12. atherectomy.ti,ab.

13. ((coronary or aortocoronary) adj2 bypass).ti,ab.

14. (cabg or stent$).ti,ab.

15. stents/

16. or/5-15

17. 4 and 16

18. incidence/

19. Mortality/

20. Follow-Up Studies/

21. prognos$.ti,ab.

22. predict$.ti,ab.

23. course.ti,ab.

24. or/18-23

25. 17 and 24

1.6 Lifestyle

Question 43,51. Regular physical activity

Medline 1966- Wk 3 Nov 2004 via Ovidweb

Search date: 29/11/04

Update search wk3 nov 2004- wk 4 may 2006

Search date: 06/06/06

1. Cardiovascular Diseases/pc, th, rh [Prevention & Control, Therapy, Rehabilitation]

2. Coronary Disease/pc, th, rh [Prevention & Control, Therapy, Rehabilitation]

3. exp Myocardial Infarction/

4. ((myocardial or infarct$ or MI or coronary or cardiovascular or chd or cvd or heart attack$ or cardiac event$) adj4 (prevent$ or secondary or post or previous$ or prior or history or follow$)).ti,ab.

5. or/1-4

6. *Exercise Therapy/

7. ((regular$ or frequen$ or ongoing or on-going or long-term or longterm or life-long or lifelong) adj3 exercise$).ti,ab.

8. ((regular$ or frequen$ or ongoing or on-going or long-term or longterm or life-long or lifelong) adj3 physical$ activ$).ti,ab.

9. ((regular$ or frequen$ or ongoing or on-going or long-term or longterm or life-long or lifelong) adj3 physical training).ti,ab.

10. ((regular$ or frequen$ or ongoing or on-going or long-term or longterm or life-long or lifelong) adj3 formal training).ti,ab.

11. ((regular$ or frequen$ or ongoing or on-going or long-term or longterm or life-long or lifelong) adj3 aerobic$).ti,ab.

12. ((phase 4 or phase-4 or phase IV or phase-IV or phase four or phase-four) adj3 (exercise$ or physical$ activ$ or physical training or formal training or aerobic$)).ti,ab.

13. ((intensive$ or intensity) adj3 (exercise$ or physical$ activ$ or physical training or formal training or aerobic$)).ti,ab.

14. (duration adj3 (exercise$ or physical$ activ$ or physical training or formal training or aerobic$)).ti,ab.

15. (adherence adj3 (exercise$ or physical$ activ$ or physical training or formal training or aerobic$)).ti,ab.

16. or/6-15

17. 5 and 16

18. (systematic$ adj review$).ab.

19. review.pt.

20. meta-analysis.ab.

21. meta-analysis.pt.

22. meta-analysis.ti.

23. or/18-22

24. 17 and 23

25. randomized controlled trial.pt.

26. controlled clinical trial.pt.

27. randomized controlled trials.sh.

28. random allocation.sh.

29. double blind method.sh.

30. single blind method.sh.

31. or/25-30

32. clinical trial.pt.

33. exp clinical trials/

34. (clin$ adj5 trial$).ti,ab.

35. ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).ti,ab.

36. placebos.sh.

37. placebo$.ti,ab.

38. random$.ti,ab.

39. or/32-38

40. 31 or 39

41. 17 and 40

42. 24 or 41

43. (letter or editorial or comment).pt.

44. 42 not 43

Question 44-45. Alcohol consumption

Medline 1966-Nov wk 3 2004 via Ovidweb

Search date: 23/12/04

Update search Nov wk 3 2004-May wk 4 2006

Search date: 05/06/06

1. Cardiovascular Diseases/pc, ep [Prevention & Control, epidemiology]

2. Coronary Disease/pc, ep [Prevention & Control, epidemiology]

3. exp Myocardial Infarction/

4. ((myocardial or infarct$ or MI or coronary or cardiovascular or chd or cvd or heart attack$ or cardiac event$) adj4 (prevent$ or secondary or post or previous$ or prior or history or follow$)).ti,ab.

5. or/1-4

6. alcohol drinking/

7. temperance/

8. (alcohol$ adj2 (consum$ or drink$ or intake$ or beverage$ or abstinence or abstain$)).ti,ab.

9. (drink$ adj2 (non or low or lower or light or occasional$ or moderat$ or regular$ or heavy or heavily)).ti,ab.

10. (temperance or intemperance or teetotal$).ti,ab.

11. or/6-10

12. 5 and 11

13. (systematic$ adj review$).ab.

14. review.pt.

15. meta-analysis.ab.

16. meta-analysis.pt.

17. meta-analysis.ti.

18. or/13-17

19. 12 and 18

20. randomized controlled trial.pt.

21. controlled clinical trial.pt.

22. randomized controlled trials.sh.

23. random allocation.sh.

24. double blind method.sh.

25. single blind method.sh.

26. or/20-25

27. clinical trial.pt.

28. exp clinical trials/

29. (clin$ adj5 trial$).ti,ab.

30. ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).ti,ab.

31. placebos.sh.

32. placebo$.ti,ab.

33. random$.ti,ab.

34. or/27-33

35. 26 or 34

36. 12 and 35

37. 19 or 36

38. (letter or editorial or comment).pt.

39. 37 not 38

Question 41-42. Changing dietary regime

Medline 1966- Nov wk 3 2004 via Ovidweb

Search date: 24/11/04

Update search: Nov wk 3 2004-May wk 4 2006

Search date: 05/06/06

1. Cardiovascular Diseases/pc, dh [Prevention & Control, Diet Therapy]

2. Coronary Disease/dh, pc [Diet Therapy, Prevention & Control]

3. exp Myocardial Infarction/

4. ((myocardial or infarct$ or MI or coronary or cardiovascular or chd or cvd or heart attack$ or cardiac event$) adj4 (prevent$ or secondary or post or previous$ or prior or history or follow$)).ti,ab.

5. or/1-4

6. Diet, Fat-Restricted.mp. [mp=title, original title, abstract, name of substance word, subject heading word]

7. ((reduc$ or modify or modification or low or lower$ or decreas$) adj2 fat$1).ti,ab.

8. DIET, FAT-RESTRICTED/

9. Fish Oils/

10. Fatty Acids, Omega-3/

11. ((oily or oil or oils or fatty) adj fish).ti,ab.

12. (omega-3 or omega 3 or n-3 fatty acid$ or n-3 polyunsaturated fatty acid$ or pufa).ti,ab.

13. rapeseed oil$.ti,ab.

14. ANTIOXIDANTS/ad, tu

15. dietary fiber/

16. Folic acid/ad, tu

17. ((antioxidant$ or anti-oxidant$ or folate$) adj (vitamin$ or supplement$)).ti,ab.

18. ((fruit$ or vegetable$ or fibre$ or fiber$ or folate$) adj3 (high$ or increas$)).ti,ab.

19. (mediterranean adj2 diet$).ti,ab.

20. Diet, Mediterranean/

21. Phytosterols/

22. (phytosterols or plant sterols or stanol esters).ti,ab.

23. ((low$ or reduc$ or decreas$ or modify or modification) adj2 (glycemic diet$ or glycaemic diet$)).ti,ab.

24. ((cardioprotect$ or cardio-protect$) adj2 diet$).ti,ab.

25. (diet$ adj3 (advice or advis$ or inform$ or guide$ or guidance or educat$)).ti,ab.

26. (nutrition$ adj3 (advice or advis$ or inform$ or guide$ or guidance or educat$)).ti,ab.

27. or/6-26

28. 5 and 27

29. (systematic$ adj review$).ab.

30. review.pt.

31. meta-analysis.ab.

32. meta-analysis.pt.

33. meta-analysis.ti.

34. or/29-33

35. 28 and 34

36. randomized controlled trial.pt.

37. controlled clinical trial.pt.

38. randomized controlled trials.sh.

39. random allocation.sh.

40. double blind method.sh.

41. single blind method.sh.

42. or/36-41

43. clinical trial.pt.

44. exp clinical trials/

45. (clin$ adj5 trial$).ti,ab.

46. ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).ti,ab.

47. placebos.sh.

48. placebo$.ti,ab.

49. random$.ti,ab.

50. or/43-49

51. 42 or 50

52. 28 and 51

53. Epidemiologic Studies/

54. exp case control studies/

55. exp cohort studies/

56. case control.tw.

57. (cohort adj (study or studies)).tw.

58. ((followup or follow-up) adj (study or studies)).tw.

59. ((incidence or concurrent) adj (study or studies)).tw.

60. longitudinal.tw.

61. retrospective.tw.

62. cross sectional.tw.

63. Cross-Sectional Studies/

64. cohort analy$.tw.

65. or/53-64

66. 28 and 65

67. 35 or 52 or 66

68. (editorial or comment or letter).pt.

69. 67 not 68

70. animals/

71. humans/

72. 70 not (70 and 71)

73. 69 not 72

1.7 Cardiac Rehabilitation

Question 30-32. Comprehensive cardiac rehabilitation or exercise only rehabilitation

Medline 1999-Nov wk 3 2004 via Ovidweb

Search date: 19/01/05

Update search Nov wk 3 2004-may wk 4 2006

Search date: 06/06/06

1. CARDIOVASCULAR DISEASES/

2. CORONARY DISEASE/

3. exp MYOCARDIAL INFARCTION/

4. ((myocardial or infarct$ or mi or coronary or cardiovascular or chd or cvd or heart attack$ or cardiac event$) adj4 (prevent$ or secondary or post or previous$ or prior or history or follow$)).ti,ab.

5. or/1-4

6. exp Rehabilitation/

7. "Recovery of Function"/

8. activities of daily living/

9. exercise/

10. exercise therapy/

11. rehabilitat$.ti,ab.

12. (exercise$ adj2 (rehabilitat$ or therap$ or training or program$ or activit$ or toleran$ or prescribe$ or prescription$ or structure$ or unstructure$ or un-structure$ or supervise$ or unsupervise$ or un-supervise$ or guided or unguided or dynamic or regime$)).ti,ab.

13. (physical adj2 (exercise$ or educat$ or training or program$ or activit$ or regime$)).ti,ab.

14. (aerobic$ adj2 (exercise$ or training or program$ or activit$ or regime$)).ti,ab.

15. (strength$ adj (exercise$ or training)).ti,ab.

16. (endurance adj (exercise$ or training)).ti,ab.

17. (fitness adj2 (training or program$ or regime$)).ti,ab.

18. ((resistance or resistive) adj (exercise$ or training)).ti,ab.

19. (isometric adj2 (exercise$ or training or program$ or activit$ or regime$)).ti,ab.

20. ((high$ frequency or low$ frequency) adj2 (exercise$ or training or program$ or activit$ or regime$)).ti,ab.

21. ((high$ intensi$ or low$ intensi$) adj2 (exercise$ or training or program$ or activit$ or regime$)).ti,ab.

22. Managed Care Programs/

23. ((multifactor$ or multifacet$ or managed care) adj program$).ti,ab.

24. or/6-23

25. 5 and 24

26. (systematic$ adj review$).ab.

27. review.pt.

28. meta-analysis.ab.

29. meta-analysis.pt.

30. meta-analysis.ti.

31. or/26-30

32. 25 and 31

33. (letter or editorial or comment).pt.

34. animals/

35. humans/

36. 34 not (34 and 35)

37. 32 and 36

38. 37 not 33

Question 33. Safety in the exercise component of comprehensive cardiac rehabilitation

Medline 1966-Jan wk 3 2005 via Ovidweb

Search date: 29/01/05

Update search: Jan wk 3 2005-May wk 4 2006

Search date: 06/06/06

1. CARDIOVASCULAR DISEASES/rh [Rehabilitation]

2. CORONARY DISEASE/rh [Rehabilitation]

3. exp MYOCARDIAL INFARCTION/rh [Rehabilitation]

4. ((myocardial or infarct$ or mi or coronary or cardiovascular or chd or cvd or heart attack$ or cardiac event$) adj4 (prevent$ or secondary or post or previous$ or prior or history or follow$)).ti,ab.

5. or/1-4

6. exercise/

7. exercise therapy/

8. exercise tolerance/

9. (exercise$ adj2 (rehabilitat$ or therap$ or training or program$ or activit$ or toleran$ or prescribe$ or prescription$ or structure$ or unstructure$ or un-structure$ or supervise$ or unsupervise$ or un-supervise$ or guided or unguided or dynamic or regime$)).ti,ab.

10. (physical adj2 (exercise$ or educat$ or training or program$ or activit$ or regime$)).ti,ab.

11. (aerobic$ adj2 (exercise$ or training or program$ or activit$ or regime$)).ti,ab.

12. (strength$ adj (exercise$ or training)).ti,ab.

13. (endurance adj (exercise$ or training)).ti,ab.

14. (fitness adj2 (training or program$ or regime$)).ti,ab.

15. ((resistance or resistive) adj (exercise$ or training)).ti,ab.

16. (isometric adj2 (exercise$ or training or program$ or activit$ or regime$)).ti,ab.

17. ((high$ frequency or low$ frequency) adj2 (exercise$ or training or program$ or activit$ or regime$)).ti,ab.

18. ((high$ intensi$ or low$ intensi$) adj2 (exercise$ or training or program$ or activit$ or regime$)).ti,ab.

19. or/6-18

20. safety/

21. risk/

22. (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab.

23. (negative adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab.

24. (undesirable adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab.

25. (safe or safety or safely).ti,ab.

26. ((high or higher or greater or increas$ or rise or raise or raising) adj risk).ti,ab.

27. or/20-24

28. 5 and 19 and 27

29. (letter or editorial or comment or case report).pt.

30. 28 not 29

31. Animals/

32. Humans/

33. 31 not (31 and 32)

Question 34. Individualised comprehensive cardiac rehabilitation

Medline 1966-Feb wk 4 2005 via Ovidweb

Search date: 08/03/05

Update search: Feb wk 4 2005-May wk 4 2006

Search date: 06/06/06

1. cardiovascular diseases/

2. Coronary Disease/

3. exp myocardial infarction/

4. ((myocardial or infarct$ or mi or coronary or cardiovascular or chd or cvd or heart attack$ or cardiac event$) adj4 (prevent$ or secondary or post or previous$ or prior or history or follow$)).ti,ab.

5. or/1-4

6. ((individualis$ or individualiz$) adj3 (exercise$ or rehabilit$)).ti,ab.

7. (tailor$ adj3 (exercise$ or rehabilit$)).ti,ab.

8. ((menu-based or menubased) adj3 (exercise$ or rehabilit$)).ti,ab.

9. (personalis$ adj3 (exercise$ or rehabilit$)).ti,ab.

10. (personaliz$ adj3 (exercise$ or rehabilit$)).ti,ab.

11. or/6-10

12. 5 and 11

1.7.1 Patient Engagement

Question 40. Patient engagement in comprehensive cardiac rehabilitation

Medline 1966-April wk 4 2005 via Ovidweb

Search date: 07/04/05

Update search April wk 4 2005-May wk 4 2006

Search date: 06/06/06

1. CARDIOVASCULAR DISEASES/

2. CORONARY DISEASE/

3. exp MYOCARDIAL INFARCTION/

4. ((myocardial or infarct$ or mi or coronary or cardiovascular or chd or cvd or heart attack$ or cardiac event$) adj4 (prevent$ or secondary or post or previous$ or prior or history or follow$)).ti,ab.

5. or/1-4

6. exp Rehabilitation/

7. "Recovery of Function"/

8. activities of daily living/

9. exercise therapy/

10. (exercise$ adj3 (rehabilitat$ or therap$ or training or program$)).ti,ab.

11. rehabilitat$.ti,ab.

12. Managed Care Programs/

13. ((multifactor$ or multifacet$ or managed care) adj program$).ti,ab.

14. or/6-13

15. (enrollment or enrolment or enroling or enrolling).ti,ab.

16. participat$.ti,ab.

17. motivation$.ti,ab.

18. uptake.ti,ab.

19. referral.ti,ab.

20. (compliance or adherence).ti,ab.

21. (attend$ or non-attend$).ti,ab.

22. barrier$.ti,ab.

23. (engaging or engagement).ti,ab.

24. health services accessibility/

25. Patient Compliance/

26. "Referral and Consultation"/

27. Patient Satisfaction/

28. patient participation/

29. Self Efficacy/

30. Motivation/

31. or/15-30

32. 5 and 14 and 31

1.7.2 Education & Information

Question 35. Education & information needs of patients

Medline 1966-Feb wk 2 2005 via Ovidweb

Search date: 23/02/05

Update search: Feb wk 2 2005-May wk 5 2006

Search date: 08/06/06

1. Cardiovascular Diseases/nu, pc, rh [nursing, prevention & control, rehabilitation]

2. Coronary Disease/nu, pc, rh [nursing, prevention & control, rehabilitation]

3. exp myocardial infarction/

4. ((myocardial or infarct$ or mi or coronary or cardiovascular or chd or cvd or heart attack$ or cardiac event$) adj4 (prevent$ or secondary or post or previous$ or prior or history or follow$)).ti,ab.

5. or/1-4

6. Health Knowledge, Attitudes, Practice/

7. Patient Education/

8. teaching materials/

9. audiovisual aids/

10. counseling/

11. (Patient adj2 (education$ or information or knowledge)).ti,ab.

12. ((information or education$) adj (need or needs)).ti,ab.

13. ((information or education$) adj (provision or provide or providing or require$)).ti,ab.

14. (learning adj (need or needs)).ti,ab.

15. (rehab$ adj2 (information or education$ or guidance)).ti,ab.

16. (health adj2 (advice or information or guidance)).ti,ab.

17. ((needed or wanted) adj information).ti,ab.

18. ((medicat$ or diet$ or physical$ or activit$ or exercise$ or lifestyle$ or life-style$) adj2 (information or advice)).ti,ab.

19. (information adj support$).ti,ab.

20. (cardiac patient learning needs or cplni).ti,ab.

21. (education$ adj (class or classes)).ti,ab.

22. ((teaching or education$) adj (material$ or program$ or intervention$ or session$ or group or groups or individual$ or one to one or one-to-one)).ti,ab.

23. (counseling or counselling).ti,ab.

24. ((pamphlet$ or booklet$ or leaflet$ or video$ or cassette$ or audiotape$ or audio-tape$ or handout$ or hand-out$ or web or internet) adj2 (information or education$)).ti,ab.

25. or/6-24

26. 5 and 25

27. (systematic$ adj review$).ab.

28. review.pt.

29. meta-analysis.ab.

30. meta-analysis.pt.

31. meta-analysis.ti.

32. or/27-31

33. 26 and 32

34. randomized controlled trial.pt.

35. controlled clinical trial.pt.

36. randomized controlled trials.sh.

37. random allocation.sh.

38. double blind method.sh.

39. single blind method.sh.

40. or/34-39

41. clinical trial.pt.

42. exp clinical trials/

43. (clin$ adj5 trial$).ti,ab.

44. ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).ti,ab.

45. placebos.sh.

46. placebo$.ti,ab.

47. random$.ti,ab.

48. or/41-47

49. 40 or 48

50. 26 and 49

51. (letter or editorial or comment).pt.

52. 33 or 50

53. 52 not 51

1.7.3 Psychological support

Question 37. Psychological and social support for patients

Medline 1966-Feb wk 4 2005 via Ovidweb

Search date: 03/03/05

Update search Feb wk 4 2005-may wk 5 2006

Search date: 08/06/06

1. Cardiovascular Diseases/

2. Coronary Disease/

3. exp Myocardial Infarction/

4. ((myocardial or infarct$ or MI or heart attack or cardiovascular or coronary or cvd or chd or cardiac event$) adj4 (prevent or secondary or post or previous$ or prior or history or follow$)).ti,ab.

5. Counseling/

6. Cognitive Therapy/

7. Psychotherapy, Group/

8. Social Support/

9. Self-Help Groups/

10. (counselling or counseling).ti,ab.

11. ((Cognitive or cognition) adj2 (therap$ or psychotherap$)).ti,ab.

12. (group adj (therap$ or psychotherap$)).ti,ab.

13. cbt.ti,ab.

14. (social adj (support or network$)).ti,ab.

15. ((Psychosocial or psychological$) adj (support$ or intervention$ or treatment$ or rehabilitation)).ti,ab.

16. ((carer or carers spouse or family or families or partner$) adj2 support$).ti,ab.

17. ((peer or peers or lay) adj2 support$).ti,ab.

18. (emotional$ adj support$).ti,ab.

19. or/1-4

20. or/5-18

21. 19 and 20

22. (systematic$ adj review$).ab.

23. review.pt.

24. meta-analysis.ab.

25. meta-analysis.pt.

26. meta-analysis.ti.

27. or/22-26

28. 21 and 27

29. randomized controlled trial.pt.

30. controlled clinical trial.pt.

31. randomized controlled trials.sh.

32. random allocation.sh.

33. double blind method.sh.

34. single blind method.sh.

35. or/29-34

36. clinical trial.pt.

37. exp clinical trials/

38. (clin$ adj5 trial$).ti,ab.

39. ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).ti,ab.

40. placebos.sh.

41. placebo$.ti,ab.

42. random$.ti,ab.

43. or/36-42

44. 35 or 43

45. 21 and 44

46. 28 or 45

47. (letter or editorial or comment).pt.

48. 46 not 47

49. limit 48 to english language

1.7.4 Sexual activity

Question 38. Interventions for sexual dysfunction

Medline 1966-Feb wk 4 2005 via Ovidweb

Search date: 08/03/05

Update search Feb wk 4 2005-May wk 5 2006

Search date: 08/06/06

1. cardiovascular diseases/

2. coronary disease/

3. myocardial infarction/

4. ((myocardial or infarct$ or mi or coronary or cardiovascular or chd or cvd or heart attack$ or cardiac event$) adj4 (prevent$ or secondary or post or previous$ or prior or history or follow$)).ti,ab.

5. or/1-4

6. exp Sex Disorders/

7. Sexual Dysfunctions, Psychological/

8. libido/

9. ((sexual or psychosexual or psycho-sexual) adj (dysfunction$ or problem$ or difficult$ or dissatisf$ or concern$ or disorder$)).ti,ab.

10. (erectile adj (dysfunction$ or disorder$ or problem$ or difficult$ or concern$)).ti,ab.

11. ((premature$ or pre-mature$) adj ejaculat$).ti,ab.

12. (impoten$ or frigidity or libido or dyspareunia).ti,ab.

13. (sexual adj (activit$ or intercourse or satisfaction)).ti,ab.

14. coitus/

15. or/6-14

16. incidence/

17. Sex Counseling/

18. (sildenafil or viagra).ti,ab.

19. piperazines/

20. phosphodiesterase inhibitors/

21. (phosphodiesterase adj3 inhibitor$).ti,ab.

22. piperazines.ti,ab.

23. (counseling or counselling).ti,ab.

24. Relaxation Techniques/

25. (relaxation adj2 (technique$ or training or therap$)).ti,ab.

26. ((stress or anxiety or anxious$) adj2 (manag$ or treatment$ or intervention$ or control$ or prevent$)).ti,ab.

27. or/16-26

28. 5 and 15 and 27

Q.6 National Service Framework from Coronary Heart Disease definition of phases of comprehensive cardiac rehabilitation

Phase 1: before discharge from hospital

- assessment of physical, psychological needs for cardiac rehabilitation
- negotiation of a written individual plan for meeting these identified needs
- individual advice on lifestyle (smoking cessation, diet, physical activity, alcohol consumption, sexual activity and employment
- prescription of effective medication and education about its use, benefits and harms
- involvement of relevant informal carer(s)
- provision of information about cardiac support groups
- provision of locally relevant written information about cardiac rehabilitation

Phase 2: early post-discharge period

- comprehensive assessment of cardiac risk, including physical, psychological and social needs for cardiac rehabilitation; and a review of the initial plan for meeting these needs
- provision of lifestyle advice and psychological interventions according to the agreed plan from a relevantly trained therapist who has access to support from a cardiologist
- maintain involvement of relevant informal carer(s)
- review information with cardiac support groups
- offer resuscitation training for family carers

Phase 3: four weeks after acute cardiac event, as early post-discharge period plus

- structured exercise sessions to meet the assessed needs of individual patients
- maintain access to relevant advice and support from people trained to offer advice about exercise, relaxation, psychological interventions, health promotion and vocational advice

Phase 4: long-term maintenance of changed behaviour

- long-term follow up in primary care
- offer involvement with local cardiac support groups
- referral to specialist cardiac, behavioural (exercise, smoking cessation) or psychological services as clinically indicated

Q.7 Omega-3 fatty acids content of various oily fish required to provide approximately 1g of EPA plus DHA per day

Table 282: Omega-3 fatty acids (eicosapentiaenoic acid, C20:5n-3 (EPA) and docosahexaenoic acid, C22:6n-3 (DHA) content of various oily fish required to provide approximately 1g of EPA plus DHA per day

Fish	Amount required to provide approximately 1g of EPA plus DHA
Canned tuna	340
Fresh tuna	56-200
Herring	56
Mackerel	56-225
Salmon	56-85
Sardines	56-85
Trout	100

(a) P.M Kris-Etherton, W.S. Harris, L.J. Appel. "Fish Consumption, Fish Oil, Omega-3 Fatty Acids and Cardiovascular Disease." Circulation. 2002; 106-2747

The intakes of fish given are very rough estimates because oil content can vary markedly with species, season, diet, packaging and cooking methods.

Appendix R: Bibliography

1 Improvement in prognosis of myocardial infarction by long-term beta-adrenoreceptor blockade using practolol. A multicentre international study. BMJ. 1975; 3(5986):735-740

2 Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. New England Journal of Medicine. 1981; 304(14):801-807

3 A controlled comparison of aspirin and oral anticoagulants in prevention of death after myocardial infarction. New England Journal of Medicine. 1982; 307(12):701-708

4 A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. JAMA. 1982; 247(12):1707-1714

5 Reduction of infarct size with the early use of timolol in acute myocardial infarction. New England Journal of Medicine. 1984; 310(1):9-15

6 Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. New England Journal of Medicine. 1987; 316(23):1429-1435

7 Oral captopril versus placebo among 13,634 patients with suspected acute myocardial infarction: interim report from the Chinese Cardiac Study (CCS-1). Lancet. 1995; 345(8951):686-687

8 Effects of enalapril on left ventricular function and exercise performance after a first acute myocardial infarction. The EDEN Study Investigators. International Journal of Cardiology. 1997; 59(3):257-265

9 Effects of long-term, moderate-intensity oral anticoagulation in addition to aspirin in unstable angina. The Organization to Assess Strategies for Ischemic Syndromes (OASIS) Investigators. Journal of the American College of Cardiology. 2001; 37(2):475-484

10 Warfarin prevents more stroke than clopidogrel and aspirin in afib. Journal of Family Practice. 2006; 55(9):753

11 Aarsetoy H, Ponitz V, Nilsen OB, Grundt H, Harris WS, Nilsen DW. Low levels of cellular omega-3 increase the risk of ventricular fibrillation during the acute ischaemic phase of a myocardial infarction. Resuscitation. Ireland 2008; 78(3):258-264

12 Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. Lancet. 1993; 342(8875):821-828

13 Ades PA, Pashkow FJ, Nestor JR. Cost-effectiveness of cardiac rehabilitation after myocardial infarction. Journal of Cardiopulmonary Rehabilitation. Copyright: University of York, 2000. 1997; 17(4):222-231

14 Aerospace Medical Association Medical Guidelines Taskforce. Medical Guidelines for Airline Travel 2nd Edition. Aviation Space and Environmental Medicine. 2005; 74(5 (Supp)):A1-A19

15 Aish AE, Isenberg M. Effects of Orem-based nursing intervention on nutritional self-care of myocardial infarction patients. International Journal of Nursing Studies. 1996; 33(3):259-270

16 Akbulut M, Ozbay Y, Karaca I, Ilkay E, Gundogdu O, Arslan N. The effect of long-term clopidogrel use on neointimal formation after percutaneous coronary intervention. Coronary Artery Disease. 2004; 15(6):347-352

17 Akkerhuis KM, Neuhaus KL, Wilcox RG, Vahanian A, Boland JL, Hoffmann J et al. Safety and preliminary efficacy of one month glycoprotein IIb/IIIa inhibition with lefradafiban in patients with acute coronary syndromes without ST-elevation; a phase II study. European Heart Journal. 2000; 21(24):2042-2055

18 Al-Foraih N, Kwok S, France M, El-Omar M, Soran H. Omega-3 fatty acid consumption in post-myocardial infarction patients; nice recommendation, practicality and compliance. Atherosclerosis. 2011; 218(2):e1

19 Al-Mallah MH, Tleyjeh IM, Abdel-Latif AA, Weaver WD. Angio-converting enzyme inhibitors in coronary artery disease and preserved left ventricular systolic function: a systematic review and meta-analysis of randomized controlled trials. Journal of the American College of Cardiology. 2006; 47(8):1576-1583

20 Alexander JH, Lopes RD, James S, Kilaru R, He Y, Mohan P et al. Apixaban with antiplatelet therapy after acute coronary syndrome. New England Journal of Medicine. 2011; 365(8):699-708

21 Ali AM, Jagan N, Ahmad S. Behavioural changes among post-myocardial infarction patients undergoing cardiac rehabilitation-medication therapy adherence clinic (CR-MTAC). International Journal of Pharmacy and Pharmaceutical Sciences. 2012; 4(SUPPL.1):646-651

22 Ali M, Qadir F, Javed S, Khan ZN, Asad S, Hanif B. Factors affecting outpatient cardiac rehabilitation attendance after acute myocardial infarction and coronary revascularization--a local experience. JPMA Journal of the Pakistan Medical Association. 2012; 62(4):347-351

23 Anand SS, Yusuf S. Oral anticoagulant therapy in patients with coronary artery disease: a meta-analysis. JAMA. Database of Abstracts of Reviews of Effectiveness. Produced by the NHS Centre for Reviews and Dissemination, University of York. Copyright: University of York. 1999; 282(21):2058-2067

24 Anand SS, Yusuf S, Pogue J, Weitz JI, Flather M. Long-term oral anticoagulant therapy in patients with unstable angina or suspected non-Q-wave myocardial infarction: organization to assess strategies for ischemic syndromes (OASIS) pilot study results. Circulation. 1998; 98(11):1064-1070

25 Anderson JP MRJ. Parasite screening and treatment among Indochinese refugees: Cost-benefit/utility and the General Health Policy Model. JAMA. 1985; 253(15):2229-2235

26 Anderson AN, Moodley I, Kropman K. A South African pharmaco-economic analysis of the acute infarction ramipril efficacy (AIRE) study. Cardiovascular Journal of Southern Africa. South Africa 2000; 11(2):89-94

27 Andrade JG, Deyell MW, Khoo C, Lee M, Humphries K, Cairns JA. Risk of bleeding on triple antithrombotic therapy after percutaneous coronary intervention/stenting: a systematic review and meta-analysis. Canadian Journal of Cardiology. 2013; 29(2):204-212

28 Arnetz JE, Winblad U, Hoglund AT, Lindahl B, Spangberg K, Wallentin L et al. Is patient involvement during hospitalization for acute myocardial infarction associated with post-discharge treatment outcome? An exploratory study. Health Expectations. 2010; 13(3):298-311

29 Arnold JMO, Yusuf S, Young J, Mathew J, Johnstone D, Avezum A et al. Prevention of heart failure in patients in the Heart Outcomes Prevention Evaluation (HOPE) study. Circulation. 2003; 107(9):1284-1290

30 Aronow WS, Ahn C, Kronzon I. Effect of beta blockers alone, of angiotensin-converting enzyme inhibitors alone, and of beta blockers plus angiotensin-converting enzyme inhibitors on new coronary events and on congestive heart failure in older persons with healed myocardial infarcts and asymptomatic left ventricular systolic dysfunction. American Journal of Cardiology. 2001; 88(11):1298-1300

31 Ashe ED. The effects of a relapse prevention program on adherence to a phase II cardiac exercise program Florida State University; 1993.

32 Astin F, Atkin K, Darr A. Family support and cardiac rehabilitation: a comparative study of the experiences of South Asian and White-European patients and their carer's living in the United Kingdom. European Journal of Cardiovascular Nursing. 2008; 7(1):43-51

33 Atar I, Korkmaz ME, Atar I, Gulmez O, Ozin B, Bozbas H et al. Effects of metoprolol therapy on cardiac troponin-I levels after elective percutaneous coronary interventions. European Heart Journal. 2006; 27(5):547-552

34 Atary JZ, van der Hoeven BL, Liem SS, Jukema JW, van der Bom JG, Atsma DE et al. Three-year outcome of sirolimus-eluting versus bare-metal stents for the treatment of ST-segment elevation myocardial infarction (from the MISSION! Intervention Study). American Journal of Cardiology. 2010; 106(1):4-12

35 Athyros VG, Kakafika AI, Papageorgiou AA, Tziomalos K, Peletidou A, Vosikis C et al. Effect of a plant stanol ester-containing spread, placebo spread, or Mediterranean diet on estimated cardiovascular risk and lipid, inflammatory and haemostatic factors. Nutrition Metabolism & Cardiovascular Diseases. Germany 2011; 21(3):213-221

36 Aurbach A, Russ W, Battegay E, Bucher HC, Brecht JG, Schadlich PK et al. Cost-effectiveness of ramipril in patients at high risk for cardiovascular events: a Swiss perspective. Swiss Medical Weekly. Switzerland 2004; 134(27-28):399-405

37 Baber NS, Evans DW, Howitt G, Thomas M, Wilson T, Lewis JA et al. Multicentre post-infarction trial of propranolol in 49 hospitals in the United Kingdom, Italy, and Yugoslavia. British Heart Journal. 1980; 44(1):96-100

38 Backhouse ME, Richter A, Gaffney L. Economic evaluation of ramipril in the treatment of patients at high risk for cardiovascular events. Journal of Drug Assessment. Copyright: University of York, 2004. 2000; 3(Part 4):253-265

39 Baigi A, Bering C, Fridlund B, Almerud-+ûsterberg S. Knowledge and beliefs about risk factor information among non-attendees in cardiac rehabilitation programs. Nordic Journal of Nursing Research & Clinical Studies. 2011; 31(1):29-33

40 Balcon R, Jewitt DE, Davies JP, Oram S. A controlled trial of propranolol in acute myocardial infarction. Lancet. 1966; 2(7470):918-920

41 Ball SG, Hall AS, Murray GD. Angiotensin-converting enzyme inhibitors after myocardial infarction: indications and timing. Journal of the American College of Cardiology. 1995; 25(7 Suppl):42S-46S

42 Banerjee AT, Grace SL, Thomas SG, Faulkner G. Cultural factors facilitating cardiac rehabilitation participation among Canadian South Asians: a qualitative study. Heart and Lung. 2010; 39(6):494-503

43 Barber JM, Murphy FM, Merrett JD. Clinical trial of propranolol in acute myocardial infarction. Ulster Medical Journal. 1967; 36(2):127-130

44 Bartorelli AL, Tamburino C, Trabattoni D, Galassi A, Serdoz R, Sheiban I et al. Comparison of two antiplatelet regimens (aspirin alone versus aspirin + ticlopidine or clopidogrel) after intracoronary implantation of a carbofilm-coated stent. American Journal of Cardiology. 2007; 99(8):1062-1066

45 Basat O, Ucak S, Seber S, Oztekin E, Altuntas Y. After myocardial infarction carvedilol improves insulin resistance compared to metoprolol. Clinical Research in Cardiology. 2006; 95(2):99-104

46 Basu S, Senior R, Raval U, van der Does R, Bruckner T, Lahiri A. Beneficial effects of intravenous and oral carvedilol treatment in acute myocardial infarction. A placebo-controlled, randomized trial. Circulation. 1997; 96(1):183-191

47 Bazzino O, Navarro Estrada JL, Sosa Liprandi A, Presti C, Masoli O, Santopinto J et al. Early treatment with low-dose enalapril after acute myocardial infarction: an equilibrium radionuclide angiographic study. Enalapril despues del Infarto (EDI) Trial Investigators. Journal of Nuclear Cardiology. 1997; 4(2 Pt 1):133-139

48 Beauchamp A, Peeters A, Tonkin A, Turrell G. Best practice for prevention and treatment of cardiovascular disease through an equity lens: a review. European Journal of Cardiovascular Prevention & Rehabilitation. 2010; 17(5):599-606

49 Beckie TM, Beckstead JW. Predicting cardiac rehabilitation attendance in a gender-tailored randomized clinical trial. Journal of Cardiopulmonary Rehabilitation & Prevention. 2010; 30(3):147-156

50 Beckwith C, Munger MA. Effect of angiotensin-converting enzyme inhibitors on ventricular remodeling and survival following myocardial infarction. Annals of Pharmacotherapy. 1993; 27(6):755-766

51 Behar S, Brunner D, Kaplinsky E, Mandelzweig L, Benderly M. Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease: The bezafibrate infarction prevention (BIP) study. Circulation. United States 2000; 102(1):21-27

52 Berger JS, Bhatt DL, Cannon CP, Chen Z, Jiang L, Jones JB et al. The relative efficacy and safety of clopidogrel in women and men a sex-specific collaborative meta-analysis. Journal of the American College of Cardiology. 2009; 54(21):1935-1945

53 Berger JS, Brown DL, Becker RC. Low-dose aspirin in patients with stable cardiovascular disease: a meta-analysis. American Journal of Medicine. 2008; 121(1):43-49

54 Berger PB, Bhatt DL, Fuster V, Steg PG, Fox KA, Shao M et al. Bleeding complications with dual antiplatelet therapy among patients with stable vascular disease or risk factors for vascular disease: results from the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial. Circulation. 2010; 121(23):2575-2583

55 Bernardi V, Szarfer J, Summay G, Mendiz O, Sarmiento R, Alemparte MR et al. Long-term versus short-term clopidogrel therapy in patients undergoing coronary stenting (from the Randomized Argentine Clopidogrel Stent [RACS] trial). American Journal of Cardiology. 2007; 99(3):349-352

56 Bertrand ME, McFadden EP, Fruchart JC, Van B, Commeau P, Grollier G et al. Effect of pravastatin on angiographic restenosis after coronary balloon angioplasty. The PREDICT Trial Investigators. Prevention of Restenosis by Elisor after Transluminal Coronary Angioplasty. Journal of the American College of Cardiology. UNITED STATES 1997; 30(4):863-869

57 Bestehorn HP, Rensing UF, Roskamm H, Betz P, Benesch L, Schemeitat K et al. The effect of simvastatin on progression of coronary artery disease. The Multicenter coronary Intervention Study (CIS). European Heart Journal. 1997; 18(2):226-234

58 Beswick AD, Rees K, Griebsch I, Taylor FC, Burke M, West RR. Provision, uptake and cost of cardiac rehabilitation programmes: improving services to under-represented groups. Health Technology Assessment. This record is part of the Health Technology Database produced by the NHS Centre for Reviews and Dissemination, University of York. The 2004; 8(41)

59 Beta-Blocker Heart Attack Trial Research Group. A randomized trial of propanolol in patients with acute myocardial infarction: II morbidity results. JAMA. 1983; 250:2814-2819

60 Betell HJN, Turner SC, Flint EJ, Rose L. The BACR database of cardiac rehabilitation units in the UK. Coronary Health Care. 2000; 4:92-95

61 Bethell HJ, Turner SC, Evans JA, Rose L. Cardiac rehabilitation in the United Kingdom. How complete is the provision? Journal of Cardiopulmonary Rehabilitation. 2001; 21(2):111-115

62 Bhala N, Taggar J. Clopidogrel and metoprolol in myocardial infarction. Lancet. 2006; 367(9513):812-813

63 Bhatt DL, Chew DP, Hirsch AT, Ringleb PA, Hacke W, Topol EJ. Superiority of clopidogrel versus aspirin in patients with prior cardiac surgery. Circulation. 2001; 103(3):363-368

64 Bhatt DL, Fox KAA, Hacke W, Berger PB, Black HR, Boden WE et al. Clopidogrel and aspirin versus aspirin alone for the prevention of Atherothrombotic events. New England Journal of Medicine. 2006; 354

65 Bhatt DL, Flather MD, Hacke W, Berger PB, Black HR, Boden WE et al. Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial. Journal of the American College of Cardiology. 2007; 49(19):1982-1988

66 Bjorholt I, Andersson FL, Kahan T, Ostergren J. The cost-effectiveness of ramipril in the treatment of patients at high risk of cardiovascular events: a Swedish sub-study to the HOPE study. Journal of Internal Medicine. 2002; 251(6):508-517

67 Blake E, Tsakirides C, Ingle L. Hospital versus community-based phase III cardiac rehabilitation. British Journal of Nursing. 2009; 18(2):116-122

68 Blanchard CM, Reid RD, Morrin LI, Beaton LJ, Pipe A, Courneya KS et al. Correlates of physical activity change in patients not attending cardiac rehabilitation. Journal of Cardiopulmonary Rehabilitation. 2006; 26(6):377-383

69 Blanchard C, Rainham D, McSweeney J, Spence J, McDonnell L, Rhodes R et al. Community SES, perceived environment, and physical activity during home-based cardiac rehabilitation: is there a need to consider the urban vs. rural distinction? Journal of Urban Health. 2012; 89(2):285-295

70 Blanchard CM, Reid RD, Morrin LI, Beaton LJ, Pipe A, Courneya KS et al. Barrier self-efficacy and physical activity over a 12-month period in men and women who do and do not attend cardiac rehabilitation. Rehabilitation Psychology. 2007; 52(1):65-73

71 Blanchard CM, Reid RD, Morrin LI, McDonnell L, McGannon K, Rhodes RE et al. Demographic and clinical determinants of moderate to vigorous physical activity during home-based cardiac rehabilitation: the home-based determinants of exercise (HOME) study. Journal of Cardiopulmonary Rehabilitation & Prevention. 2010; 30(4):240-245

72 Borghi C, Ambrosioni E, Novo S, Vinereanu D, Ambrosio G, Working P. Comparison between zofenopril and ramipril in combination with acetylsalicylic acid in patients with left ventricular systolic dysfunction after acute myocardial infarction: results of a randomized, double-blind, parallel-group, multicenter, European study (SMILE-4). Clinical Cardiology. 2012; 35(7):416-423

73 Borghi C, Ambrosioni E, Survival of Myocardial Infarction Long-term Evaluation Study Group. Effects of zofenopril on myocardial ischemia in post-myocardial infarction patients with preserved left ventricular function: the Survival of Myocardial Infarction Long-term Evaluation (SMILE)-ISCHEMIA study. American Heart Journal. 2007; 153(3):445-14

74 Bosch J, Gerstein HC, Dagenais GR, Diaz R, Dyal L, Jung H et al. n-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. New England Journal of Medicine. 2012; 367(4):309-318

75 Bowry ADK, Brookhart MA, Choudhry NK. Meta-analysis of the efficacy and safety of clopidogrel plus aspirin as compared to antiplatelet monotherapy for the prevention of vascular events. American Journal of Cardiology. 2008; 101(7):960-966

76 Braunwald E, Domanski MJ, Fowler SE, Geller NL, Gersh BJ, Hsia J et al. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. New England Journal of Medicine. United States 2004; 351(20):2058-2068

77 Brezinka V, Dusseldorp E, Maes S. Gender differences in psychosocial profile at entry into cardiac rehabilitation. Journal of Cardiopulmonary Rehabilitation. 1998; 18(6):445-449

78 Briggs A, Mihaylova B, Sculpher M, Hall A, Wolstenholme J, Simoons M et al. Cost effectiveness of perindopril in reducing cardiovascular events in patients with stable coronary artery disease using data from the EUROPA study. Heart. 2007; 93(9):1081-1086

79 British National Formulary. British National Formulary. 2007. Available from: http://www.bnf.org/bnf/bnf/current/112801.htm?q=%22omacor%22#_hit

80 Brouwer IA, Zock PL, Camm AJ, Bocker D, Hauer RN, Wever EF et al. Effect of fish oil on ventricular tachyarrhythmia and death in patients with implantable cardioverter defibrillators: the Study on Omega-3 Fatty Acids and Ventricular Arrhythmia (SOFA) randomized trial. JAMA. 2006; 295(22):2613-2619

81 Brouwer MA, van den Bergh PJPC, Aengevaeren WRM, Veen G, Luijten HE, Hertzberger DP et al. Aspirin plus coumarin versus aspirin alone in the prevention of reocclusion after fibrinolysis for acute myocardial infarction: results of the Antithrombotics in the Prevention of Reocclusion In Coronary Thrombolysis (APRICOT)-2 Trial. Circulation. 2002; 106(6):659-665

82 Brual J, Gravely-Witte S, Suskin N, Stewart DE, Macpherson A, Grace SL. Drive time to cardiac rehabilitation: at what point does it affect utilization? International Journal of Health Geographics. 2010; 9:27

83 Buch P, Rasmussen S, Abildstrom SZ, Kober L, Carlsen J, Torp-Pedersen C. The long-term impact of the angiotensin-converting enzyme inhibitor trandolapril on mortality and hospital admissions in patients with left ventricular dysfunction after a myocardial infarction: follow-up to 12 years. European Heart Journal. 2005; 26(2):145-152

84 Buckland G, Gonzalez CA, Agudo A, Vilardell M, Berenguer A, Amiano P et al. Adherence to the mediterranean diet and risk of coronary heart disease in the spanish EPIC cohort study. American Journal of Epidemiology. 2009; 170(12):1518-1529

85 Buresly K, Eisenberg MJ, Zhang X, Pilote L. Bleeding complications associated with combinations of aspirin, thienopyridine derivatives, and warfarin in elderly patients following acute myocardial infarction. Archives of Internal Medicine. 2005; 165(7):784-789

86 Burr ML, Fehily AM, Gilbert JF, Rogers S, Holliday RM, Sweetnam PM et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). Lancet. England 1989; 2(8666):757-761

87 Burr ML, shfield-Watt PA, Dunstan FD, Fehily AM, Breay P, Ashton T et al. Lack of benefit of dietary advice to men with angina: results of a controlled trial. European Journal of Clinical Nutrition. 2003; 57(2):193-200

88 Butler MJ, Eccleston D, Clark DJ, Ajani AE, Andrianopoulos N, Brennan A et al. The effect of intended duration of clopidogrel use on early and late mortality and major adverse cardiac events in patients with drug-eluting stents. American Heart Journal. 2009; 157(5):899-907

89 Byrne RA, Schulz S, Mehilli J, Iijima R, Massberg S, Neumann FJ et al. Rationale and design of a randomized, double-blind, placebo-controlled trial of 6 versus 12 months clopidogrel therapy after implantation of a drug-eluting stent: The Intracoronary Stenting and Antithrombotic Regimen: Safety And EFficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting (ISAR-SAFE) study. American Heart Journal. 2009; 157(4):620-624

90 Caldwell PH, Arthur HM. The influence of a "culture of referral" on access to care in rural settings after myocardial infarction. Health & Place. 2009; 15(1):180-185

91 Califf RM, Lokhnygina Y, Velazquez EJ, McMurray JJV, Leimberger JD, Lewis EF et al. Usefulness of beta blockers in high-risk patients after myocardial infarction in conjunction with captopril and/or valsartan (from the VALsartan In Acute Myocardial Infarction [VALIANT] trial). American Journal of Cardiology. 2009; 104(2):151-157

92 Cannon CP, Harrington RA, James S, Ardissino D, Becker RC, Emanuelsson H et al. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. Lancet. 2010; 375(9711):283-293

93 Carrero JJ, Fonollá J, Marti JL, Jiménez J, Boza JJ, López-Huertas E. Intake of fish oil, oleic acid, folic acid, and vitamins B-6 and E for 1 year decreases plasma C-reactive protein and reduces

coronary heart disease risk factors in male patients in a cardiac rehabilitation program. Journal of Nutrition. 2007; 137(2):384-390

94 Carroll DL, Rankin SH, Cooper BA. The effects of a collaborative peer advisor/advanced practice nurse intervention: cardiac rehabilitation participation and rehospitalization in older adults after a cardiac event. Journal of Cardiovascular Nursing. 2007; 22(4):313-319

95 Carter NJ, Keating GM. Controlled-release carvedilol. American Journal of Cardiovascular Drugs. 2008; 8(4):271-282

96 Casey E, Hughes JW, Waechter D, Josephson R, Rosneck J. Depression predicts failure to complete phase-II cardiac rehabilitation. Journal of Behavioral Medlicine. 2008; 31(5):421-431

97 Cassese S, Byrne RA, Tada T, King LA, Kastrati A. Clinical impact of extended dual antiplatelet therapy after percutaneous coronary interventions in the drug-eluting stent era: A meta-analysis of randomized trials. European Heart Journal. 2012; 33(24):3078-3087

98 Castro IA, Monteiro VC, Barroso LP, Bertolami MC. Effect of eicosapentaenoic/docosahexaenoic fatty acids and soluble fibers on blood lipids of individuals classified into different levels of lipidemia. Nutrition. United States 2007; 23(2):127-137

99 Caulin-Glaser T, Schmeizel R. Impact of educational initiatives on gender referrals to cardiac rehabilitation. Journal of Cardiac Rehabilitation. 2000; 20(5):302

100 Cay S, Cagirci G, Sen N, Atak R, Demir AD, Erbay AR. Ivabradine improves short-term outcomes after primary percutaneous coronary intervention in patients presenting with acute ST-segment elevation myocardial infarction. European Heart Journal. 2011; 32:868

101 Chase JA. Systematic review of physical activity intervention studies after cardiac rehabilitation. Journal of Cardiovascular Nursing. 2011; 26(5):351-358

102 Chatterjee S, Chaudhuri D, Vedanthan R, Fuster V, Ibanez B, Bangalore S et al. Early intravenous beta blockers improve in-hospital and short-term mortality without increasing the risk of cardiogenic shock in patients with acute coronary syndrome-a meta-analysis. Circulation. 2011; 124(21 SUPPL. 1)

103 Chauhan U, Baker D, Lester H, Edwards R. Exploring uptake of cardiac rehabilitation in a minority ethnic population in England: a qualitative study. European Journal of Cardiovascular Nursing. 2010; 9(1):68-74

104 Chen J, Bhatt DL, Dunn ES, Shi C, Caro JJ, Mahoney EM et al. Cost-effectiveness of clopidogrel plus aspirin versus aspirin alone for secondary prevention of cardiovascular events: results from the CHARISMA trial. Value in Health. 2009; 12(6):872-879

105 Chen J, Shi C, Mahoney EM, Dunn ES, Rinfret S, Caro JJ et al. Economic evaluation of clopidogrel plus aspirin for secondary prevention of cardiovascular events in Canada for patients with established cardiovascular disease: Results from the CHARISMA trial. Canadian Journal of Cardiology. 2011; 27(2):222-231

106 Chen ZM, Jiang LX, Chen YP, Xie JX, Pan HC, Peto R et al. Addition of clopidogrel to aspirin in 45852 patients with acute myocardial infarction:randomised placebo-controlled trial. Lancet. 2005; 366(9497):1607-1621

107 Chen ZM, Pan HC, Chen YP, Peto R, Collins R. Early intravenous then oral metoprolol 45852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet. 2005; 366(9497):1622-1632

108 Chin CT, Roe MT, Fox KA, Prabhakaran D, Marshall DA, Petitjean H et al. Study design and rationale of a comparison of prasugrel and clopidogrel in medically managed patients with unstable angina/non-ST-segment elevation myocardial infarction: the TaRgeted platelet Inhibition to cLarify the Optimal strateGy to medicallY manage Acute Coronary Syndromes (TRILOGY ACS) trial. American Heart Journal. 2010; 160(1):16-22

109 Clark AM, Barbour RS, White M, MacIntyre PD. Promoting participation in cardiac rehabilitation: patient choices and experiences. Journal of Advanced Nursing. 2004; 47(1):5-14

110 Clark AM, Hartling L, Vandermeer B, McAlister FA. Meta-analysis: secondary prevention programs for patients with coronary artery disease. Annals of Internal Medicine. 2005; 143(9):659-672

111 Clark AM, King-Shier KM, Thompson DR, Spaling MA, Duncan AS, Stone JA et al. A qualitative systematic review of influences on attendance at cardiac rehabilitation programs after referral. American Heart Journal. 2012; 164(6):835-845

112 Clark AM, Whelan HK, Barbour R, MacIntyre PD. A realist study of the mechanisms of cardiac rehabilitation. Journal of Advanced Nursing. 2005; 52(4):362-371

113 Cohen M, Parry G, Adams PC, Xiong J, Chamberlain D, Wieczorek I et al. Prospective evaluation of a prostacyclin-sparing aspirin formulation and heparin/warfarin in aspirin users with unstable angina or non-Q wave myocardial infarction at rest. The Antithrombotic Therapy in Acute Coronary Syndromes Research Group. European Heart Journal. 1994; 15(9):1196-1203

114 Cohen M, Xiong J, Parry G, Adams PC, Chamberlain D, Wieczorek I et al. Prospective comparison of unstable angina versus non-Q wave myocardial infarction during antithrombotic therapy. Antithrombotic Therapy in Acute Coronary Syndromes Research Group. Journal of the American College of Cardiology. 1993; 22(5):1338-1343

115 Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. New England Journal of Medicine.: Massachusetts Medical Society. 2001; 345(23):1667-1675

116 Collet JP, Montalescot G, Steg PG, Steinhubl SR, Fox KA, Hu TF et al. Clinical outcomes according to permanent discontinuation of clopidogrel or placebo in the CHARISMA trial. Archives of Cardiovascular Diseases. 2009; 102(6-7):485-496

117 Concepcion J, Reyes MRS, Peraira JRPM, Soria SSD, Pineda CPG, Parra SPP et al. Therapeutic adherence and health education: From problem to solution. European Journal of Cardiovascular Nursing. 2010; 9(1 Suppl):S18

118 Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A et al. Dabigatran versus warfarin in patients with atrial fibrillation. New England Journal of Medicine. 2009; 361(12):1139-1151

119 Connolly SJ, Ezekowitz MD, Yusuf S, Reilly PA, Wallentin L, Randomized Evaluation of Long-Term Anticoagulation Therapy Investigators. Newly identified events in the RE-LY trial. New England Journal of Medicine. 2010; 363(19):1875-1876

120 Cook JR, Glick HA, Gerth W, Kinosian B, Kostis JB. The cost and cardioprotective effects of enalapril in hypertensive patients with left ventricular dysfunction. American Journal of Hypertension. Copyright: University of York, 2004. 1998; 11(12):1433-1441

121 Cooper AF, Weinman J, Hankins M, Jackson G, Horne R. Assessing patients' beliefs about cardiac rehabilitation as a basis for predicting attendance after acute myocardial infarction. Heart. 2007; 93(1):53-58

122 Coronary Drug Project Research Group. Clofibrate and niacin in coronary heart disease. JAMA. UNITED STATES 1975; 231(4):360-381

123 Cossette S, D'Aoust LX, Morin M, Heppell S, Frasure-Smith N. The systematic development of a nursing intervention aimed at increasing enrollment in cardiac rehabilitation for acute coronary syndrome patients. Progress in Cardiovascular Nursing. 2009; 24(3):71-79

124 Cossette S, Frasure-Smith N, Heppell S, Loyer J, Dupuis J, Juneau M et al. Effect of a nursing intervention on cardiac rehabilitation intake in patients hospitalized for an acute coronary syndrome: A randomized controlled trial. Canadian Journal of Cardiology. 2010; 26:162D

125 Cossette S, Frasure-Smith N, Dupuis J, Juneau M, Guertin MC. Randomized controlled trial of tailored nursing interventions to improve cardiac rehabilitation enrollment. Nursing Research. 2012; 61(2):111-120

126 Coumadin Aspirin Reinfarction Study (CARS) Investigators. Randomised double-blind trial of fixed low-dose warfarin with aspirin after myocardial infarction. Lancet. ENGLAND 1997; 350(9075):389-396

127 Courtney-Pratt H, Johnson C, Cameron-Tucker H, Sanderson S. Investigating the feasibility of promoting and sustaining delivery of cardiac rehabilitation in a rural community. Rural & Remote Health. 2011; 11(4):1-9

128 Crouse JR, Byington RP, Bond MG, Espeland MA, Craven TE, Sprinkle JW et al. Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries (PLAC-II). American Journal of Cardiology. UNITED STATES 1995; 75(7):455-459

129 Curtis L. Unit costs of health and social care 2011. Canterbury: Personal Social Services Reseach Unit, University of Kent; 2011

130 Dalal HM, Evans PH, Campbell JL, Taylor RS, Watt A, Read KLQ et al. Home-based versus hospital-based rehabilitation after myocardial infarction: A randomized trial with preference arms--Cornwall Heart Attack Rehabilitation Management Study (CHARMS). International Journal of Cardiology. 2007; 119(2):202-211

131 Dalal HM, Wingham J, Palmer J, Taylor R, Petre C, Lewin R. Why do so few patients with heart failure participate in cardiac rehabilitation? A cross-sectional survey from England, Wales and Northern Ireland. BMJ Open. 2012; 2(2)

132 Daltroy LH. Improving cardiac patient adherence to exercise regimens: a clinical trial of health education. Journal of Cardiac Rehabilitation. 1985; 5:40-49

133 Dankner R, Geulayov G, Ziv A, Novikov I, Goldbourt U, Drory Y. The effect of an educational intervention on coronary artery bypass graft surgery patients' participation rate in cardiac rehabilitation programs: a controlled health care trial. BMC Cardiovascular Disorders. 2011; 11:60

134 Darasz KH, Bayliss J, Underwood SR, Keegan J, Poole-Wilson PA, Sutton GC. Left ventricular volume in thrombolysed patients with acute anterior myocardial infarction: the effect of captopril and xamoterol. International Journal of Cardiology. 1995; 51(2):137-142

135 Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. Lancet. England 2001; 357(9266):1385-1390

136 Davies MK, Hobbs FDR, Davis RC, Kenkre JE, Roalfe aK, Hare R et al. Prevalence of left-ventricular systolic dysfunction and heart failure in the Echocardiographic Heart of England Screening study: a population based study. Lancet. 2001; 358:439-444

137 de Faire U, Ericsson CG, Grip L, Nilsson J, Svane B, Hamsten A. Secondary preventive potential of lipid-lowering drugs. The Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT). European Heart Journal. ENGLAND 1996; 17 Suppl F:37-42

138 de la Sierra A. Main results and clinical interpretations from the TRANSCEND study. Journal of Hypertension Supplement. 2009; 27(2):S22-S25

139 De Luca G, Cassetti E, Marino P. Impact of duration of clopidogrel prescription on outcome of DES as compared to BMS in primary angioplasty: a meta-regression analysis of randomized trials. Journal of Thrombosis and Thrombolysis. 2009; 27(4):365-378

140 De Luca G, Ucci G, Cassetti E, Marino P. Benefits from small molecule administration as compared with abciximab among patients with ST-segment elevation myocardial infarction treated with primary angioplasty: a meta-analysis. Journal of the American College of Cardiology. 2009; 53(18):1668-1673

141 Dean J, Yujie Z, Yingxin Z, Yuyang L, Yonghe G, Wanjun C et al. Prolonged dual antiplatelet therapy improves clinical outcomes in high-risk patients implanted with sirolimus-eluting stents. Clinical Cardiology. 2009; 32(3):164-168

142 Deedwania PC. Angiotensin-converting enzyme inhibitors in congestive heart failure. Archives of Internal Medicine. 1990; 150(9):1798-1805

143 DeEugenio D, Kolman L, DeCaro M, Andrel J, Chervoneva I, Duong P et al. Risk of major bleeding with concomitant dual antiplatelet therapy after percutaneous coronary intervention in patients receiving long-term warfarin therapy. Pharmacotherapy. 2007; 27(5):691-696

144 Deligiannis P, Kouidis N, Farmakiotis A, Kouidi E, Deligiannis A. Efficacy of telemonitoring service in cardiac rehabilitation programs in public gyms. European Journal of Cardiovascular Prevention & Rehabilitation. 2010; 17:S106

145 Deo SV, Dunlay SM, Shah IK, Altarabsheh SE, Erwin PJ, Boilson BA et al. Dual anti-platelet therapy after coronary artery bypass grafting: is there any benefit? A systematic review and meta-analysis. Journal of Cardiac Surgery. 2013; 28(2):109-116

146 Department of Health. Health Survey for England 1996. The Stationary Office, 1998 Available from: http://www.archive.official-documents.co.uk/document/doh/survey96/ehtitle.htm

147 Department of Health. Coronary Heart Disease: National Service Framework for Coronary Heart Disease. London. Department of Health, 2000

148 Department of Health. Dept of Health Reference Costs 2005, 2005 Available from: http://www.dh.gov.uk/PolicyAndGuidance/OrganisationPolicy/FinanceAndPlanning/NHSCostingManual/fs/en.

149 Deskur-Smielecka E, Borowicz-Bienkowska S, Brychcy A, Wilk M, Przywarska I, Dylewicz P. Why patients after acute coronary syndromes do not participate in an early outpatient rehabilitation programme? Kardiologia Polska. 2009; 67(6):632-638

150 Dewilde WJ, Oirbans T, Verheugt FW, Kelder JC, De Smet BJ, Herrman JP et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. Lancet. 2013; 381(9872):1107-1115

151 Dews I, VandenBurg M. A 52-week, open-label, dose-titration safety study of imidapril in the treatment of mild to moderate hypertension. Current Therapeutic Research, Clinical and Experimental. 2001; 62(2):167-176

152 DeYoung JP, Ruedy N, Wright JM. The antihypertensive efficacy of captopril given once, twice, and three times daily. Current Therapeutic Research, Clinical and Experimental. 1987; 41(4):464-471

153 Di Pasquale P, Barone G, Paterna S, Cannizzaro S, Giubilato A. Efficacy of captopril before thrombolysis in acute myocardial infarction: preliminary findings. Drugs Under Experimental and Clinical Research. 1990; 16(11):581-589

154 Di Pasquale P, Paterna S, Bucca V, Maringhini G, Magatti M. Effects of the administration of captopril, metoprolol and of the captopril-metoprolol combination as adjuvant therapy during thrombolysis in acute myocardial infarction. International Journal of Cardiology. 1994; 46(2):107-112

155 Di Pasquale P, Paterna S, Cannizzaro S, Bucca V. Does captopril treatment before thrombolysis in acute myocardial infarction attenuate reperfusion damage? Short-term and long-term effects. International Journal of Cardiology. 1994; 43(1):43-50

156 Di PP, Valdes L, Albano V, Bucca V, Scalzo S, Pieri D et al. Early captopril treatment reduces plasma endothelin concentrations in the acute and subacute phases of myocardial infarction: a pilot study. Journal of Cardiovascular Pharmacology. 1997; 29(2):202-208

157 Dickstein K, Kjekshus J, OPTIMAAL Steering Committee of the OPTIMAAL Study Group. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Lancet. England 2002; 360(9335):752-760

158 Ding H, Varnfield M, Lee C-K, VanVeen J, Arnold D, Keightley A et al. An innovative home care delivery model reduces the rate of dropouts found with traditional cardiac rehabilitation. Circulation. 2012; 125(10 SUPPL. 1)

159 Dobesh PP, Beavers CJ, Herring HR, Spinler SA, Stacy ZA, Trujillo TC. Key articles and guidelines in the management of acute coronary syndrome and in percutaneous coronary intervention: 2012 Update. Pharmacotherapy. 2012; 32(12):e348-e386

160 Dolansky MA, Moore SM, Visovsky C. Older adults' views of cardiac rehabilitation program: is it time to reinvent? Journal of Gerontological Nursing. 2006; 32(2):37-44

161 Dollow S, Murray N, Little S. Comparison of the effects of cilazapril in an elderly and nonelderly hypertensive general practice population. Journal of Human Hypertension. 1994; 8(10):781-784

162 Dotremont G, De GH. The use of propranolol (inderal) in acute myocardial infarction. Acta Clinica Belgica. 1968; 23(3):163-176

163 Dressler C, Pattenden J, Lewin RJ, Atkin K. Interventions to increase the uptake of cardiac rehabilitation: Systematic review. British Journal of Cardiac Nursing. 2012; 7(7):338-345

164 Duncan K, Pozehl B, Rosado K. The effects of behavioural feed back on adherence to dietary sodium intake for patients with congestive heart failure. Journal of Cardiopulmonary Rehabilitation. 2001; 21:304

165 Duncan KA, Pozehl B. Staying on course: the effects of an adherence facilitation intervention on home exercise participation. Progress in Cardiovascular Nursing. 2002; 17(2):59-65, 71

166 Dunlay SM, Witt BJ, Allison TG, Hayes SN, Weston SA, Koepsell E et al. Barriers to participation in cardiac rehabilitation. American Heart Journal. 2009; 158(5):852-859

167 Dunn SL, Stommel M, Corser WD, Holmes-Rovner M. Hopelessness and its effect on cardiac rehabilitation exercise participation following hospitalization for acute coronary syndrome. Journal of Cardiopulmonary Rehabilitation & Prevention. 2009; 29(1):32-39

168 Eagle KA, Guyton RA, Davidoff R, Edwards FH, Ewy GA, Gardner TJ et al. ACC/AHA 2004 Guideline update for coronary artery bypass graft surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery). 2004. Available from: www.acc.org

169 Eder B, Hofmann P, von Duvillard SP, Brandt D, Schmid JP, Pokan R et al. Early 4-week cardiac rehabilitation exercise training in elderly patients after heart surgery. Journal of Cardiopulmonary Rehabilitation & Prevention. 2010; 30(2):85-92

170 Edwards J, Goodman SG, Yan RT, Welsh RC, Kornder JM, DeYoung JP et al. Has the ClOpidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) of early beta-blocker use in acute coronary syndromes impacted on clinical practice in Canada? Insights from the Global Registry of Acute Coronary Events (GRACE). American Heart Journal. 2011; 161(2):291-297

171 Eftekhari H, Marson P, Mattu R, Trevelyan J, Needham T. Improving a cardiac rehabilitation programme for Asian patients in Coventry. Coronary Health Care. 2005; 4(4):210-222

172 Einvik G, Klemsdal TO, Sandvik L, Hjerkinn EM. A randomized clinical trial on n-3 polyunsaturated fatty acids supplementation and all-cause mortality in elderly men at high cardiovascular risk. European Journal of Cardiovascular Prevention & Rehabilitation. 2010; 17(5):588-592

173 Eisenstein EL, Anstrom KJ, Kong DF, Shaw LK, Tuttle RH, Mark DB et al. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. JAMA. 2007; 297(2):159-168

174 Erhardt L, Ball S, Andersson F, Bergentoft P, Martinez C. Cost effectiveness in the treatment of heart failure with ramipril: a Swedish substudy of the AIRE study. Pharmacoeconomics. Copyright: University of York, 2001. 1997; 12(2):256-266

175 Eritsland J, Arnesen H, Gronseth K, Fjeld NB, Abdelnoor M. Effect of dietary supplementation with n-3 fatty acids on coronary artery bypass graft patency. American Journal of Cardiology. 1996; 77(1):31-36

176 Erkkila AT, Schwab US, de Mello VD, Lappalainen T, Mussalo H, Lehto S et al. Effects of fatty and lean fish intake on blood pressure in subjects with coronary heart disease using multiple medications. European Journal of Nutrition. Germany 2008; 47(6):319-328

177 Erling J, Oldridge NB. Effect of spousal support program on compliance with cardiac rehabilitation. Medicine and Science in Sports and Exercise. 1985; 17(2):284

178 Evans JA, Turner SC, Bethell HJN. Cardiac rehabilitation: are the NSF milestones achievable. Heart. 2002; 87(Supp ii):41

179 Exner DV, Dries DL, Waclawiw MA, Shelton B, Domanski MJ. Beta-adrenergic blocking agent use and mortality in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a post hoc analysis of the Studies of Left Ventricular Dysfunction. Journal of the American College of Cardiology. UNITED STATES 1999; 33(4):916-923

180 Ezekowitz MD, Reilly PA, Nehmiz G, Simmers TA, Nagarakanti R, Parcham-Azad K et al. Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO Study). American Journal of Cardiology. 2007; 100(9):1419-1426

181 Fasullo S, Cannizzaro S, Maringhini G, Ganci F, Giambanco F, Vitale G et al. Comparison of ivabradine versus metoprolol in early phases of reperfused anterior myocardial infarction with impaired left ventricular function: preliminary findings. Journal of Cardiac Failure. 2009; 15(10):856-863

182 Faynyk A, Abrahamovych O, Nechay O, Sorokivsky M. Antiarrhytmic effect and impact on heart rate of nebivolol in patients with acute segment ST elevation myocardial infarction. European Heart Journal. 2010; 31:765

183 Fernandez RS, Davidson P, Griffiths R, Salamonson Y. Overcoming barriers to guideline implementation: the case of cardiac rehabilitation. Quality and Safety in Health Care. 2010; 19(6):e15

184 Fernandez RS, Davidson P, Griffiths R. Cardiac rehabilitation coordinators' perceptions of patient-related barriers to implementing cardiac evidence-based guidelines. Journal of Cardiovascular Nursing. 2008; 23(5):449-457

185 Fernandez RS, Davidson P, Griffiths R, Salamonson Y. Improving cardiac rehabilitation services--challenges for cardiac rehabilitation coordinators. European Journal of Cardiovascular Nursing. 2011; 10(1):37-43

186 Ferrari R, Perindopril and Remodeling in Elderly with Acute Myocardial Infarction Investigators. Effects of angiotensin-converting enzyme inhibition with perindopril on left ventricular remodeling and clinical outcome: results of the randomized Perindopril and Remodeling in Elderly with Acute Myocardial Infarction (PREAMI) Study. Archives of Internal Medicine. 2006; 166(6):659-666

187 Filip J, McGillen C, Mosca L. Patient preferences for cardiac rehabilitation and desired program elements. Journal of Cardiopulmonary Rehabilitation. 1999; 19(6):339-343

188 Fiore LD, Ezekowitz MD, Brophy MT, Lu D, Sacco J, Peduzzi P et al. Department of Veterans Affairs Cooperative Studies Program Clinical Trial comparing combined warfarin and aspirin with aspirin alone in survivors of acute myocardial infarction: primary results of the CHAMP study. Circulation. United States 2002; 105(5):557-563

189 Flather M, Pipilis A, Collins R, Budaj A, Hargreaves A, Kolettis T et al. Randomized controlled trial of oral captopril, of oral isosorbide mononitrate and of intravenous magnesium sulphate started early in acute myocardial infarction: safety and haemodynamic effects. ISIS-4 (Fourth International Study of Infarct Survival) Pilot Study Investigators. European Heart Journal. 1994; 15(5):608-619

190 Flather MD, Lonn EM, Yusuf S. Effects of ACE inhibitors on mortality when started in the early phase of myocardial infarction: evidence from the larger randomized controlled trials. Journal of Cardiovascular Risk. 1995; 2(5):423-428

191 Flather MD, Yusuf S, Kober L, Pfeffer M, Hall A, Murray G et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. Lancet. Database of Abstracts of Reviews of Effectiveness. Produced by the NHS Centre for Reviews and Dissemination, University of York. Copyright: University of York. 2000; 355(9215):1575-1581

192 Flu WJ, van Kuijk JP, Chonchol M, Winkel TA, Verhagen HJM, Bax JJ et al. Timing of pre-operative Beta-blocker treatment in vascular surgery patients: influence on post-operative outcome. Journal of the American College of Cardiology. 2010; 56(23):1922-1929

193 Fonarow GC, Wright RS, Spencer FA, Fredrick PD, Dong W, Every N et al. Effect of statin use within the first 24 hours of admission for acute myocardial infarction on early morbidity and mortality. American Journal of Cardiology. 2005; 96(5):611-616

194 Fonarow GC, Lukas MA, Robertson M, Colucci WS, Dargie HJ. Effects of carvedilol early after myocardial infarction: analysis of the first 30 days in Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN). American Heart Journal. 2007; 154(4):637-644

195 Fox KM. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet. England 2003; 362(9386):782-788

196 Fox KAA, Mehta SR, Peters R, Zhao F, Lakkis N, Gersh BJ et al. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) Trial. Circulation. 2004; 110(10):1202-1208

197 Foy SG, Crozier IG, Turner JG, Richards AM, Frampton CM, Nicholls MG et al. Comparison of enalapril versus captopril on left ventricular function and survival three months after acute myocardial infarction (the "PRACTICAL" study). American Journal of Cardiology. 1994; 73(16):1180-1186

198 Franzosi MG, Brunetti M, Marchioli R, Marfisi RM, Tognoni G, Valagussa F et al. Cost-effectiveness analysis of n-3 polyunsaturated fatty acids (PUFA) after myocardial infarction: results from Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto (GISSI)-Prevenzione Trial. Pharmacoeconomics. New Zealand 2004; 19(4):411-420

199 Freeman JV, Zhu RP, Owens DK, Garber AM, Hutton DW, Go AS et al. Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in atrial fibrillation. Annals of Internal Medicine. 2011; 154(1):1-11

200 Freemantle N, Cleland J, Young P, Mason J, Harrison J. Beta-blockade after myocardial infarction: systematic review and meta regression analysis. BMJ. Database of Abstracts of Reviews of Effectiveness. Produced by the NHS Centre for Reviews and Dissemination, University of York. Copyright: University of York. 1999; 318:1730-1737

201 French DP, Lewin RJP, Watson N, Thompson DR. Do illness perceptions predict attendance at cardiac rehabilitation and quality of life following myocardial infarction? Journal of Psychosomatic Research. 2005; 59(5):315-322

202 French JK, Amos DJ, Williams BF, Cross DB, Elliott JM, Hart HH et al. Effects of early captopril administration after thrombolysis on regional wall motion in relation to infarct artery blood flow. Journal of the American College of Cardiology. 1999; 33(1):139-145

203 Frilling B, Schiele R, Gitt AK, Zahn R, Schneider S, Glunz HG et al. Too little aspirin for secondary prevention after acute myocardial infarction in patients at high risk for cardiovascular events: Results from the MITRA study. American Heart Journal. 2004; 148(2):306-311

204 Fujita M, Yamashita T, Nakata M, Nishikido T, Chinen T, Kikuchi T et al. Low dose landiolol during very acute phase of acute myocardial infarction improves brain natriuretic peptide level in the chronic phase. Journal of Cardiac Failure. 2010; 16(9 SUPPL. 1):S150-S151

205 Galan P, Briancon S, Blacher J, Czernichow S, Hercberg S. The SU.FOL.OM3 Study: a secondary prevention trial testing the impact of supplementation with folate and B-vitamins and/or Omega-3 PUFA on fatal and non fatal cardiovascular events, design, methods and participants characteristics. Trials [Electronic Resource]. England 2008; 9:35

206 Galan P, Kesse-Guyot E, Czernichow S, Briancon S, Blacher J, Hercberg S. Effects of B vitamins and omega 3 fatty acids on cardiovascular diseases: A randomised placebo controlled trial. BMJ. 2011; 342(7787):36

207 Galatro KM, Adams PC, Cohen M, McBride R, Blanke H. Bleeding complications and INR control of combined warfarin and low-dose aspirin therapy in patients with unstable angina and Non-Q-Wave myocardial infarction. Journal of Thrombosis and Thrombolysis. 1998; 5(3):249-255

208 Galcera-Tomas J, Nuno de la Rosa JA, Torres-Martinez G, Rodriguez-Garcia P, Castillo-Soria FJ, Canton-Martinez A et al. Effects of early use of captopril on haemodynamics and short-term ventricular remodelling in acute anterior myocardial infarction. European Heart Journal. 1993; 14(2):259-266

209 Galdas PM, Kang HBK. Punjabi Sikh patients' cardiac rehabilitation experiences following myocardial infarction: A qualitative analysis. Journal of Clinical Nursing. 2010; 19(21-22):3134-3142

210 Galdas PM, Ratner PA, Oliffe JL. A narrative review of South Asian patients' experiences of cardiac rehabilitation. Journal of Clinical Nursing. 2012; 21(1-2):149-159

211 Galli C, Rise P. Fish consumption, omega 3 fatty acids and cardiovascular disease. The science and the clinical trials. Nutrition and Health. 2009; 20(1):11-20

212 Garbagnati F, Cairella G, De MA, Multari M, Scognamiglio U, Venturiero V et al. Is antioxidant and n-3 supplementation able to improve functional status in poststroke patients? Results from the Nutristroke Trial. Cerebrovascular Diseases. 2009; 27(4):375-383

213 Gardener H, Wright CB, Gu Y, Demmer RT, Boden-Albala B, Elkind MSV et al. Mediterranean-style diet and risk of ischemic stroke, myocardial infarction, and vascular death: The Northern Manhattan study. American Journal of Clinical Nutrition. 2011; 94(6):1458-1464

214 Gelbrich G, Edelmann F, Inkrot S, Lainscak M, Apostolovic S, Neskovic AN et al. Is target dose the treatment target? Uptitrating beta-blockers for heart failure in the elderly. International Journal of Cardiology. 2012; 155(1):160-166

215 Geleijnse J, Giltay E, Kromhout D. Effects of n-3 fattyacids on cognitive decline: A randomized double-blind, placebo-controlled trial in stable myocardial infarction patients. Alzheimer's and Dementia. 2011; 7(4 SUPPL. 1):S512

216 Geleijnse JM, de GJ, Brouwer IA. Alpha-linolenic acid: Is It Essential to Cardiovascular Health? Current Atherosclerosis Reports. 2010; 12(6):359-367

217 Geleijnse JM, Giltay EJ, Schouten EG, de GJ, Oude Griep LM, Teitsma-Jansen AM et al. Effect of low doses of n-3 fatty acids on cardiovascular diseases in 4,837 post-myocardial infarction patients: Design and baseline characteristics of the Alpha Omega Trial. American Heart Journal. 2010; 159(4):539

218 General Register Office for Scotland. Mid-2003 Population Estimates. 2004. Available from: http://www.gro-scotland.gov.uk/statistics/theme/population/estimates/mid-year/archive/2003/index.html

219 General Register Office for Scotland. Vital Events Reference Tables 2003. Section 6: Deaths - causes. 2004. Available from: http://www.gro-scotland.gov.uk/statistics/theme/vital-events/general/ref-tables/archive/2003/03reference-table6.html

220 Geng DF, Liu M, Jin DM, Wu W, Deng J, Wang JF. Cilostazol-based triple antiplatelet therapy compared to dual antiplatelet therapy in patients with coronary stent implantation: a meta-analysis of 5,821 patients. Cardiology. 2012; 122(3):148-157

221 Gent M. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet. 1996; 348(9038):1329-1339

222 Gharacholou SM, Reid KJ, Arnold SV, Spertus J, Rich MW, Pellikka PA et al. Cognitive impairment and outcomes in older adult survivors of acute myocardial infarction: Findings from the Translational Research Investigating Underlying disparities in acute Myocardial infarction Patients' Health Status registry. American Heart Journal. 2011; 162(5):860

223 Giallauria F, Lucci R, Pilerci F, De Lorenzo A, Manakos A, Psaroudaki M et al. Efficacy of telecardiology in improving the results of cardiac rehabilitation after acute myocardial infarction. Monaldi Archives for Chest Disease = Archivio Monaldi Per Le Malattie Del Torace / Fondazione Clinica Del Lavoro, IRCCS [and] Istituto Di Clinica Tisiologica e Malattie Apparato Respiratorio, Universita Di Napoli, Secondo Ateneo. 2006; 66(1):8-12

224 Gianetti J, Gensini G, De CR. A cost-effectiveness analysis of aspirin versus oral anticoagulants after acute myocardial infarction in Italy: equivalence of costs as a possible case for oral anticoagulants. Thrombosis and Haemostasis. Copyright: University of York, 2001. 1998; 80(6):887-893

225 Giannuzzi P, Marchioli R, Temporelli PL, Gattone M, Marfisi RM, Griffo R et al. Mediterranean dietary habits predict prognosis in post-MI patients: Results of the GOSPEL study. European Heart Journal. 2009; 30(Suppl 1):154

226 Giannuzzi P, Temporelli PL, Marchioli R, Maggioni AP, Balestroni G, Ceci V et al. Global secondary prevention strategies to limit event recurrence after myocardial infarction: results of the GOSPEL study, a multicenter, randomized controlled trial from the Italian Cardiac Rehabilitation Network. Archives of Internal Medicine. 2008; 168(20):2194-2204

227 Gibler KB, Huskamp HA, Sabatine MS, Murphy SA, Cohen DJ, Cannon CP. Cost-effectiveness analysis of short-term clopidogrel therapy for ST elevation myocardial infarction. Critical Pathways in Cardiology. 2010; 9(1):14-18

228 GISSI Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Lancet. 1999; 354(9177):447-455

229 Goa KL, Balfour JA, Zuanetti G. Lisinopril. A review of its pharmacology and clinical efficacy in the early management of acute myocardial infarction. Drugs. 1996; 52(4):564-588

230 Goldman L, Sia ST, Cook EF, Rutherford JD, Weinstein MC. Costs and effectiveness of routine therapy with long-term beta-adrenergic antagonists after acute myocardial infarction. New England Journal of Medicine. Copyright: Department of Health, 1994. 1988; 319(3):152-157

231 Gorin L, Fauchier L, Nonin E, de Labriolle A, Haguenoer K, Cosnay P et al. Antithrombotic treatment and the risk of death and stroke in patients with atrial fibrillation and a CHADS2 score=1. Thrombosis and Haemostasis. 2010; 103(4):833-840

232 Gosselin G, Teo KK, Tanguay J-F, Gokhale R, Hartigan PM, Maron DJ et al. Effectiveness of percutaneous coronary intervention in patients with silent myocardial ischemia (post hoc analysis of the COURAGE trial). American Journal of Cardiology. 2012; 109(7):954-959

233 Gottlieb SS, McCarter RJ. Comparative effects of three beta blockers (atenolol, metoprolol, and propranolol) on survival after acute myocardial infarction. American Journal of Cardiology. 2001; 87(7):823-826

234 Gottlieb SS, McCarter RJ, Vogel RA. Effect of beta-blockade on mortality among high-risk and low-risk patients after myocardial infarction. New England Journal of Medicine. 1998; 339(8):489-497

235 Gotzsche CO, Sogaard P, Ravkilde J, Thygesen K. Effects of captopril on left ventricular systolic and diastolic function after acute myocardial infarction. American Journal of Cardiology. 1992; 70(2):156-160

236 Goulding L, Furze G, Birks Y. Randomized controlled trials of interventions to change maladaptive illness beliefs in people with coronary heart disease: systematic review. Journal of Advanced Nursing. 2010; 66(5):946-961

237 Government Actuaries Department. Government Actuaries Department. (GAD) Interim Life Tables 2003-05. 2006. Available from: http://www.gad.gov.uk/life_tables/interim_life_tables.htm

238 Grace SL, Gravely-Witte S, Kayaniyil S, Brual J, Suskin N, Stewart DE. A multisite examination of sex differences in cardiac rehabilitation barriers by participation status. Journal of Women's Health. 2009; 18(2):209-216

239 Grace SL, Grewal K, Stewart DE. Factors affecting cardiac rehabilitation referral by physician specialty. Journal of Cardiopulmonary Rehabilitation & Prevention. 2008; 28(4):248-252

240 Grace SL, Russell KL, Reid RD, Oh P, Anand S, Rush J et al. Effect of cardiac rehabilitation referral strategies on utilization rates: a prospective, controlled study. Archives of Internal Medicine. 2011; 171(3):235-241

241 Grace SL, Scholey P, Suskin N, Arthur HM, Brooks D, Jaglal S et al. A prospective comparison of cardiac rehabilitation enrollment following automatic vs usual referral. Journal of Rehabilitation Medicine. 2007; 39(3):239-245

242 Grace SL, Tan Y, Simpson C, Chessex C. Perceptions of cardiac specialists and rehabilitation programs regarding patient access to cardiac rehabilitation and referral strategies. Journal of Cardiopulmonary Rehabilitation & Prevention. 2012; 32(3):135-140

243 Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet. 2003; 362(9386):772-776

244 Greaves SC, Zhi G, Lee RT, Solomon SD, MacFadyen J, Rapaport E et al. Incidence and natural history of left ventricular thrombus following anterior wall acute myocardial infarction. American Journal of Cardiology. 1997; 80(4):442-448

245 Grewal K, Leung YW, Safai P, Stewart DE, Anand S, Gupta M et al. Access to cardiac rehabilitation among South-Asian patients by referral method: a qualitative study. Rehabilitation Nursing. 2010; 35(3):106-112

246 Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. Lancet. ENGLAND 1994; 343(8906):1115-1122

247 Guiraud T, Granger R, Gremeaux V, Bousquet M, Richard L, Soukarie L et al. Accelerometer as a tool to assess sedentarity and adherence to physical activity recommendations after cardiac rehabilitation program. Annals of Physical and Rehabilitation Medicine. 2012; 55(5):312-321

248 Gwon HC, Hahn JY, Park KW, Song YB, Chae IH, Lim DS et al. Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) randomized, multicenter study. Circulation. 2012; 125(3):505-513

249 Hagan NA, Botti MA, Watts RJ. Financial, family, and social factors impacting on cardiac rehabilitation attendance. Heart and Lung. 2007; 36(2):105-113

250 Haghshenas A, Davidson PM, Rotem A. Negotiating norms, navigating care: findings from a qualitative study to assist in decreasing health inequity in cardiac rehabilitation. Australian Health Review. 2011; 35(2):185-190

251 Halcox J, Lindsay S, Begg A, Griffith K, Mead A, Barr B. Lifestyle advice and drug therapy post-myocardial infarction: A survey of UK current practice. British Journal of Cardiology. 2011; 18(4):178

252 Hall JP, Wiseman VL, King MT, Ross DL, Kovoor P, Zecchin RP et al. Economic evaluation of a randomised trial of early return to normal activities versus cardiac rehabilitation after acute myocardial infarction. Heart, Lung & Circulation. Australia 2002; 11(1):10-18

253 Hamaad A, Kaeng LW, Lip GYH, MacFadyen RJ. Oral omega n3-PUFA therapy (Omacor) has no impact on indices of heart rate variability in stable post myocardial infarction patients. Cardiovascular Drugs and Therapy. 2006; 20(5):359-364

254 Hanada K, Higuma T, Nishizaki F, Sukekawa T, Yokota T, Yamada M et al. Randomized study on the efficacy and safety of landiolol, an ultra-short-acting beta1-adrenergic blocker, in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention. Circulation Journal. 2012; 76(2):439-445

255 Hansen DA, Jurgensen HJ, Pedersen-Bjergaard O. Effect of acute and long term beta-andrenergic blockade with alprenolol in definite or suspected acute myocardial infarction. Acta Medica Scandinavica. 1984; S680:50-58

256 Hansen D, Berger J, Dendale P, De Rybel R, Meeusen R. Training adherence in early cardiac rehabilitation: effect of exercise session duration. Journal of Cardiopulmonary Rehabilitation & Prevention. 2009; 29(3):179-182

257 Hansen ML, Sorensen R, Clausen MT, Fog-Petersen ML, Raunso J, Gadsboll N et al. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. Archives of Internal Medicine. 2010; 170(16):1433-1441

258 Hansen SN, Harris WS. New evidence for the cardiovascular benefits of long chain omega-3 fatty acids. Current Atherosclerosis Reports. 2007; 9(6):434-440

259 Hansteen V, Moinichen E, Lorentsen E, Andersen A, Strom O, Soiland K et al. One year's treatment with propranolol after myocardial infarction: preliminary report of Norwegian multicentre trial. BMJ. 1982; 284(6310):155-160

260 Hardie K HGJKBRAC. Ten-year risk of first recurrent stroke and disability after first-ever stroke in the Perth Community Stroke Study. Stroke. 2004; 35:731-735

261 Hargreaves AD, Kolettis T, Jacob AJ, Flint LL, Turnbull LW, Muir AL et al. Early vasodilator treatment in myocardial infarction: appropriate for the majority or minority? British Heart Journal. 1992; 68(4):369-373

262 Harrington RA, Block PC. Clopidogrel for high atherothrombotic risk, ischemic stabilization, management, and avoidance: The CHARISMA trial. ACC Cardiosource Review Journal. 2006; 15(9):70-75

263 Hart WM, Rubio-Terres C, Pajuelo F, Juanatey JR. Cost-effectiveness of the treatment of heart failure with ramipril: a Spanish analysis of the AIRE study. European Journal of Heart Failure. Copyright: University of York, 2003. 2002; 4(4):553-558

264 Hartwell D, Colquitt J, Loveman E, Clegg AJ, Brodin H, Waugh N et al. Clinical effectiveness and cost-effectiveness of immediate angioplasty for acute myocardial infarction: systematic review and economic evaluation. Health Technology Assessment. 2005; 9(17):1-iv

265 Harvard CEA Registry. Cost-effectiveness analysis (CEA) Registry. 1997. Available from: http://www.tufts-nemc.org/cearegistry/index.html

266 Heeg B, Damen J, van HB. Oral antiplatelet therapy in secondary prevention of cardiovascular events: an assessment from the payer's perspective. Pharmacoeconomics. 2007; 25(12):1063-1082

267 Henderson RA, Pocock SJ, Clayton TC, Knight R, Fox KA, Julian DG et al. Seven-year outcome in the RITA-2 trial: coronary angioplasty versus medical therapy. Journal of the American College of Cardiology. 2003; 42(7):1161-1170

268 Henderson RA, Pocock SJ, Sharp SJ, Nanchahal K, Sculpher MJ, Buxton MJ et al. Long-term results of RITA-1 trial: clinical and cost comparisons of coronary angioplasty and coronary-artery bypass grafting. Randomised Intervention Treatment of Angina. Lancet. 1998; 352(9138):1419-1425

269 Herlitz J, Holm J, Peterson M, Karlson BW, Haglid E, Erhardt L et al. Effect of fixed low-dose warfarin added to aspirin in the long term after acute myocardial infarction; the LoWASA Study. European Heart Journal. England 2004; 25(3):232-239

270 Hillebrand T, Frodermann H, Lehr D, Wirth A. Increased participation in coronary groups by means of an outpatient group. Herz Kreislauf. 1995; 27:346-349

271 Hohnloser SH, Oldgren J, Yang S, Wallentin L, Ezekowitz M, Reilly P et al. Myocardial ischemic events in patients with atrial fibrillation treated with dabigatran or warfarin in the RE-LY (Randomized evaluation of long-term anticoagulation therapy) trial. Circulation. 2012; 125(5):669-676

272 Hooper DL. The effects of a telephone contact on exercise adherence of cardiac patients University of Denver; 1995.

273 Hooper L, Griffiths E, Abrahams B, Alexander W, Atkins S, Atkinson G et al. Dietetic guidelines: diet in secondary prevention of cardiovascular disease (first update, June 2003). Journal of Human Nutrition and Dietetics. 2004; 17(4):337-349

274 Houghton T, Freemantle N, Cleland JG. Are beta-blockers effective in patients who develop heart failure soon after myocardial infarction: a meta-regression analysis of randomised trials. European Journal of Heart Failure. Database of Abstracts of Reviews of Effectiveness. Produced by the NHS Centre for Reviews and Dissemination, University of York. Copyright: University of York. 2000; 2(3):333-340

275 Houle J, Doyon O, Vadeboncoeur N, Campagna L, Diaz A, Poirier P. Compliance to physical activity and cardiovascular risk factors: A positive effect of the pedometer-based activity program led by clinical nurse specialist at 12 months follow-up. Journal of Cardiopulmonary Rehabilitation & Prevention. 2009; 29(5):333

276 Huerin M. Compliance withn cardiovascular rehabilitation: comparison of standard and new adherence strategies. Journal of the American College of Cardiology. 1998; 31(2):171A-172A

277 Hughes AR, Gillies F, Kirk AF, Mutrie N, Hillis WS, MacIntyre PD. Exercise consultation improves short-term adherence to exercise during phase IV cardiac rehabilitation: a randomized, controlled trial. Journal of Cardiopulmonary Rehabilitation. United States 2002; 22(6):421-425

278 Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. New England Journal of Medicine. United States 2002; 347(13):969-974

279 Hurlen M, Eikvar L, Seljeflot I, Arnesen H. Occult bleeding in three different antithrombotic regimes after myocardial infarction. A WARIS-II subgroup analysis. Thrombosis Research. 2006; 118(4):433-438

280 Hussain T, Shu LY, Xiang C, Sosorburam T. Effect of captopril and age factor among Chinese cardiovascular patients. Australasian Medical Journal. 2010; 3(11):707-711

281 Huynh T, Theroux P, Bogaty P, Nasmith J, Solymoss S. Aspirin, warfarin, or the combination for secondary prevention of coronary events in patients with acute coronary syndromes and prior coronary artery bypass surgery. Circulation. 2001; 103(25):3069-3074

282 Iestra J, Knoops K, Kromhout D, De GL, Grobbee D, Van SW. Lifestyle, Mediterranean diet and survival in European post-myocardial infarction patients. European Journal of Cardiovascular Prevention & Rehabilitation. 2006; 13(6):894-900

283 Imich J. Home-based cardiac rehabilitation. Nursing Times. 1997; 93(50):48-49

284 Innovus Research (UK) Ltd. Cost-effectiveness analysis of omacor for myocardial infarction survivors in the UK. High Wycombe. Innovus Research (UK) Ltd, 2004

285 ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. Lancet. ENGLAND 1995; 345(8951):669-685

286 Izawa KP, Watanabe S, Omiya K, Hirano Y, Oka K, Osada N et al. Effect of the self-monitoring approach on exercise maintenance during cardiac rehabilitation: a randomized, controlled trial. American Journal of Physical Medicine and Rehabilitation. 2005; 84(5):313-321

287 Jackson AM, McKinstry B, Gregory S, Amos A. A qualitative study exploring why people do not participate in cardiac rehabilitation and coronary heart disease self-help groups, and their rehabilitation experience without these resources. Primary Health Care Research and Development. 2012; 13(1):30-41

288 James S, Armstrong P, Califf R, Husted S, Kontny F, Niemminen M et al. Safety and efficacy of abciximab combined with dalteparin in treatment of acute coronary syndromes. European Heart Journal. 2002; 23(19):1538-1545

289 James SK, Alexander JH, Mohan P, Wallentin L, Harrington RA. Apixaban for prevention of acute ischemic events in patients with acute coronary syndromes. Journal of Thrombosis and Haemostasis. 2011; 9:20

290 Jansson JH, Boman K, Nilsson TK. Enalapril related changes in the fibrinolytic system in survivors of myocardial infarction. European Journal of Clinical Pharmacology. 1993; 44(5):485-488

291 Jiang X, Sit JW, Wong TKS. A nurse-led cardiac rehabilitation programme improves health behaviours and cardiac physiological risk parameters: evidence from Chengdu, China. Cardiac Nursing. 2006;1886-1897

292 Johansen H NCTG. Variation in angiography and bypass surgery. Health Reports Winter.: Statistics Canada. 1998; 10(3):63-76

293 Johnson NA, Inder KJ, Ewald BD, James EL, Bowe SJ. Association between participation in outpatient cardiac rehabilitation and self-reported receipt of lifestyle advice from a healthcare provider: results of a population-based cross-sectional survey. Rehabilitation Research and Practice. 2010; 2010:541741

294 Joliffe JA, Rees K, Taylor R, Thompson D, Oldridge N, Ebrahim S. Exercise-based rehabilitation for coronary heart disease. Cochrane Library. Chichester: John Wiley & Sons Ltd. 2003;(Issue 3)

295 Jolly K, Bradley F, Sharp S, Smith H, Thompson S, Kinmonth AL et al. Randomised controlled trial of follow up care in general practice of patients with myocardial infarction and angina: final results of the Southampton heart integrated care project (SHIP). BMJ. 1999; 318(7185):706-711

296 Jolly K, Lip GYH, Taylor RS, Raftery J, Mant J, Lane D et al. The Birmingham rehabilitation uptake maximisation study (BRUM): a randomised controlled trial comparing home-based with centre-based cardiac rehabilitation. Heart. 2009; 95(1):36-42

297 Jones MI, Greenfield S, Jolly K. Patients' experience of home and hospital based cardiac rehabilitation: a focus group study. European Journal of Cardiovascular Nursing. 2009; 8(1):9-17

298 Jones M, Jolly K, Raftery J, Lip GYH, Greenfield S, BRUM Steering Committee. 'DNA' may not mean 'did not participate': a qualitative study of reasons for non-adherence at home- and centre-based cardiac rehabilitation. Family Practice. 2007; 24(4):343-357

299 Jong P, Yusuf S, Rousseau MF, Ahn SA, Bangdiwala SI. Effect of enalapril on 12-year survival and life expectancy in patients with left ventricular systolic dysfunction: a follow-up study. Lancet. 2003; 361(9372):1843-1848

300 Jonsson G, Abdelnoor M, Seljeflot I, Arnesen H, Hostmark AT, Kjeldsen SE et al. The antioxidative effects of long-term treatment are more pronounced for carvedilol than for atenolol in post-myocardial infarction patients. Journal of Cardiovascular Pharmacology. 2007; 49(1):27-32

301 Jugdutt BI. Prevention of ventricular remodelling post myocardial infarction: timing and duration of therapy. Canadian Journal of Cardiology. 1993; 9(1):103-114

302 Jukema JW, Bruschke AV, van Boven AJ, Reiber JH, Bal ET, Zwinderman AH et al. Effects of lipid lowering by pravastatin on progression and regression of coronary artery disease in symptomatic men with normal to moderately elevated serum cholesterol levels. The Regression Growth Evaluation Statin Study (REGRESS). Circulation. 1995; 91(10):2528-2540

303 Julian DG, Chamberlain DA, Pocock SJ. A comparison of aspirin and anticoagulation following thrombolysis for myocardial infarction (the AFTER study): a multicentre unblinded randomised clinical trial. BMJ. 1996; 313(7070):1429-1431

304 Jump DB, Depner CM, Tripathy S. Omega-3 fatty acid supplementation and cardiovascular disease. Journal of Lipid Research. 2012; 53(12):2525-2545

305 Kalayi C, Rimmer F, Maxwell M. Improving referral for cardiac rehabilitation: an interface. Journal of Clinical Governance. 1999; 7:143-145

306 Kaplan RC HSFCPBM. Predictors of subsequent coronary events, stroke, and death among survivors of first hospitalized myocardial infarction. Journal of Clinical Epidemiology. 2002; 55(7):654-664

307 Karjalainen PP, Porela P, Ylitalo A, Vikman S, Nyman K, Vaittinen MA et al. Safety and efficacy of combined antiplatelet-warfarin therapy after coronary stenting. European Heart Journal. 2007; 28(6):726-732

308 Karnon J, Bakhai B, Brennan A, Pandor A, Flather M, Warren E et al. A cost-utility analysis of clopidogrel in patients with non-ST-segment-elevation acute coronary syndromes in the UK. International Journal of Cardiology. 2006; 109:307-316

309 Karnon J, Holmes MW, Williams R, Bakhai A, Brennan A. A cost-utility analysis of clopidogrel in patients with ST elevation acute coronary syndromes in the UK. International Journal of Cardiology. 2010; 140(3):315-322

310 Kasanuki H, Hagiwara N, Hosoda S, Sumiyoshi T, Honda T, Haze K et al. Angiotensin II receptor blocker-based vs. non-angiotensin II receptor blocker-based therapy in patients with angiographically documented coronary artery disease and hypertension: the Heart Institute of Japan Candesartan Randomized Trial for Evaluation in Coronary Artery Disease (HIJ-CREATE). European Heart Journal. 2009; 30(10):1203-1212

311 Kereiakes DJ, Lincoff AM, Miller DP, Tcheng JE, Cabot CF, Anderson KM et al. Abciximab therapy and unplanned coronary stent deployment: favorable effects on stent use, clinical outcomes, and bleeding complications. EPILOG Trial Investigators. Circulation. 1998; 97(9):857-864

312 Khurram Z, Chou E, Minutello R, Bergman G, Parikh M, Naidu S et al. Combination therapy with aspirin, clopidogrel and warfarin following coronary stenting is associated with a significant risk of bleeding. Journal of Invasive Cardiology. 2006; 18(4):162-164

313 Kingma JH, van Gilst WH, Peels CH, Dambrink JH, Verheugt FW, Wielenga RP. Acute intervention with captopril during thrombolysis in patients with first anterior myocardial infarction. Results from the Captopril and Thrombolysis Study (CATS). European Heart Journal. 1994; 15(7):898-907

314 Kleber FX, Sabin GV, Winter UJ, Reindl I, Beil S, Wenzel M et al. Angiotensin-converting enzyme inhibitors in preventing remodeling and development of heart failure after acute myocardial infarction: results of the German multicenter study of the effects of captopril on cardiopulmonary exercise parameters (ECCE). American Journal of Cardiology. 1997; 80(3A):162A-167A

315 Ko DT, Hebert PR, Coffey CS, Sedrakyan A, Curtis JP, Krumholz HM. Beta-blocker therapy and symptoms of depression, fatigue, and sexual dysfunction. JAMA. Database of Abstracts of Reviews of Effectiveness. Produced by the NHS Centre for Reviews and Dissemination, University of York. Copyright: University of York. 2002; 288(3):351-357

316 Kober L, Torp-Pedersen C, Carlsen JE, Bagger H, Eliasen P, Lyngborg K et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. New England Journal of Medicine. 1995; 333(25):1670-1676

317 Kolman L, Shin N-M, Krishnan SM, Schwartz S, Gracik T, Jackson EA et al. Psychological distress in cardiac rehabilitation participants. Journal of Cardiopulmonary Rehabilitation & Prevention. 2011; 31(2):81-86

318 Kondo J, Sone T, Tsuboi H, Mukawa H, Morishima I, Uesugi M et al. Effects of low-dose angiotensin II receptor blocker candesartan on cardiovascular events in patients with coronary artery disease. American Heart Journal. United States 2003; 146(6):1022-1027

319 Kongstad-Rasmussen O, Blomstrand P, Broqvist M, Dahlstrom U, Wranne B. Treatment with ramipril improves systolic function even in patients with mild systolic dysfunction and symptoms of heart failure after acute myocardial infarction. Clinical Cardiology. 1998; 21(11):807-811

320 Konstantino Y, Iakobishvili Z, Porter A, Sandach A, Zahger D, Hod H et al. Aspirin, warfarin and a thienopyridine for acute coronary syndromes. Cardiology. 2006; 105(2):80-85

321 Kontopoulos AG, Athyros VG, Papageorgiou AA, Boudoulas H. Effect of quinapril or metoprolol on circadian sympathetic and parasympathetic modulation after acute myocardial infarction. American Journal of Cardiology. 1999; 84(10):1164-1169

322 Kouvaras G, Chronopoulos G, Soufras G, Sofronas G, Solomos D, Bakirtzis A et al. The effects of long-term antithrombotic treatment on left ventricular thrombi in patients after an acute myocardial infarction. American Heart Journal. 1990; 119(1):73-78

323 Krasemann EO, Busch T. What can an information pamphlet really achieve? Offentliche Gesundheitswesen. 2006; 50:96-98

324 Kromhout D, Giltay EJ, Geleijnse JM, Alpha Omega Trial Group. n-3 fatty acids and cardiovascular events after myocardial infarction. New England Journal of Medicine. 2010; 363(21):2015-2026

325 Krumholz HM, Radford MJ, Wang Y, Chen J, Heiat A, Marciniak TA. National use and effectiveness of beta-blockers for the treatment of elderly patients after acute myocardial infarction: National Cooperative Cardiovascular Project. JAMA. 1998; 280(7):623-629

326 Kubitza D, Becka M, Muck W, Schwers S. Effect of co-administration of rivaroxaban and clopidogrel on bleeding time, pharmacodynamics and pharmacokinetics: A phase I study. Pharmaceuticals. 2012; 5(3):279-296

327 Kulik A, LeMay MR, Voisine P, Tardiff JC, DelArochelliere R, Naidoo S et al. Aspirin plus clopidogrel versus aspirin alone after coronary artery bypass grafting. Circulation. 2010; 122:2680-2687

328 Lack ER. Group therapy and the cardiac rehabilitation process; a study in improving patient compliance Temple University; 1985.

329 Lamberts M, Olesen JB, Ruwald MH, Hansen CM, Karasoy D, Kristensen SL et al. Bleeding after initiation of multiple antithrombotic drugs, including triple therapy, in atrial fibrillation patients following myocardial infarction and coronary intervention: a nationwide cohort study. Circulation. 2012; 126(10):1185-1193

330 Lamotte M, Annemans L, Kawalec P, Zoellner Y. A multi-country health economic evaluation of highly concentrated N-3 polyunsaturated fatty acids in secondary prevention after myocardial infarction. Pharmacoeconomics. 2006; 24(8):783-795

331 Lamy A, Wang X, Gao P, Tong W, Gafni A, Dans A et al. The cost implications of the use of telmisartan or ramipril in patients at high risk for vascular events: The ONTARGET study. Journal of Medical Economics. 2011; 14(6):792-797

332 Latini R, Avanzini F, De NA, Rocchetti M. Effects of lisinopril and nitroglycerin on blood pressure early after myocardial infarction: the GISSI-3 pilot study. Clinical Pharmacology and Therapeutics. 1994; 56(6 Pt 1):680-692

333 Lau-Walker M. Importance of illness beliefs and self-efficacy for patients with coronary heart disease. Journal of Advanced Nursing. 2007; 60(2):187-198

334 law M, Rudnicka AR. Statin safety: a systematic review. American Journal of Cardiology. 2006; 97(8a):S52-S60

335 Le Grande MR, Murphy BM, Higgins RO, Worcester MUC, Parkinson A, Brown SL et al. Physical activity and negative emotional response after percutaneous coronary intervention. European Journal of Cardiovascular Prevention & Rehabilitation. 2006; 13(2):254-260

336 Leaf A, Albert CM, Josephson M, Steinhaus D, Kluger J, Kang JX et al. Prevention of fatal arrhythmias in high-risk subjects by fish oil n-3 fatty acid intake. Circulation. 2005; 112(18):2762-2768

337 Lengenfelder B, Stoerk S, Boes L, Strotmann J, Ertl G, Voelker W et al. Long-term reduction of mortality in the 4-year follow up of tirofiban therapy in elective percutaneous coronary interventions (TOPSTAR) trial. Journal of Invasive Cardiology. 2011; 23(4):128-132

338 Leon MB, Baim DS, Popma JJ, Gordon PC, Cutlip DE, Ho KK et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. New England Journal of Medicine. 1998; 339(23):1665-1671

339 LePen C, Lilliu H, Keller T, Fiessinger S. The economics of TRACE:a cost-effectiveness analysis of trandolapril in postinfarction patients with left ventricular dysfunction. Pharmacoeconomics. Copyright: University of York, 1999. 1998; 14(1):49-58

340 Leslie M, Schuster PA. Effect of contingency contracting on adherence and knowledge of exercise regimens. Patient Education and Counseling. 1991; 18:231-241

341 Levin LA, Perk J, Hedback B. Cardiac rehabilitation--a cost analysis. Journal of Internal Medicine. England 1991; 230(5):427-434

342 Levitan EB, Wolk A, Mittleman MA. Fatty fish, marine omega-3 fatty acids and incidence of heart failure. European Journal of Clinical Nutrition. England 2010; 64(6):587-594

343 Lewin B, Robertson IH, Cay EL, Irving JB, Campbell M. Effects of self-help post-myocardial-infarction rehabilitation on psychological adjustment and use of health services. Lancet. 1992; 339(8800):1036-1040

344 Liem AH, van Boven AJ, Veeger NJ, Withagen AJ, Robles de Medina RM, Tijssen JG et al. Effect of fluvastatin on ischaemia following acute myocardial infarction: a randomized trial. European Heart Journal. England 2002; 23(24):1931-1937

345 Lindsay HS, Zaman AG, Cowan JC. ACE inhibitors after myocardial infarction: patient selection or treatment for all? British Heart Journal. 1995; 73(5):397-400

346 Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. New England Journal of Medicine. 1998; 339(19):1349-1357

347 Lopes RD, White JA, Atar D, Keltai M, Kleiman NS, White HD et al. Antithrombotic use and outcomes in patients with atrial fibrillation complicating acute coronary syndromes. Circulation. 2011; 124(21 SUPPL. 1)

348 Lu CY. Treatment of acute myocardial infarction with oral captopril. A randomized, double blind and placebo controlled pilot study. Chinese Medical Journal. 1993; 106:717

349 Lubarsky L, Coplan NL. Angiotensin-converting enzyme inhibitors in acute myocardial infarction: a clinical approach. Preventive Cardiology. 2007; 10(3):156-159

350 Lucioni C, Mazzi S, Gozzo M, Lazzeri G. Economic evaluation of ticagrelor vs clopidogrel in ACS patients. Pharmacoeconomics - Italian Research Articles. 2011; 13(2):53-64

351 Macchi C, Fattirolli F, Lova RM, Conti AA, Luisi ML, Intini R et al. Early and late rehabilitation and physical training in elderly patients after cardiac surgery. American Journal of Physical Medicine and Rehabilitation / Association of Academic Physiatrists. 2007; 86(10):826-834

352 MacInnes JD. The illness perceptions of women following acute myocardial infarction: implications for behaviour change and attendance at cardiac rehabilitation. Women and Health. 2005; 42(4):105-121

353 MacMahon S, Sharpe N, Gamble G, Clague A, Mhurchu CN, Clark T et al. Randomized, placebo-controlled trial of the angiotensin-converting enzyme inhibitor, ramipril, in patients with coronary or other occlusive arterial disease. PART-2 Collaborative Research Group. Prevention of Atherosclerosis with Ramipril. Journal of the American College of Cardiology. 2000; 36(2):438-443

354 Madden M, Furze G, Lewin RJP. Complexities of patient choice in cardiac rehabilitation: qualitative findings. Journal of Advanced Nursing. 2011; 67(3):540-549

355 Madsen T, Christensen JH, Schmidt EB. C-reactive protein and n-3 fatty acids in patients with a previous myocardial infarction: a placebo-controlled randomized study. European Journal of Nutrition. 2007; 46(7):428-430

356 Maggioni AP. ACE inhibitor treatment after myocardial infarction. European Heart Journal, Supplement. 1999; 1(Q):Q7-Q10

357 Maggioni AP, Geraci E. Very early administration of ACE-inhibitors in acute myocardial infarction. International Journal of Cardiology. 1998; 65 Suppl 1:S61-S64

358 Mahaffey KW, White HD, Nessel CC, Goodman SG, Piccini JP, Patel MR et al. Ischemic cardiac outcomes in patients with af treated with vitamin k antagonism or factor XA inhibition: Results from the rocket AF Trial. Circulation. 2011; 124(21 SUPPL. 1)

359 Mahler HI, Kulik JA, Tarazi RY. Effects of a videotape information intervention at discharge on diet and exercise compliance after coronary bypass surgery. Journal of Cardiopulmonary Rehabilitation. 1999; 19(3):170-177

360 Main C, Palmer S, Griffin S, Jones L, Orton V, Sculpher M. Clopidogrel used in combination with aspirin compared with aspirin alone in the treatment of non-ST-segment-elevation acute coronary syndromes: a systematic review and economic evaluation. Health Technology Assessment. 2004; 8(40):1-156

361 Malik IS, Bhatia VK, Kooner JS. Cost effectiveness of ramipril treatment for cardiovascular risk reduction. Heart (British Cardiac Society). Copyright: University of York, 2004. 2001; 85(5):539-543

362 Manger MS, Strand E, Ebbing M, Seifert R, Refsum H, Nordrehaug JE et al. Dietary intake of n-3 long-chain polyunsaturated fatty acids and coronary events in Norwegian patients with coronary artery disease. American Journal of Clinical Nutrition. 2010; 92(1):244-251

363 Mannacio VA, Di Tommaso L, Antignan A, De Amicis V, Vosa C. Aspirin plus clopidogrel for optimal platelet inhibition following off-pump coronary artery bypass surgery: results from the CRYSSA (prevention of Coronary arteRY bypaSS occlusion After off-pump procedures) randomised study. Heart. 2012; 98(23):1710-1715

364 Mantovani LG, Belisari A, Szucs TD. Captopril in the management of patients after acute myocardial infarctions:a cost effectiveness analysis in Italy. Pharmacological Research. Copyright:University of York, 1999. 1998; 37(5):345-351

365 Manzano-Fernandez S, Pastor FJ, Marin F, Cambronero F, Caro C, Pascual-Figal DA et al. Increased major bleeding complications related to triple antithrombotic therapy usage in patients with atrial fibrillation undergoing percutaneous coronary artery stenting. Chest. 2008; 134(3):559-567

366 Marchionni N, Fattirolli F, Fumagalli S, Oldridge N, Del LF, Morosi L et al. Improved exercise tolerance and quality of life with cardiac rehabilitation of older patients after myocardial infarction: results of a randomized, controlled trial. Circulation. 2003; 107(17):2201-2206

367 Marinsek M, Sinkovic A. A randomized trial comparing the effect of ramipril and losartan in survivors of ST-elevation myocardial infarction. Journal of International Medical Research. 2009; 37(5):1577-1587

368 Marshall J, Penckofer S, Llewellyn J. Structured postoperative teaching and knowledge and compliance of patients who had coronary artery bypass surgery. Heart and Lung. UNITED STATES 1986; 15(1):76-82

369 Martin AM, Woods CB. What sustains long-term adherence to structured physical activity after a cardiac event? Journal of Aging and Physical Activity. 2012; 20(2):135-147

370 Martinez C, Ball SG. Cost-effectiveness of ramipril therapy for patients with clinical evidence of heart failure after acute myocardial infarction. British Journal of Clinical Practice. Copyright: University of York, 2000. 1995; Supplement 78:26-32

371 Matsuzaki M, Yokoyama M, Saito Y, Origasa H, Ishikawa Y, Oikawa S et al. Incremental effects of eicosapentaenoic acid on cardiovascular events in statin-treated patients with coronary artery disease. Circulation Journal. Japan 2009; 73(7):1283-1290

372 Mattichak SJ, Reed PS, Gallagher MJ, Boura JA, O'Neill WW, Kahn JK. Evaluation of safety of warfarin in combination with antiplatelet therapy for patients treated with coronary stents for acute myocardial infarction. Journal of Interventional Cardiology. 2005; 18(3):163-166

373 Mauri L, Kereiakes DJ, Normand SL, Wiviott SD, Cohen DJ, Holmes DR et al. Rationale and design of the dual antiplatelet therapy study, a prospective, multicenter, randomized, double-blind trial to assess the effectiveness and safety of 12 versus 30 months of dual antiplatelet therapy in subjects undergoing percutaneous coronary intervention with either drug-eluting stent or bare metal stent placement for the treatment of coronary artery lesions. American Heart Journal. 2010; 160(6):1035-41, 1041

374 McCorry NK, Corrigan M, Tully MA, Dempster M, Downey B, Cupples ME. Perceptions of exercise among people who have not attended cardiac rehabilitation following myocardial infarction. Journal of Health Psychology. 2009; 14(7):924-932

375 Mcdonnell LA, Blanchard CM, Reid B, Morrin L, Spence J, Rhodes R et al. Task and barrier self-efficacy and physical activity predictors in a home-based cardiac rehabilitation program: Preliminary results. Journal of Cardiopulmonary Rehabilitation & Prevention. 2008; 28(5):341

376 McGrady A, McGinnis R, Badenhop D, Bentle M, Rajput M. Effects of depression and anxiety on adherence to cardiac rehabilitation. Journal of Cardiopulmonary Rehabilitation & Prevention. 2009; 29(6):358-364

377 McKenna M. Women and the lower intensity within cardiac rehabilitation: the forgotten groups. British Association for Cardiac Rehabilitation Newsletter. 1988; 1:4

378 McMurray J, Solomon S, Pieper K, Reed S, Rouleau J, Velazquez E et al. The effect of valsartan, captopril, or both on atherosclerotic events after acute myocardial infarction: an analysis of the Valsartan in Acute Myocardial Infarction Trial (VALIANT). Journal of the American College of Cardiology. 2006; 47(4):726-733

379 McPaul J. Focus on research... Home visit versus telephone follow-up in Phase II cardiac rehabilitation following myocardial infarction: effects on anxiety, depression, attendance at Phase III and visits to A&E or readmission. British Journal of Occupational Therapy. 2008; 71(8):320

380 Mead A, Atkinson G, Albin D, Alphey D, Baic S, Boyd O et al. Dietetic guidelines on food and nutrition in the secondary prevention of cardiovascular disease - Evidence from systematic reviews of randomized controlled trials (second update, January 2006). Journal of Human Nutrition and Dietetics. 2006; 19(6):401-419

381 Mead H, Andres E, Ramos C, Siegel B, Regenstein M. Barriers to effective self-management in cardiac patients: The patient's experience. Patient Education and Counseling. 2010; 79(1):69-76

382 Mega JL, Braunwald E, Mohanavelu S, Burton P, Poulter R, Misselwitz F et al. Rivaroxaban versus placebo in patients with acute coronary syndromes (ATLAS ACS-TIMI 46): a randomised, double-blind, phase II trial. Lancet. 2009; 374(9683):29-38

383 Mehilli J, Kastrati A, Schulz S, Frungel S, Nekolla SG, Moshage W et al. Abciximab in patients with acute ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention after clopidogrel loading: a randomized double-blind trial. Circulation. 2009; 119(14):1933-1940

384 Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet. 2001; 358(9281):527-533

385 Melville MR, Packham C, Brown N, Weston C, Gray D. Cardiac rehabilitation: socially deprived patients are less likely to attend but patients ineligible for thrombolysis are less likely to be invited. Heart. 1999; 82(3):373-377

386 Merlini PA, Bauer KA, Oltrona L, Ardissino D, Cattaneo M, Belli C et al. Persistent activation of coagulation mechanism in unstable angina and myocardial infarction. Circulation. UNITED STATES 1994; 90(1):61-68

387 Michel BC, Al MJ, Remme WJ, Kingma JH, Kragten JA, van Nieuwenhuizen R et al. Economic aspects of treatment with captopril for patients with asymptomatic left ventricular dysfunction in The Netherlands. European Heart Journal. ENGLAND 1996; 17(5):731-740

388 Michie S, Fixsen D, Grimshaw JM, Eccles MP. Specifying and reporting complex behaviour change interventions: the need for a scientific method. Implementation Science. 2009; 4:40

389 Miller CD, Roe MT, Mulgund J, Hoekstra JW, Santos R, Pollack CVJ et al. Impact of acute beta-blocker therapy for patients with non-ST-segment elevation myocardial infarction. American Journal of Medicine. 2007; 120(8):685-692

390 Miller P, Wikoff R, McMahon M, Garrett MJ, Ringel K. Influence of a nursing intervention on regimen adherence and societal adjustments postmyocardial infarction. Nursing Research. 1988; 37(5):297-302

391 Miller P, Wikoff R, McMahon M, Garrett MJ, Ringel K, Collura D et al. Personal adjustments and regimen compliance 1 year after myocardial infarction. Heart and Lung. 1989; 18(4):339-346

392 Moiseev V, Dyatchuk L, Potapenko A, Abdulazizov A, Kiyakbaev G, Kobalava ZH. The efficacy of ivabradin in patients hospitalized with acute coronary syndrome. European Heart Journal. 2011; 32:731-732

393 Molloy GJ, Hamer M, Randall G, Chida Y. Marital status and cardiac rehabilitation attendance: a meta-analysis. European Journal of Cardiovascular Prevention & Rehabilitation. 2008; 15(5):557-561

394 Molloy GJ, Perkins-Porras L, Bhattacharyya MR, Strike PC, Steptoe A. Practical support predicts medication adherence and attendance at cardiac rehabilitation following acute coronary syndrome. Journal of Psychosomatic Research. 2008; 65(6):581-586

395 Montalescot G, Antoniucci D, Kastrati A, Neumann FJ, Borentain M, Migliorini A et al. Abciximab in primary coronary stenting of ST-elevation myocardial infarction: a European meta-analysis on individual patients' data with long-term follow-up. European Heart Journal. 2007; 28(4):443-449

396 Montalescot G, Drexler H, Gallo R, Pearson T, Thoenes M, Bhatt DL. Effect of irbesartan and enalapril in non-ST elevation acute coronary syndrome: results of the randomized, double-blind ARCHIPELAGO study. European Heart Journal. 2009; 30(22):2733-2741

397 Moore SM. Women's views of cardiac rehabilitation programs. Journal of Cardiopulmonary Rehabilitation. 1996; 16(2):123-129

398 Moore SM, Charvat JM, Alemi F, Gordon N, Ribisl P, Rocco M. Improving lifestyle exercise in cardiac patients: Results of the systemchange trial. Circulation. 2011; 124(21 SUPPL. 1)

399 Moore SM, Charvat JM, Gordon NH, Pashkow F, Ribisl P, Roberts BL et al. Effects of a CHANGE intervention to increase exercise maintenance following cardiac events. Annals of Behavioral Medicine. 2006; 31(1):53-62

400 Moradi B, Maleki M, Esmaeilzadeh M, Abkenar HB. Physician-related factors affecting cardiac rehabilitation referral. Journal of Tehran University Heart Center. 2011; 6(4):187-192

401 Mortarino G, Ghiringhelli S, Onofri M, Trudu A, Corda G, Lepori G. Mechanocardiographic effects of ACE-inhibitors. Acta Cardiologica. 1990; 45(6):537-546

402 Mosca L, Han R, McGillen C, Rubenfire M. Barriers for physicians to refer to cardiac rehabilitation and impact of a critical care pathway on rates of participation. Circulation. 1998; 98(S17):811

403 Mosleh SM, Kiger A, Campbell N. Improving uptake of cardiac rehabilitation: Using theoretical modelling to design an intervention. European Journal of Cardiovascular Nursing. 2009; 8(3):161-168

404 Moulaert VRMP, Verbunt JA, van Heugten CM, Bakx WGM, Gorgels APM, Bekkers SCAM et al. Activity and Life After Survival of a Cardiac Arrest (ALASCA) and the effectiveness of an early intervention service: design of a randomised controlled trial. BMC Cardiovascular Disorders. 2007; 7:26

405 Mozaffarian D, Rimm EB. Fish intake, contaminants, and human health evaluating the risks and the benefits. JAMA. 2006; 296(15):1885-1899

406 Mrdovic IB, Savic LZ, Perunicic JP, Asanin MR, Lasica RM, Jelena MM et al. Randomized active-controlled study comparing effects of treatment with carvedilol versus metoprolol in patients with left ventricular dysfunction after acute myocardial infarction. American Heart Journal. 2007; 154(1):116-122

407 Mueller E, Savage PD, Schneider DJ, Howland LL, Ades PA. Effect of a computerized referral at hospital discharge on cardiac rehabilitation participation rates. Journal of Cardiopulmonary Rehabilitation & Prevention. 2009; 29(6):365-369

408 Multicentre Anti-Atheroma Study (MAAS). Effect of simvastatin on coronary atheroma. Lancet. ENGLAND 1994; 344(8923):633-638

409 Murie J, Ross A, Lough M, Rich D. Exploring post-myocardial infarction patients' perceptions of patient-mediated interventions for the secondary prevention of coronary heart disease (SIGN Guideline 41). Quality in Primary Care. 2006; 14(2):77-83

410 Nabel EG, Topol EJ, Galeana A, Ellis SG, Bates ER, Werns SW et al. A randomized placebo-controlled trial of combined early intravenous captopril and recombinant tissue-type plasminogen activator therapy in acute myocardial infarction. Journal of the American College of Cardiology. 1991; 17(2):467-473

411 Nakagomi A, Kodani E, Takano H, Uchida T, Sato N, Ibuki C et al. Secondary preventive effects of a calcium antagonist for ischemic heart attack: randomized parallel comparison with beta-blockers. Circulation Journal. 2011; 75(7):1696-1705

412 Nakatani D, Sakata Y, Suna S, Usami M, Matsumoto S, Shimizu M et al. Impact of beta blockade therapy on long-term mortality after ST-segment elevation acute myocardial infarction in the percutaneous coronary intervention era. American Journal of Cardiology. 2013; 111(4):457-464

413 National Audit of Cardiac Rehabilitation. Annual Statistical Report 2011. London. British Heart Foundation, 2011

414 National Collaborating Centre for Chronic Conditions. Hypertension: management of hypertension in adults in primary care; partial update. London. Royal College of Physicians; British Hypertension Society, 2006

415 National Collaborating Centre for Chronic Conditions. Chronic Heart Failure: national clinical guideline for diagnosis and management in primary and secondary care. London. Royal College of Physicians, 2003

416 National Institute for Clinical Excellence. A Prophylaxis for patients who have experienced a myocardial infarction. London. NICE, 2001 Available from: http://www.nice.org.uk/page.aspx?o=16529

417 National Institute for Health & Clinical Excellence. Statins for the prevention of cardiovascular events. NICE technolocy appraisal 94. London. National Institute for Health and Clinical Excellence, 2006 Available from: http://guidance.nice.org.uk/TA94

418 National Institute for Health & Clinical Excellence. The guidelines manual, 2006

419 National Institute for Health and Clinical Excellence. Guide to the methods of technology appraisal. London: National Institute for Health and Clinical Excellence; 2008. Available from: http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf

420 National Institute for Health and Clinical Excellence. The guidelines manual. London: National Institute for Health and Clinical Excellence; 2009. Available from: http://www.nice.org.uk/aboutnice/howwework/developingniceclinicalguidelines/clinicalguidelinedevelopmentmethods/GuidelinesManual2009.jsp

421 National Institute for Health and Clinical Excellence. Hypertension: Management of hypertension in adults in primary care: partial update. London. National Institute for Health and Clinical Excellence, 2006

422 Ness AR, Hughes J, Elwood PC, Whitley E, Smith GD, Burr ML. The long-term effect of dietary advice in men with coronary disease: follow-up of the Diet and Reinfarction trial (DART). European Journal of Clinical Nutrition. England 2002; 56(6):512-518

423 Nguyen MC, Lim YL, Walton A, Lefkovits J, Agnelli G, Goodman SG et al. Combining warfarin and antiplatelet therapy after coronary stenting in the Global Registry of Acute Coronary Events: is it safe and effective to use just one antiplatelet agent? European Heart Journal. 2007; 28(14):1717-1722

424 NHS Business Services Authority. NHS electronic drug tariff. 2012. [Last accessed: 1 August 2011]

425 Nielsen LS, Angus JE, Lapum J, Dale C, Kramer-Kile M, Abramson B et al. "I can't just follow any particular textbook": Immigrants in cardiac rehabilitation. Journal of Advanced Nursing. 2012;(12):2719-2729

426 Nikolsky E, Mehran R, Dangas GD, Yu J, Parise H, Xu K et al. Outcomes of patients treated with triple antithrombotic therapy after primary percutaneous coronary intervention for st-elevation myocardial infarction (from the Harmonizing Outcomes with Revascularization and

Stents in Acute Myocardial Infarction [HORIZONS-AMI] trial). American Journal of Cardiology. 2012; 109(6):831-838

427 Nilsen DW, Albrektsen G, Landmark K, Moen S, Aarsland T, Woie L. Effects of a high-dose concentrate of n-3 fatty acids or corn oil introduced early after an acute myocardial infarction on serum triacylglycerol and HDL cholesterol. American Journal of Clinical Nutrition. 2001; 74(1):50-56

428 Nissen SE, Tuzcu EM, Libby P, Thompson PD, Ghali M, Garza D et al. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure. The CAMELOT study: A randomized controlled trial. JAMA. United States 2004; 292(18):2217-2226

429 Norris RM, Caughey DE, Scott PJ. Trial of propranolol in acute myocardial infarction. BMJ. 1968; 2(5602):398-400

430 Nyman JA, Martinson MS, Nelson D, Nugent S, Collins D, Wittes J et al. Cost-effectiveness of gemfibrozil for coronary heart disease patients with low levels of high-density lipoprotein cholesterol: the Department of Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial. Archives of Internal Medicine. United States 2002; 162(2):177-182

431 O'Connor CM, Gattis WA, Hellkamp AS, Langer A, Larsen RL, Harrington RA et al. Comparison of two aspirin doses on ischemic stroke in post-myocardial infarction patients in the warfarin (Coumadin) Aspirin Reinfarction Study (CARS). American Journal of Cardiology. 2001; 88(5):541-546

432 O'Driscoll JM, Shave R, Cushion CJ. A National Health Service Hospital's cardiac rehabilitation programme: a qualitative analysis of provision. Journal of Clinical Nursing. 2007; 16(10):1908-1918

433 O'Keefe JH, Abuissa H, Sastre A, Steinhaus DM, Harris WS. Effects of omega-3 fatty acids on resting heart rate, heart rate recovery after exercise, and heart rate variability in men with healed myocardial infarctions and depressed ejection fractions. American Journal of Cardiology. 2006; 97(8):1127-1130

434 Office for National Statistics. Mortality Statistics: Cause, England and Wales 2003. 2004. Available from: http://www.ons.gov.uk/ons/rel/vsob1/mortality-statistics--cause--england-and-wales--series-dh2--discontinued-/no--30--2003/index.html

435 Office for National Statistics. Population Estimates for UK, England and Wales, Scotland and Northern Ireland, mid 2003. 2004. Available from: http://www.ons.gov.uk/ons/rel/pop-estimate/population-estimates-for-uk--england-and-wales--scotland-and-northern-ireland/2003/index.html

436 Office for National Statistics. Office for National Statistics. Deaths by age, sex and underlying cause, 2004. 2006. Available from: http://www.statistics.gov.uk/statbase/expodata/spreadsheets/d8986.xls

437 Oldgren J, Budaj A, Granger CB, Harper R, Khder Y, Van De Werf F et al. Randomised dabigatran etexilate dose finding study in patients with acute coronary syndromes post index event with additional risk factors for cardiovascular complications also receiving aspirin and clopidogrel (RE-DEEM). Circulation. 2010; 120(21):2160-2161

438 Oldgren J, Budaj A, Granger CB, Khder Y, Roberts J, Siegbahn A et al. Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial. European Heart Journal. 2011; 32(22):2781-2789

439 Oldridge N, Furlong W, Feeny D, Torrance G, Guyatt G, Crowe J et al. Economic evaluation of cardiac rehabilitation soon after acute myocardial infarction. American Journal of Cardiology. United States 1993; 72(2):154-161

440 Oldridge NB, Jones NL. Improving patient compliance in cardiac exercise rehabilitation. Journal of Cardiac Rehabilitation. 1983; 3:257-262

441 Olsson AG, Schwartz GG, Szarek M, Sasiela WJ, Ezekowitz MD, Ganz P et al. High-density lipoprotein, but not low-density lipoprotein cholesterol levels influence short-term prognosis after acute coronary syndrome: results from the MIRACL trial. European Heart Journal. England 2005; 26(9):890-896

442 Olsson G, Levin L-A, Rehnqvist N. Economic consequences of postinfarction prophylaxis with beta blockers: cost effectiveness of metoprolol. BMJ. 1987; 294(6568):339-342

443 Olsson G, Oden A, Johansson L, Sjogren A, Rehnqvist N. Prognosis after withdrawal of chronic postinfarction metoprolol treatment: a 2-7 year follow-up. European Heart Journal. 1988; 9(4):365-372

444 Orford JL, Fasseas P, Melby S, Burger K, Steinhubl SR, Holmes DR et al. Safety and efficacy of aspirin, clopidogrel, and warfarin after coronary stent placement in patients with an indication for anticoagulation. American Heart Journal. 2004; 147(3):463-467

445 Osika JS. Cardiac Rehabilitation: evaluation of a pilot lay volunteer home visiting service and needs assessment. London: Faculty of Public Health Medicine; 2001.

446 Ozasa N, Mitsudo K, Morimoto T, Heigen H, Tamura T, Shizuta S et al. Does oral beta-blocker therapy improve long-term clinical outcomes of ST-elevation acute myocardial infarction after primary angioplasty? Journal of the American College of Cardiology. 2010; 55(10 SUPPL 1):A208

447 Pack QR, Mansour M, Barboza JS, Hibner BA, Mahan MG, Ehrman JK et al. An early appointment to outpatient cardiac rehabilitation at hospital discharge improves attendance at orientation: a randomized, single-blind, controlled trial. Circulation. 2013; 127(3):349-355

448 Packham C, Gray D, Silcocks P, Hampton J. Identifying the risk of death following hospital discharge in patients admitted with a suspected acute myocardial infarction in whom the diagnosis is not confirmed. European Heart Journal. 2000; 21:213-219

449 Palmer S, Sculpher M, and Philips Z. A cost effectiveness model comparing alternative management strategies for the use of glycoprotein IIB/IIIA anatagonists in non-st-elevation acute coronary syndrome. York. Centre for Health Economics, 2004

450 Paquet M, Bolduc N, Xhignesse M, Vanasse A. Re-engineering cardiac rehabilitation programmes: Considering the patient's point of view. Journal of Advanced Nursing. 2005; 51(6):567-576

451 Park SJ, Park DW, Kim YH, Kang SJ, Lee SW, Lee CW et al. Duration of dual antiplatelet therapy after implantation of drug-eluting stents. New England Journal of Medicine. 2010; 362(15):1374-1382

452 Parker K, Stone JA, Arena R, Lundberg D, Aggarwal S, Goodhart D et al. An early cardiac access to clinic significantly improves cardiac rehabilitation participation and completion rates in low-risk ST-elevation myocardial infarction patients. Canadian Journal of Cardiology. 2011; 27:619-627

453 Parry MJ, Watt-Watson J, Hodnett E, Tranmer J, Dennis CL, Brooks D. Cardiac Home Education and Support Trial (CHEST): a pilot study. Canadian Journal of Cardiology. 2009; 25(12):e393-e398

454 Paschos GK, Magkos F, Panagiotakos DB, Votteas V, Zampelas A. Dietary supplementation with flaxseed oil lowers blood pressure in dyslipidaemic patients. European Journal of Clinical Nutrition. England 2007; 61(10):1201-1206

455 Pasquale P, Cannizzaro S, Scalzo S, Bucca V, Maringhini G, Verso PL et al. Effects of two different ACE inhibitors, captopril and delapril, in the early phases of acute anterior myocardial infarction. Clinical Drug Investigation. 1999; 17(5):347-355

456 Patel JV, Lee KW, Tomson J, Dubb K, Hughes EA, Lip GY. Effects of omega-3 polyunsaturated fatty acids on metabolically active hormones in patients post-myocardial infarction. International Journal of Cardiology. 2007; 115(1):42-45

457 Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. New England Journal of Medicine.: Massachusetts Medical Society. 2011; 365(10):883-891

458 Patrick K. What factors influence healthcare professionals' decision to refer patients to cardiac rehabilitation phase II programmes? Heart, Lung & Circulation. 2010; 19(Suppl 1):S27

459 Pedersen TR. A multicentre study on timolol in secondary prevention after myocardial infarction. Acta Medica Scandinavica. 1983; S674(1):129

460 Pedersen TR. Six-year follow-up of the Norwegian Multicenter Study on Timolol after Acute Myocardial Infarction. New England Journal of Medicine. 1985; 313(17):1055-1058

461 Pedersen TR, Kjekshus J, Berg K, Haghfelt T, Faergeman O, Faergeman G et al. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). 1994. Atherosclerosis Supplements. Netherlands 2004; 5(3):81-87

462 Pekdemir H, Cin VG, Camsari A, Cicek D, Akkus MN, Doven O et al. A comparison of 1-month and 6-month clopidogrel therapy on clinical and angiographic outcome after stent implantation. Heart and Vessels. 2003; 18(3):123-129

463 Pell JP, Morrison CE. Factors associated with low attendance at cardiac rehabilitation. British Journal of Cardiology. 1998; 5:152-155

464 Perez MI, Musini VM, Wright JM. Effect of early treatment with anti-hypertensive drugs on short and long-term mortality in patients with an acute cardiovascular event. Cochrane Database of Systematic Reviews. 2009;(4):CD006743

465 Peters RJ, Mehta SR, Fox KA, Zhao F, Lewis BS, Kopecky SL et al. Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: observations from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study. Circulation. United States 2003; 108(14):1682-1687

466 Peters S. Comparison of efficacy of low- (80 mg/day) and high- (160-320 mg/day) dose valsartan in the prevention of in-stent restenosis after implantation of bare-metal stents in type B2/C coronary artery lesions. American Journal of Cardiovascular Drugs. 2008; 8(2):83-87

467 Peterson GM, Thompson A, Pulver LK, Robertson MB, Brieger D, Wai A et al. Management of acute coronary syndromes at hospital discharge: do targeted educational interventions improve practice quality? Journal for Healthcare Quality : Official Publication of the National Association for Healthcare Quality. 2011;

468 Petronio AS, Musumeci G, Limbruno U, De Carlo M, Baglini R, Paterni G et al. Abciximab improves 6-month clinical outcome after rescue coronary angioplasty. American Heart Journal. 2002; 143(2):334-341

469 Pettersen AA, Seljeflot I, Abdelnoor M, Arnesen H. High on-aspirin platelet reactivity and clinical outcome in patients with stable coronary artery disease: results from ASCET (Aspirin Nonresponsiveness and Clopidogrel Endpoint Trial). Journal of the American Heart Association. 2012; 1(3):e000703

470 Pfeffer MA, Braunwald E, Moye LA, Basta L. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the survival and ventricular enlargement trial. New England Journal of Medicine. 1992; 327(10):669-677

471 Pfeffer MA, Greaves SC, Arnold JM, Glynn RJ, LaMotte FS, Lee RT et al. Early versus delayed angiotensin-converting enzyme inhibition therapy in acute myocardial infarction. The healing and early afterload reducing therapy trial. Circulation. 1997; 95(12):2643-2651

472 Pfeffer MA, Lamas GA, Vaughan DE, Parisi AF, Braunwald E. Effect of captopril on progressive ventricular dilatation after anterior myocardial infarction. New England Journal of Medicine. 1988; 319(2):80-86

473 Pfeffer MA, McMurray JJ, Velazquez EJ, Rouleau JL, Kober L, Maggioni AP et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. New England Journal of Medicine. 2003; 349(20):1893-1906

474 Pfisterer M, Cox JL, Granger CB, Brener SJ, Naylor CD, Califf RM et al. Atenolol use and clinical outcomes after thrombolysis for acute myocardial infarction: the GUSTO-I experience. Global Utilization of Streptokinase and TPA (alteplase) for Occluded Coronary Arteries. Journal of the American College of Cardiology. 1998; 32(3):634-640

475 Pinto BM, Goldstein MG, Papandonatos GD, Farrell N, Tilkemeier P, Marcus BH et al. Maintenance of exercise after phase II cardiac rehabilitation: a randomized controlled trial. American Journal of Preventive Medicine. 2011; 41(3):274-283

476 Pischke CR, Scherwitz L, Weidner G, Ornish D. Long-term effects of lifestyle changes on well-being and cardiac variables among coronary heart disease patients. Health Psychology. 2008; 27(5):584-592

477 Pitt B, Mancini GB, Ellis SG, Rosman HS, Park JS, McGovern ME. Pravastatin limitation of atherosclerosis in the coronary arteries (PLAC I): reduction in atherosclerosis progression and clinical events. PLAC I investigation. Journal of the American College of Cardiology. UNITED STATES 1995; 26(5):1133-1139

478 Pitt B, O'Neill B, Feldman R, Ferrari R, Schwartz L, Mudra H et al. The QUinapril Ischemic Event Trial (QUIET): evaluation of chronic ACE inhibitor therapy in patients with ischemic heart

disease and preserved left ventricular function. American Journal of Cardiology. 2001; 87(9):1058-1063

479 Plosker GL, McTavish D. Captopril. A review of its pharmacology and therapeutic efficacy after myocardial infarction and in ischaemic heart disease. Drugs and Aging. 1995; 7(3):226-253

480 Pollard M, Sutherland C. Cardiac rehabilitation: Are we putting our hearts into it? British Journal of Cardiology. 2009; 16(5):247-249

481 Porter A, Konstantino Y, Iakobishvili Z, Shachar L, Battler A, Hasdai D. Short-term triple therapy with aspirin, warfarin, and a thienopyridine among patients undergoing percutaneous coronary intervention. Catheterization and Cardiovascular Interventions. 2006; 68(1):56-61

482 Postula M, Akram S, Akram F. Current problems, new opportunities and future directions of anti-platelet therapy - increasing role of novel antiplatelet agents in cardiovascular diseases. Recent Patents on Cardiovascular Drug Discovery. 2009; 4(1):55-60

483 Poulsen SH, Jensen SE, Egstrup K. Improvement of exercise capacity and left ventricular diastolic function with metoprolol XL after acute myocardial infarction. American Heart Journal. 2000; 140(1):E6-11

484 Prescription Pricing Authority. NHS Electronic Drug Tariff. 2006. Available from: http://www.ppa.org.uk/edt/July_2006/mindex.htm

485 Price J. A pilot trial of a coaching intervention desgined to increase woman's attendance at cardiac rehabilitation intake. Canadian Journal of Cardiology. 2012; 28(5 SUPPL. 1):S439

486 Proudfoot C, Thow M, Rafferty D. A UK survey of phase 1 cardiac rehabilitation for patients with acute coronary syndrome. Physiotherapy. 2007; 93(3):183-188

487 PSSRU. Personal Social Services Research Unit PSSRU. 2005. Available from: www.pssru.ac.uk

488 Pullen SA, Povey RC, Grogan SC. Deciding to attend cardiac rehabilitation: a female perspective... including commentary by Higginson R. International Journal of Therapy & Rehabilitation. 2009; 16(4):207-217

489 Radley A, Grove A, Wright S, Thurston H. Problems of women compared withthose of men following myocardial infarction. Coronary Health Care. 1998; 2:202-209

490 Raitt MH, Connor WE, Morris C, Kron J, Halperin B, Chugh SS et al. Fish oil supplementation and risk of ventricular tachycardia and ventricular fibrillation in patients with implantable defibrillators: a randomized controlled trial. JAMA. 2005; 293(23):2884-2891

491 Rangoonwala B, Rosenthal J. Is telmisartan clinically equivalent or more effective than ramipril? Results of the ONTARGET study. Journal of Applied Therapeutic Research. 2010; 7(3):110-117

492 Rauch B, Schiele R, Schneider S, Diller F, Victor N, Gohlke H et al. OMEGA, a randomized, placebo-controlled trial to test the effect of highly purified omega-3 fatty acids on top of modern guideline-adjusted therapy after myocardial infarction. Circulation. 2010; 122(21):2152-2159

493 Ray SG, Pye M, Oldroyd KG, Christie J, Connelly DT, Northridge DB et al. Early treatment with captopril after acute myocardial infarction. British Heart Journal. 1993; 69(3):215-222

494 Reid RD, Morrin LI, Beaton LJ, Papadakis S, Kocourek J, McDonnell L et al. Randomized trial of an internet-based computer-tailored expert system for physical activity in patients with heart disease. European Journal of Preventive Cardiology. 2012; 19(6):1357-1364

495 Renkin J. Clinical benefit of angiotensin converting enzyme inhibition after acute myocardial infarction: myocardial reperfusion revisited. Journal of Hypertension Supplement. 1996; 14(6):S15-S19

496 Ricci, Coletta R. Early randomized administration of ACE inhibitors and beta-blockers on the left ventricle remodelling after acute myocardial infarct. Giornale Italiano Di Cardiologia. 1999; 29(Suppl 3):54

497 Rich MW. Treatment of acute myocardial infarction. American Journal of Geriatric Cardiology. 2001; 10(6):328-336

498 Riegger G, Abletshauser C, Ludwig M, Schwandt P, Widimsky J, Weidinger G et al. The effect of fluvastatin on cardiac events in patients with symptomatic coronary artery disease during one year of treatment. Atherosclerosis. IRELAND 1999; 144(1):263-270

499 Ringleb PA, Bhatt DL, Hirsch AT, Topol EJ, Hacke W. Benefit of clopidogrel over aspirin is amplified in patients with a history of ischemic events. Stroke. 2004; 35(2):528-532

500 Rivett MJ, Tsakirides C, Pringle A, Carroll S, Ingle L, Dudfield M. Physical activity readiness in patient withdrawals from cardiac rehabilitation. British Journal of Nursing. 2009; 18(3):188-191

501 Rizos EC, Ntzani EE, Bika E, Kostapanos MS, Elisaf MS. Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: a systematic review and meta-analysis. JAMA. 2012; 308(10):1024-1033

502 Roberts R, Rogers WJ, Mueller HS, Lambrew CT, Diver DJ, Smith HC et al. Immediate versus deferred beta-blockade following thrombolytic therapy in patients with acute myocardial infarction. Results of the Thrombolysis in Myocardial Infarction (TIMI) II-B Study. Circulation. 1991; 83(2):422-437

503 Robinson HJ, Samani NJ, Singh SJ. Can low risk cardiac patients be 'fast tracked' to Phase IV community exercise schemes for cardiac rehabilitation? A randomised controlled trial. International Journal of Cardiology. 2011; 146(2):159-163

504 Robinson M, Palmer S, Sculpher M, Philips Z, Ginnelly L, Bowens A et al. Cost-effectiveness of alternative strategies for the initial medical management of non-ST elevation acute coronary syndrome: systematic review and decision-analytical modelling. Health Technology Assessment. 2005; 9(27):1-72

505 Rodrigues EJ, Eisenberg MJ, Pilote L. Effects of early and late administration of angiotensin-converting enzyme inhibitors on mortality after myocardial infarction. American Journal of Medicine. 2003; 115(6):473-479

506 Roe MT, Armstrong PW, Fox KAA, White HD, Prabhakaran D, Goodman SG et al. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. New England Journal of Medicine. 2012; 367(14):1297-1309

507 Rogowski W, Burch J, Palmer S, Craigs C, Golder S, Woolacott N. The effect of different treatment durations of clopidogrel in patients with non-ST-segment elevation acute coronary

syndromes: A systematic review and value of information analysis. Health Technology Assessment. 2009; 13(31):1-77

508 Rolfe DE, Sutton EJ, Landry M, Sternberg L, Price JAD. Women's experiences accessing a women-centered cardiac rehabilitation program: a qualitative study. Journal of Cardiovascular Nursing. 2010; 25(4):332-341

509 Roque F, Amuchastegui LM, Lopez Morillos MA, Mon GA, Girotti AL, Drajer S et al. Beneficial effects of timolol on infarct size and late ventricular tachycardia in patients with acute myocardial infarction. Circulation. 1987; 76(3):610-617

510 Rossini R, Musumeci G, Lettieri C, Molfese M, Mihalcsik L, Mantovani P et al. Long-term outcomes in patients undergoing coronary stenting on dual oral antiplatelet treatment requiring oral anticoagulant therapy. American Journal of Cardiology. 2008; 102(12):1618-1623

511 Rubboli A, Magnavacchi P, Guastaroba P, Saia F, Vignali L, Giacometti P et al. Antithrombotic management and 1-year outcome of patients on oral anticoagulation undergoing coronary stent implantation (from the Registro Regionale Angioplastiche Emilia-Romagna Registry). American Journal of Cardiology. 2012; 109(10):1411-1417

512 Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. New England Journal of Medicine. UNITED STATES 1999; 341(6):410-418

513 Ruiz-Nodar JM, Marin F, Manzano-Fernandez S, Valencia-Martin J, Hurtado JA, Roldan V et al. An evaluation of the CHADS2 stroke risk score in patients with atrial fibrillation who undergo percutaneous coronary revascularization. Chest. 2011; 139(6):1402-1409

514 Russell KL, Holloway TM, Brum M, Caruso V, Chessex C, Grace SL. Cardiac rehabilitation wait times: effect on enrollment. Journal of Cardiopulmonary Rehabilitation & Prevention. 2011; 31(6):373-377

515 Sabatine MS, Cannon CP, Gibson CM, López-Sendón JL, Montalescot G, Theroux P et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. New England Journal of Medicine. 2005; 352(12):1179-1189

516 Sabatine MS, Cannon CP, Gibson CM, Lopez-Sendon JL, Montalescot G, Theroux P et al. Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolytics: the PCI-CLARITY study. JAMA. 2005; 294(10):1224-1232

517 Sacks FM, Tonkin AM, Shepherd J, Braunwald E, Cobbe S, Hawkins CM et al. Effect of pravastatin on coronary disease events in subgroups defined by coronary risk factors: the Prospective Pravastatin Pooling Project. Circulation. UNITED STATES 2000; 102(16):1893-1900

518 Sadeghzadeh V. Improved quality of life with cardiac rehabilitation for post-myocardial infarction patients in Critical Care Unit. European Journal of Cardiovascular Prevention & Rehabilitation. 2011; 18(1 SUPPL. 1):S45

519 Salam AM. Clinical trials evaluating angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in the setting of acute myocardial infarction. Expert Opinion on Investigational Drugs. 2003; 12(3):501-507

520 Sanderson BK, Shewchuk RM, Bittner V. Cardiac rehabilitation and women: What keeps them away? Journal of Cardiopulmonary Rehabilitation & Prevention. 2010; 30(1):12-21

521 Sanon S, Lee V-V, Elayda M, Wilson JM. Use of aspirin versus clopidogrel plus Aspirin after coronary artery bypass graft surgery. Clinical and Applied Thrombosis/Hemostasis. 2009; 15(5):540-544

522 Sarafoff N, Ndrepepa G, Mehilli J, Dorrler K, Schulz S, Iijima R et al. Aspirin and clopidogrel with or without phenprocoumon after drug eluting coronary stent placement in patients on chronic oral anticoagulation. Journal of Internal Medicine. 2008; 264(5):472-480

523 Sarkar U, Schillinger D, Bibbins-Domingo K, Napoles A, Karliner L, Perez-Stable EJ. Patient-physicians' information exchange in outpatient cardiac care: Time for a heart to heart? Patient Education and Counseling. 2011; 85(2):173-179

524 Schadlich PK, Huppertz E, Brecht JG. Cost-effectiveness analysis of ramipril in heart failure after myocardial infarction:economic evaluation of the Acute Infarction Ramipril Efficacy (AIRE) Study for Germany from the perspective of statutory health insurance. Pharmacoeconomics. Copyright: University of York, 1999. 1998; 14(6):653-669

525 Schömig A, Schmitt C, Dibra A, Mehilli J, Volmer C, Schühlen H et al. One year outcomes with abciximab vs. placebo during percutaneous coronary intervention after pre-treatment with clopidogrel. European Heart Journal. 2005; 26(14):1379-1384

526 Schreiber TL, Miller DH, Silvasi D, McNulty A, Zola BE. Superiority of warfarin over aspirin long term after thrombolytic therapy for acute myocardial infarction. American Heart Journal. 1990; 119(6):1238-1244

527 Schulman SP, Fessler HE. Management of acute coronary syndromes. American Journal of Respiratory and Critical Care Medicine. 2001; 164(6):917-922

528 Schulman SP, Weiss JL, Becker LC, Guerci AD, Shapiro EP, Chandra NC et al. Effect of early enalapril therapy on left ventricular function and structure in acute myocardial infarction. American Journal of Cardiology. 1995; 76(11):764-770

529 Schwalm JD, Ahmad M, Salehian O, Eikelboom JW, Natarajan MK. Warfarin after anterior myocardial infarction in current era of dual antiplatelet therapy: a randomized feasibility trial. Journal of Thrombosis and Thrombolysis. 2010; 30(2):127-132

530 Scott IA, Eyeson-Annan ML, Huxley SL, West MJ. Optimising care of acute myocardial infarction: results of a regional quality improvement project. Journal of Quality in Clinical Practice. 2000; 20(1):12-19

531 Scott LB, Sexton TR, Brzostek S, Cizmeli C, Brown DL. Patient navigation significantly improves rates of enrollment into outpatient cardiac rehabilitation. Journal of Cardiopulmonary Rehabilitation & Prevention. 2012; 32(4):228-229

532 Seierstad SL, Seljeflot I, Johansen O, Hansen R, Haugen M, Rosenlund G et al. Dietary intake of differently fed salmon; the influence on markers of human atherosclerosis. European Journal of Clinical Investigation. 2005; 35(1):52-59

533 Serra-Majem L, Roman B, Estruch R. Scientific evidence of interventions using the Mediterranean Diet: A systematic review. Nutrition Reviews. 2006; 64(Feb 2(Pt 2)):S27-S47

534 Serruys PW, de F, Macaya C, Kokott N, Puel J, Vrolix M et al. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial. JAMA. United States 2002; 287(24):3215-3222

535 Serruys PW, Foley DP, Jackson G, Bonnier H, Macaya C, Vrolix M et al. A randomized placebo-controlled trial of fluvastatin for prevention of restenosis after successful coronary balloon angioplasty; final results of the fluvastatin angiographic restenosis (FLARE) trial. European Heart Journal. ENGLAND 1999; 20(1):58-59

536 Shanks LC, Moore SM, Zeller RA. Predictors of cardiac rehabilitation initiation. Rehabilitation Nursing. 2007; 32(4):152-157

537 Sharp J, Freeman C. Patterns and predictors of uptake and adherence to cardiac rehabilitation. Journal of Cardiopulmonary Rehabilitation & Prevention. 2009; 29(4):241-247

538 Sharpe N, Murphy J, Smith H, Hannan S. Treatment of patients with symptomless left ventricular dysfunction after myocardial infarction. Lancet. 1988; 1(8580):255-259

539 Sharpe N, Smith H, Murphy J, Greaves S, Hart H, Gamble G. Early prevention of left ventricular dysfunction after myocardial infarction with angiotensin-converting-enzyme inhibition. Lancet. 1991; 337(8746):872-876

540 Shaw R, Gillies M, Barber J, MacIntyre K, Harkins C, Findlay IN et al. Pre-exercise screening and health coaching in CHD secondary prevention: A qualitative study of the patient experience. Health Education Research. 2012; 27(3):424-436

541 Shen W, Li M, Hu H, Zhang X, Gong L. Cardiac protection by long-term treatment with captopril in patients with acute myocardial infarction. Chinese Medical Journal. 1998; 111(2):139-141

542 Shirotani M, Yokota R, Kouchi I, Hirai T, Uemori N, Haba K et al. Influence of atenolol on coronary artery spasm after acute myocardial infarction in a Japanese population. International Journal of Cardiology. 2010; 139(2):181-186

543 Sinclair AJ, Conroy SP, Davies M, Bayer AJ. Post-discharge home-based support for older cardiac patients: a randomised controlled trial. Age and Ageing. England 2005; 34(4):338-343

544 Smith MG, Neville AM, Middleton JC. Clinical and economic benefits of ramipril: an Australian analysis of the HOPE study. Internal Medicine Journal. Australia 2003; 33(9-10):414-419

545 Smith P. Long-term anticoagulant treatment after acute myocardial infarction. The Warfarin Re-Infarction Study. Annals of Epidemiology. UNITED STATES 1992; 2(4):549-552

546 Smith PK, Goodnough LT, Levy JH, Poston RS, Short MA, Weerakkody GJ et al. Mortality benefit with prasugrel in the TRITON-TIMI 38 coronary artery bypass grafting cohort: risk-adjusted retrospective data analysis. Journal of the American College of Cardiology. 2012; 60(5):388-396

547 Sniehotta FF, Gorski C, Araujo-Soares V. Adoption of community-based cardiac rehabilitation programs and physical activity following phase III cardiac rehabilitation in Scotland: A prospective and predictive study. Psychology & Health. 2010; 25(7):839-854

548 Sniehotta FF, Scholz U, Schwarzer R. Action plans and coping plans for physical exercise: A longitudinal intervention study in cardiac rehabilitation. British Journal of Health Psychology. 2006; 11(Pt 1):23-37

549 Sniehotta FF, Solz U, Schwarzer R, Fuhrmann, Kiwus U, Voller H. Long-term effects of two psychological intervention on physical exercise and self-regulation following coronary rehabilitation. International Journal of Behavioural Medicine. 2005; 12(4):244-255

550 Sogaard P, Gotzsche CO, Ravkilde J, Norgaard A, Thygesen K. Ventricular arrhythmias in the acute and chronic phases after acute myocardial infarction. Effect of intervention with captopril. Circulation. 1994; 90(1):101-107

551 Sogaard P, Gotzsche CO, Ravkilde J, Thygesen K. Effects of captopril on ischemia and dysfunction of the left ventricle after myocardial infarction. Circulation. 1993; 87(4):1093-1099

552 Soleimani A, Abbasi A, Nejatian M, Salarifar M, Darabian S, Karimi AA et al. Factors predicting discontinuation of a hospital-based cardiac rehabilitation programme. Kardiologia Polska. 2009; 67(2):140-146

553 SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. Lancet. 1991; 325(5):293-302

554 SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. New England Journal of Medicine. 1992; 327(10):685-691

555 Spinar J, Vitovec J, Pluhacek L, Spinarova L, Fischerova B, Toman J. First dose hypotension after angiotensin converting enzyme inhibitor captopril and angiotensin II blocker losartan in patients with acute myocardial infarction. International Journal of Cardiology. 2000; 75(2-3):197-204

556 Squizzato A, Keller T, Romualdi E, Middeldorp S. Clopidogrel plus aspirin versus aspirin alone for preventing cardiovascular disease. Cochrane Database of Systematic Reviews. 2011; Issue 1:CD005158. DOI:10.1002/14651858.CD005158.pub3

557 Sriskantharajah J, Kai J. Promoting physical activity among South Asian women with coronary heart disease and diabetes: What might help? Family Practice. 2007;(1):71-76

558 Steg PG, James S, Harrington RA, Ardissino D, Becker RC, Cannon CP et al. Ticagrelor versus clopidogrel in patients with ST-elevation acute coronary syndromes intended for reperfusion with primary percutaneous coronary intervention: A Platelet Inhibition and Patient Outcomes (PLATO) trial subgroup analysis. Circulation. 2010; 122(21):2131-2141

559 Steinhubl SR, Berger PB, Tift Mann J, Fry ETA, DeLago A, Wilmer C et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention. JAMA. 2002; 288:2411-2420

560 Suskin N, Wisenberg G, Barnett P, Pellizzari J, Murray-Parsons N. Physician (MD) endorsement improves cardiac rehabilitation (CR) participation. Journal of Cardiac Rehabilitation. 2000; 20(306)

561 Suzuki H, Geshi E, Nanjyo S, Nakano H, Yamazaki J, Sato N et al. Inhibitory effect of valsartan against progression of left ventricular dysfunction after myocardial infarction: T-VENTURE study. Circulation Journal. 2009; 73(5):918-924

562 Swardfager W, Herrmann N, Marzolini S, Saleem M, Farber SB, Kiss A et al. Major depressive disorder predicts completion, adherence, and outcomes in cardiac rehabilitation: A prospective

cohort study of 195 patients with coronary artery disease. Journal of Clinical Psychiatry. 2011; 72(9):1181-1188

563 Swedberg K, Held P, Kjekshus J, Rasmussen K, Ryden L, Wedel H. Effects of the early administration of enalapril on mortality in patients with acute myocardial infarction. Results of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II). New England Journal of Medicine. 1992; 327(10):678-684

564 Sweet SN, Tulloch H, Fortier MS, Pipe AL, Reid RD. Patterns of motivation and ongoing exercise activity in cardiac rehabilitation settings: A 24-month exploration from the TEACH study. Annals of Behavioral Medicine. 2011; 42(1):55-63

565 Syed M, Borzak S, Jafri SM. Angiotensin-converting enzyme inhibition after acute myocardial infarction with special reference to the Fourth International Study of Infarct Survival (ISIS-4). Progress in Cardiovascular Diseases. 1996; 39(2):201-206

566 Tada T, Natsuaki M, Morimoto T, Furukawa Y, Nakagawa Y, Byrne RA et al. Duration of dual antiplatelet therapy and long-term clinical outcome after coronary drug-eluting stent implantation: landmark analyses from the CREDO-Kyoto PCI/CABG Registry Cohort-2. Circulation Cardiovascular Interventions. 2012; 5(3):381-391

567 Tamburino C, Russo G, Nicosia A, Galassi AR, Foti R, Scriffignano V et al. Prophylactic abciximab in elective coronary stenting: results of a randomized trial. Journal of Invasive Cardiology. 2002; 14(2):72-79

568 Tanaka K, Ishikawa Y, Yokoyama M, Origasa H, Matsuzaki M, Saito Y et al. Reduction in the recurrence of stroke by eicosapentaenoic acid for hypercholesterolemic patients: subanalysis of the JELIS trial. Stroke. 2008; 39(7):2052-2058

569 Tang WJ, Tang HQ, Yang LL, Wang XQ, Sun YH, Huang XH. Effects of fish oil on prevention of cardiovascular events: a systematic review. Chinese Journal of Evidence-Based Medicine. 2009; 9(11):1200-1206

570 Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R et al. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet. 2008; 372(9645):1223-1230

571 Taylor M, Scuffham PA, Chaplin S, Papo NL. An economic evaluation of valsartan for post-MI patients in the UK who are not suitable for treatment with ACE inhibitors. Value in Health. 2009; 12(4):459-465

572 Taylor RS, Brown A, Ebrahim S, Jolliffe J, Noorani H, Rees K et al. Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. American Journal of Medicine. 2004; 116(10):682-692

573 Taylor SH, Silke B, Ebbutt A, Sutton GC, Prout BJ, Burley DM. A long-term prevention study with oxprenolol in coronary heart disease. New England Journal of Medicine. 1982; 307(21):1293-1301

574 ten Berg JM, Kelder JC, Suttorp MJ, Mast EG, Bal E, Ernst SM et al. Effect of coumarins started before coronary angioplasty on acute complications and long-term follow-up: a randomized trial. Circulation. 2000; 102(4):386-391

575 Teo KK, Burton JR, Buller CE, Plante S, Catellier D, Tymchak W et al. Long-term effects of cholesterol lowering and angiotensin-converting enzyme inhibition on coronary atherosclerosis: The Simvastatin/Enalapril Coronary Atherosclerosis Trial (SCAT). Circulation. UNITED STATES 2000; 102(15):1748-1754

576 The Capricorn Investigators. Effect of cardvedilol on outcome after myocardial in patients with left-ventricular dysfunction: the CAPRICORN (Carvedilol Post-Infact Survival Control in LV Dysfunction) randomised trial. Lancet. 2001; 357:1385-1390

577 The ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. New England Journal of Medicine.: Massachusetts Medical Society. 2008; 358(15):1547-1559

578 Thow M, Rafferty D, Kelly H. Exercise motives of long-term phase IV cardiac rehabilitation participants. Physiotherapy. 2008; 94(4):281-285

579 Throndson K, Sawatzky JA. Improving outcomes following elective percutaneous coronary intervention: the key role of exercise and the advanced practice nurse. Canadian Journal of Cardiovascular Nursing. 2009; 19(2):17-24

580 Thurston SJ, Heeg B, de CF, van HB. Cost-effectiveness of clopidogrel in STEMI patients in the Netherlands: a model based on the CLARITY trial. Current Medical Research and Opinion. 2010; 26(3):641-651

581 Tod AM, Wadsworth E, Asif S, Gerrish K. Cardiac rehabilitation: the needs of South Asian cardiac patients. British Journal of Nursing. 2001; 10(16):1028-1033

582 Tognoni G. Use and abuse of clinical trials. Is the timing of treatment critical? Cardiology. 1994; 85 Suppl 1:7-12

583 Tolg R, Witt M, Schwarz B, Kurz T, Kurowski V, Hartmann F et al. Comparison of carvedilol and metoprolol in patients with acute myocardial infarction undergoing primary coronary intervention--the PASSAT Study. Clinical Research in Cardiology. 2006; 95(1):31-41

584 Tolmie EP, Lindsay GM, Kelly T, Tolson D, Baxter S, Belcher PR. Are older patients' cardiac rehabilitation needs being met? Journal of Clinical Nursing. 2009; 18(13):1878-1888

585 Toobert DJ, Glasgow RE, Nettekoven LA, Brown JE. Behavioral and psychosocial effects of intensive lifestyle management for women with coronary heart disease. Patient Education and Counseling. 1998; 35(3):177-188

586 Trichopoulou A, Bamia C, Norat T, Overvad K, Schmidt EB, Tjonneland A et al. Modified Mediterranean diet and survival after myocardial infarction: The EPIC-Elderly study. European Journal of Epidemiology. 2007; 22(12):871-881

587 Tsevat J, Duke D, Goldman L, Pfeffer MA, Lamas GA, Soukup JR et al. Cost-effectiveness of captopril therapy after myocardial infarction. Journal of the American College of Cardiology. UNITED STATES 1995; 26(4):914-919

588 Tuttle KR, Shuler LA, Packard DP, Milton JE, Daratha KB, Bibus DM et al. Comparison of low-fat versus mediterranean-style dietary intervention after first myocardial infarction. American Journal of Cardiology. 2008; 101(11):1523-1530

589 Tytus RH, Burgess ED, Assouline L, Vanjaka A. Effectiveness of a trandolapril-based treatment regimen in subjects with isolated systolic hypertension in Canada. Current Medical Research and Opinion. 2009; 25(6):1379-1384

590 Udell JA, Wang JT, Gladstone DJ, Tu JV. Anticoagulation after anterior myocardial infarction and the risk of stroke. PLoS ONE. 2010; 5(8):e12150

591 Ussia GP, Scarabelli M, Mulè M, Barbanti M, Sarkar K, Cammalleri V et al. Dual antiplatelet therapy versus aspirin alone in patients undergoing transcatheter aortic valve implantation. American Journal of Cardiology. 2011; 108(12):1772-1776

592 Valgimigli M, Campo G, Percoco G, Monti M, Ferrari F, Tumscitz C et al. Randomized comparison of 6- versus 24-month clopidogrel therapy after balancing anti-intimal hyperplasia stent potency in all-comer patients undergoing percutaneous coronary intervention Design and rationale for the PROlonging Dual-antiplatelet treatment after Grading stent-induced Intimal hyperplasia study (PRODIGY). American Heart Journal. 2010; 160(5):804-811

593 Valgimigli M, Campo G, Monti M, Vranckx P, Percoco G, Tumscitz C et al. Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial. Circulation. 2012; 125(16):2015-2026

594 Valgimigli M, Tebaldi M, Campo G, Gambetti S, Bristot L, Monti M et al. Prasugrel versus tirofiban bolus with or without short post-bolus infusion with or without concomitant prasugrel administration in patients with myocardial infarction undergoing coronary stenting: the FABOLUS PRO (Facilitation through Aggrastat By drOpping or shortening Infusion Line in patients with ST-segment elevation myocardial infarction compared to or on top of PRasugrel given at loading dOse) trial. JACC Cardiovascular Interventions. 2012; 5(3):268-277

595 Van Bergen PFMM, Jonker JJC, Van der Meer FJM, Azar AJ, Meeter K, Deckers JW et al. Effect of long-term oral anticoagulant treatment on mortality and cardiovascular after myocardial infarction. Lancet. United Kingdom 1994; 343(8896):499-503

596 Van Bergen PFMM, Jonker JJC, van Hot BA, van Domburg RT, Azar AJ, Hofman A. Costs and effects of long-term oral anticoagulant treatment after myocardial infarction. JAMA. Copyright: University of York, 1995. 1995; 273(12):925-928

597 van den Bergh PJPC, Kievit PC, Brouwer MA, Aengevaeren WRM, Veen G, Verheugt FWA. Prolonged anticoagulation therapy adjunctive to aspirin after successful fibrinolysis: from early reduction in reocclusion to improved long-term clinical outcome. American Heart Journal. 2009; 157(3):532-540

598 van Es RF, Jonker JJ, Verheugt FW, Deckers JW, Grobbee DE. Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study): a randomised controlled trial. Lancet. England 2002; 360(9327):109-113

599 Van RJ, Burger H, Van Melle JP, Slaets JP, De JP. Depression, access to cardiac aftercare and drop-out in rehabilitation programs. Journal of Psychosomatic Research. 2010; 68(6):672

600 Vantrimpont P, Rouleau JL, Wun CC, Ciampi A, Klein M, Sussex B et al. Additive beneficial effects of beta-blockers to angiotensin-converting enzyme inhibitors in the Survival and Ventricular Enlargement (SAVE) Study. SAVE Investigators. Journal of the American College of Cardiology. UNITED STATES 1997; 29(2):229-236

601 Varnfield M, Karunanithi M, Ding H, Honeyman E, Arnold D, Keightley A et al. Technology based home-care model improves outcomes of uptake, adherence and health in cardiac rehabilitation. European Heart Journal. 2012; 33:445

602 Vasmant D, Lendresse P, Lemarie JC, Gallet M. Comparison of response rates to the angiotensin-converting enzyme inhibitor ramipril in mild-to-moderate hypertension in a double-blind, parallel-group study and an open single-blind study. Journal of Cardiovascular Pharmacology. 1991; 18 Suppl 2:S144-S146

603 Vavuranakis M, Latsios G, Aggelis D, Bosinakou I, Karambelas I, Tousoulis D et al. Randomized comparison of the effects of ASA plus clopidogrel versus ASA alone on early platelet activation in acute coronary syndromes with elevated high-sensitivity C-reactive protein and soluble CD40 ligand levels. Clinical Therapeutics. 2006; 28(6):860-871

604 Veeger NJGM, Zijlstra F, Hillege HL, van der Meer J, CABADAS Research Group of the Interuniversity Cardiology Institute of The Netherlands. Fourteen-year follow-up from CABADAS: vitamin K antagonists or dipyridamole not superior to aspirin. Annals of Thoracic Surgery. 2010; 90(5):1515-1521

605 Visram S, Crosland A, Unsworth J, Long S. Engaging women from South Asian communities in cardiac rehabilitation. British Journal of Community Nursing. 2007; 12(1):13-18

606 Visram S, Crosland A, Unsworth J, Long S. Engaging women from South Asian communities in cardiac rehabilitation. International Journal of Therapy & Rehabilitation. 2008; 15(7):298-304

607 Wagner A, Herkner H, Schreiber W, Bur A, Woisetschlager C, Stix G et al. Ramipril prior to thrombolysis attenuates the early increase of PAI-1 in patients with acute myocardial infarction. Thrombosis and Haemostasis. 2002; 88(2):180-185

608 Wang C, Harris WS, Chung M, Lichtenstein AH, Balk EM, Kupelnick B et al. n-3 Fatty acids from fish or fish-oil supplements, but not alpha-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: a systematic review. American Journal of Clinical Nutrition. United States 2006; 84(1):5-17

609 Wang JT, Hoffman B, Blumenthal JA. Management of depression in patients with coronary heart disease: association, mechanisms, and treatment implications for depressed cardiac patients. Expert Opinion on Pharmacotherapy. 2011; 12(1):85-98

610 Waring WS. Early initiation of ACE inhibitor treatment after acute myocardial infarction--a missed therapeutic opportunity? Journal of the Renin-Angiotensin-Aldosterone System. 2000; 1(3):245-251

611 Weber HS, Selimi D, Huber G. Prevention of cardiovascular diseases and highly concentrated n-3 polyunsaturated fatty acids (PUFAs). Herz. Germany 2006; 31 Suppl 3:24-30

612 Webster RA, Thompson DR, Mayou RA. The experiences and needs of Gujarati Hindu patients and partners in the first month after a myocardial infarction. European Journal of Cardiovascular Nursing. 2002; 1(1):69-76

613 Weir MR. Speed and duration of dose titration with the angiotensin converting enzyme inhibitor quinapril: relationship with efficacy in patients with moderate hypertension. Journal of Human Hypertension. 1994; 8(9):725-730

614 West R. Cardiac rehabilitation of older patients. Reviews in Clinical Gerontology. 2003; 13(3):241-255

615 Whelton A, Miller WE, Dunne BJ, Hait HI, Tresznewsky ON. Once-daily lisinopril compared with twice-daily captopril in the treatment of mild to moderate hypertension: assessment of office and ambulatory blood pressures. Journal of Clinical Pharmacology. 1990; 30(12):1074-1080

616 White CM. Angiotensin-converting-enzyme inhibition in heart failure or after myocardial infarction. American Journal of Health-System Pharmacy. 2000; 57 Suppl 1:S18-S25

617 Wiisanen ME, Moliterno DJ. The use of single versus dual antiplatelet therapy beyond 1 year following drug-eluting stent implantation. Current Cardiology Reports. 2010; 12(5):357-360

618 Wilcox RG, Roland JM, Banks DC, Hampton JR, Mitchell JR. Randomised trial comparing propranolol with atenolol in immediate treatment of suspected myocardial infarction. BMJ. 1980; 280(6218):885-888

619 Wilk JB, Tsai MY, Hanson NQ, Gaziano JM, Djousse L. Plasma and dietary omega-3 fatty acids, fish intake, and heart failure risk in the Physicians' Health Study. American Journal of Clinical Nutrition. 2012; 96(4):882-888

620 Wolkanin-Bartnik J, Pogorzelska H, Bartnik A. Patient education and quality of home-based rehabilitation in patients older than 60 years after acute myocardial infarction. Journal of Cardiopulmonary Rehabilitation & Prevention. 2011; 31(4):249-253

621 Wu N, Fan Z. Secondary prevention of cardiac events following myocardial infarction: effects of atenolol and enalapril. Beijing Collaborative Study Group. Chinese Medical Journal. 1997; 110(8):602-606

622 Wyer SJ, Earll L, Joseph S, Harrison J, Giles M, Johnston M. Increasing attendance at a cardiac rehabilitation programme: An intervention study using the Theory of Planned Behaviour. Coronary Health Care. United Kingdom 2001; 5(3):154-159

623 Yalfani A, Yohannes AM, Doherty P, Brett J, Bundy C. Perceptions of healthcare staff in relation to referral for cardiac rehabilitation. British Journal of Cardiology. 2006; 13(2):138-140

624 Yan HB, Wang SP. What is the optimal initiation timing of angiotensin converting enzyme inhibitor treatment for maximum benefits in acute myocardial infarction patients? Chinese Medical Journal. 2011; 124(3):464-466

625 Yano H, Hibi K, Nozawa N, Ozaki H, Kusama I, Ebina T et al. Effects of valsartan, an angiotensin II receptor blocker, on coronary atherosclerosis in patients with acute myocardial infarction who receive an angiotensin-converting enzyme inhibitor. Circulation Journal. 2012; 76(6):1442-1451

626 Yener G, Aran S, Bahceci M, Ozdemir K, Gultekin F, Lowe W. Quinapril for treatment of hypertension in Turkey: dose titration and diuretic combination treatment strategies. Clinical Drug Investigation. 2007; 27(9):613-622

627 Yohannes AM, Yalfani A, Doherty P, Bundy C. Predictors of drop-out from an outpatient cardiac rehabilitation programme. Clinical Rehabilitation. 2007; 21(3):222-229

628 Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet. 2007; 369(9567):1090-1098

629 Yoshitomi Y, Kojima S, Yano M, Sugi T, Matsumoto Y, Kuramochi M. Long-term effects of bisoprolol compared with imidapril on left ventricular remodeling after reperfusion in acute myocardial infarction: an angiographic study in patients with maintained vessel patency. American Heart Journal. 2000; 140(6):E27

630 Young JB. Angiotensin-converting enzyme inhibitors post-myocardial infarction. Cardiology Clinics. 1995; 13(3):379-390

631 Young RF, Kahana E. Age, medical advice about cardiac risk reduction, and patient compliance. Journal of Aging and Health. 1989; 1(1):121-134

632 Yusuf S, Flather M, Pogue J, Hunt D, Varigos J, Piegas L et al. Variations between countries in invasive cardiac procedures and outcomes in patients with suspected unstable angina or myocardial infarction without initial ST elevation. OASIS (Organisation to Assess Strategies for Ischaemic Syndromes) Registry Investigators. Lancet. ENGLAND 1998; 352(9127):507-514

633 Yusuf S, Mehta SR, Zhao F, Gersh BJ, Commerford PJ, Blumenthal J et al. Early and late effects of clopidogrel in patients with acute coronary syndromes. Circulation. 2003; 107:966-972

634 Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. Progress in Cardiovascular Diseases. 1985; 27(5):335-371

635 Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. New England Journal of Medicine. 2000; 342(3):145-153

636 Yusuf S, Teo K, Anderson C, Pogue J, Dyal L, Copland I et al. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. Lancet. 2008; 372(9644):1174-1183

637 Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. New England Journal of Medicine. United States 2001; 345(7):494-502

638 Zedigh C, Alho A, Hammar E, Karlsson T, Kellerth T, Svensson L et al. Aspects on the intensity and the relief of pain in the prehospital phase of acute coronary syndrome: experiences from a randomized clinical trial. Coronary Artery Disease. 2010; 21(2):113-120

639 Zhang Z, Kolm P, Mosse F, Jackson J, Zhao L, Weintraub WS. Long-term cost-effectiveness of clopidogrel in STEMI patients. International Journal of Cardiology. 2009; 135(3):353-360

640 Zhou YH, Wei X, Lu J, Ye XF, Wu MJ, Xu JF et al. Effects of combined aspirin and clopidogrel therapy on cardiovascular outcomes: a systematic review and meta-analysis. PLoS ONE. 2012; 7(2):e31642