National Clinical Guideline Centre

Draft for consultation

Acute heart failure

Acute heart failure: diagnosing and managing acute heart failure in adults

Clinical Guideline <...>

Appendices A - R

25 March 2014

Draft for Consultation

Commissioned by the National Institute for Health and Care Excellence

Royal College of Physicians

The Royal College of Surgeons of England

RCGP Royal College of General Practitioners

Royal College of Nursing

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1

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Contents

National Clinical Guideline Centre 1
Appendix A: Scope 5
Appendix B: Declarations of interest 14
Appendix C: Review protocols 34
Appendix D: Clinical article selection 68
Appendix E: Economic article selection 86
Appendix F: Literature search strategies 87
Appendix G: Clinical evidence tables 122
Appendix H: Economic evidence tables 272
Appendix I: Forest plots 300
Appendix J: Natriuretic peptides: diagnostic meta-analysis methods 369
Appendix K: Excluded clinical studies 388
Appendix L: Excluded economic studies 424
Appendix M: Cost-effectiveness analysis 427
Appendix N: Unit costs 462
Appendix O: Research recommendations 467
References 483

1

1

Appendix A: Scope

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SCOPE

1 Guideline title

Acute heart failure: diagnosing and managing acute heart failure in adults

1.1 Short title

Acute heart failure

2 The remit

The Department of Health has asked NICE: 'To prepare a guideline on the diagnosis and management of acute heart failure'.

3 Clinical need for the guideline

3.1 Epidemiology

a) Acute heart failure can present as new-onset heart failure in people without known cardiac dysfunction, or as acute decompensation of chronic heart failure (that is, a significant deterioration in heart function).

b) Acute heart failure can be categorised as follows: acute heart failure with pulmonary oedema, cardiogenic shock, acute right-sided heart failure and acute decompensated heart failure.

c) Acute heart failure is a common cause of admission to hospital, and the leading cause of hospital admission in people 65 years or older in the UK. According to the 2010/11 UK National Heart Failure Audit, most people admitted to hospital with acute heart failure are aged over 60, with 25% aged between 60 and 74 and 68% over 75. Men and women seem to be equally affected, but men are usually 5 years younger than women at the time of

2

hospital admission (mean age 75 years for men and 80 years for women).

d) In 2009/10, 67,158 people in England and Wales were discharged from hospital with a primary diagnosis of heart failure. European registry data show that nearly 50% of people admitted to hospital with acute heart failure are re-admitted within 12 months. The risk of re-admission or death within 60 days is 30–50%. The rate of hospital admission for acute heart failure is similar to that for acute coronary syndrome, but the mortality rate for acute heart failure is higher.

e) Mortality from acute and chronic heart failure is high. The 2010/11 UK National Heart Failure Audit showed that about a third of people with acute heart failure die during their first hospitalisation or in the year after.

3.2 Current practice

a) A range of methods are used to diagnose acute heart failure. These include clinical evaluation, electrocardiogram (ECG), chest X-ray and other imaging techniques, laboratory tests and echocardiography. The availability of facilities and techniques for diagnosing acute heart failure varies. There is currently variation in access to diagnostic blood tests, echocardiography and specialist clinical assessment.

b) Monitoring and diagnostic procedures begins as early as possible. Monitoring techniques may be non-invasive (for example, measuring blood pressure, ECG and pulse oximetry) or invasive (for example, using arterial lines, central venous pressure lines or pulmonary artery catheters). Several factors influence which level and type of monitoring is most effective; these include the severity of the condition and response to initial treatment.

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c) There is a difference of opinion among healthcare professionals about the use of respiratory support, diuretics, vasodilators and inotropic agents in people with acute heart failure, particularly during emergency care.

d) Different management strategies are used depending on whether the condition is associated with pulmonary oedema or cardiogenic shock, or is acute right-sided heart failure or acute decompensated heart failure. There is also variation in that some people are treated in critical care settings and others receive care in general medical wards.

e) Preventing renal damage is an important consideration for people with acute heart failure. However, it is not clear what level of renal support should be offered in clinical practice.

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 will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

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

4.1 Population

4.1.1 Groups that will be covered

a) Adults (aged 18 years or older) who have a diagnosis of acute heart failure, or have possible acute heart failure, or are being investigated for acute heart failure.

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b) Specific consideration will be given to subgroups with pulmonary oedema, cardiogenic shock, acute right-sided heart failure or acute decompensated heart failure.

4.1.2 Groups that will not be covered

a) Children and young people under 18 years.

4.2 Healthcare setting

a) Hospital settings.

b) Community settings.

4.3 Clinical management

4.3.1 Key clinical issues that will be covered

Diagnosis, assessment and monitoring

a) In addition to the standard investigations (such as ECG, chest X-ray and blood tests), the added benefit of using natriuretic peptides or echocardiography.

b) Indications for, and types of, invasive (arterial lines, central venous pressure lines and pulmonary artery catheters) monitoring when non-invasive monitoring alone is no longer appropriate.

Management of acute heart failure

c) Specialist management units.

Initial treatment

Oxygen and ventilatory support

d) The use of supplementary oxygen, ventilatory support (CPAP), non-invasive (NIPPV) or invasive ventilation to maximise oxygen delivery to the tissues to prevent multiple organ failure.

Pharmacological therapy

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e) Management with drug therapy, including diuretics, opiates, vasodilators, inotropic agents and vasopressors.

f) Discontinuing beta-blockers.

Ultrafiltration

g) Timing (initiation and duration) of ultrafiltration.

Mechanical cardiac support

h) Mechanical circulatory assistance with intra-aortic balloon counterpulsation or ventricular assist devices.

Treatment after stabilisation

Pharmacological therapy

i) Starting or re-instating treatment for new-onset acute heart failure with angiotensin-converting enzyme (ACE) inhibitors, beta-blockers and/or aldosterone antagonists.

Surgical or percutaneous treatment

j) The use of coronary revascularisation and valvular surgery when acute heart failure is a severe complication of other cardiac disorders.

Organisation of care

k) Transition from hospital to primary care after the acute phase.

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.

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4.3.2 Clinical issues that will not be covered

a) The long-term management of underlying diseases (such as congenital heart disease) and comorbidities of acute heart failure.

b) The management of perioperative acute heart failure.

c) The long-term management of acute heart failure in pregnant women.

4.4 Main outcomes

a) Mortality.

b) Major cardiovascular events (non-fatal myocardial infarction, stroke).

c) Length of hospital stay and re-admission rates.

d) Adverse events.

e) Quality of life.

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.

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4.6.2 Timing

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

5 Related NICE guidance

5.1 Published guidance

5.1.1 NICE guidance to be updated

No guidance has been identified that is likely to be updated or replaced by this guideline.

5.1.2 NICE guidance to be incorporated

There is no guidance to be incorporated.

5.1.3 Other related NICE guidance

- Patient experience in adult NHS services. NICE clinical guidance 138 (2012).
- Hypertension. NICE clinical guideline 127 (2011).
- Stable angina. NICE clinical guideline 126 (2011).
- Bivalirudin for the treatment of ST-segment elevation myocardial infarction (STEMI). NICE technology appraisal guidance 230 (2011).
- 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).
- Type 2 diabetes – newer agents. NICE clinical guideline 87 (2009).
- Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention. NICE technology appraisal guidance 182 (2009).
- Chronic kidney disease. NICE clinical guideline 73 (2008).
- Lipid modification. NICE clinical guideline 67 (2008).
- Smoking cessation services. NICE public health guidance 10 (2008).
- MI: secondary prevention. NICE clinical guideline 48 (2007).

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- Varenicline for smoking cessation. NICE technology appraisal guidance 123 (2007).
- Cardiac resynchronisation therapy for the treatment of heart failure. NICE technology appraisal guidance 120 (2007).
- Atrial fibrillation. NICE clinical guideline 36 (2006).
- Short-term circulatory support with left ventricular assist devices as a bridge to cardiac transplantation or recovery. NICE interventional procedure guidance 177 (2006).
- Brief interventions and referral for smoking cessation. NICE public health guidance 1 (2006).
- Coronary imaging: myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction. NICE technology appraisal guidance 73 (2003).

5.1.4 Related NICE quality standards

- Chronic Heart Failure quality standard. NICE quality standard 9 (2011).

5.2 Guidance under development

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

- Ivabradine for the treatment of chronic heart failure. NICE technology appraisal guidance. Publication expected December 2012.
- Myocardial infarction with ST-segment-elevation. NICE clinical guideline. Publication expected July 2013.
- MI – secondary prevention (update). NICE clinical guideline. Publication expected July 2013.
- Implantable cardioverter defibrillators for the treatment of arrhythmias and cardiac resynchronisation therapy for the treatment of heart failure (review of TA95 and TA120). NICE technology appraisal guidance. Publication expected September 2013.
- Lipid modification (update). NICE clinical guideline. Publication date to be confirmed.

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- Atrial fibrillation (update). NICE clinical guideline. Publication date to be confirmed.
- Ticagrelor for the treatment of acute coronary syndromes (ACS). NICE technology appraisal guidance. Publication date to be confirmed.

6 Further information

Information on the guideline development process is provided in the following documents, available from the NICE website:

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

Information on the progress of the guideline will also be available from the NICE website.

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Appendix B: Declarations of interest

B.1 Abdallah Al-Mohammad

GDG meeting	Declaration of Interests	Action taken
Original DoI	**Personal non-specific pecuniary interest**: I have received a £160 fee from a research company in Switzerland for my time participating in a questionnaire on the management of heart failure (May 2011) [Non-pharmacological] I received £250 fee from the organisers of the Primary Care Conference in Birmingham for delivering a lecture on the new CHF NICE guideline (May 2011) [Non-pharmacological] I received £600 fee from Pri-Med the organisers of the cardiology update conference for primary and secondary care in Manchester, for an update on heart failure (November 2011) [Non-pharmacological]	Declare and participate
GDG1 31.10.12	No new declarations of interest	None
GDG2 11.12.12	No new declarations of interest	None
GDG3 16.1.13	No new declarations of interest	None
GDG4 20.3.13	No new declarations of interest	None
GDG5 30.4.13	No new declarations of interest	None
GDG6 4.6.13	No new declarations of interest	None
GDG7 8.7.13	No new declarations of interest	None
GDG8 9.7.13	No new declarations of interest	None
GDG9 18.09.13	No new declarations of interest	None
GDG10 25.11.13	No new declarations of interest	None
GDG11 26.11.13	No new declarations of interest	None
GDG12 23.01.14	No new declarations of interest	None
GDG13	No new declarations of interest	None

24.01.14		
GDG14 26.02.14	**Personal non-pecuniary interest:** 1. Principal investigator in Sheffield for the Live:Life study of the over 70 year old patients with CHF being treated with ivabradine and having their symptoms, quality of life and progress assessed . 2. Co-investigator on REVIVED a study of the role of percutaneous coronary intervention in patients with CHF and significant coronary artery disease .	None

B.2 Martin Cowie

GDG meeting	Declaration of Interests	Action taken
Original DoI	Personal non-specific pecuniary interest Adviser to Novartis about the potential role of their new product, SeRelaxin, in HF. . SeRelaxin is only just finishing its first Phase 3 study, and is likely to have a second Phase 3 study start in 2013, completing after the end of the AHF GDG process.SeRelaxin will not be licensed during the period of the guideline development..	Reviewed and decision made by Chair to declare and participate

	Currently have consultancy agreements with ResMed (treatment and monitoring of sleep disordered breathing in chronic heart failure), Medtronic (device therapy in chronic heart failure), and Respicardia (phrenic nerve stimulation for sleep disordered breathing). These consultancies relate to the running of steering committees of development programmes, including large global randomised studies, which are either in the planning phase or running currently, and do not relate to any material that will come under the scope of the AHF guideline. **Non-personal pecuniary interest**: None related to acute heart failure, but my University department receives research funding from Medtronic for research in remote monitoring and from ResMed for treatment and monitoring of sleep disordered breathing in chronic heart failure.	Declare and participate Medtronic make prosthetic valves. However,the guideline addresses indications for valvular surgery only.
GDG1 31.10.12	No new declarations of interest	None
GDG2 11.12.12	**Personal non-pecuniary interest**: Appointed Special Advisor to NICE on Cardiovascular Interventions Dec 2012 for a 3 year term.	Reviewed and decision made by Chair to declare and participate
GDG3 16.1.13	No new declarations of interest	None
GDG4 20.3.13	No new declarations of interest	None
GDG5 30.4.13	**Personal pecuniary interest: 1)** Chaired Advisory Board for Novartis on 17 April 2013 on their heart failure	Declare and participate.

	strategy. **Non-personal pecuniary interest:** 2) Received educational grant from Novartis to hold an educational event at the RCP in October 2013 on acute heart failure –.	Novartis manufacture Co-Diovan (diuretic) and Transiderm Nitro (vasodilator). Co-Diovan has 2 active agents and not being evaulated. Transiderm Nitro is a GTN which are being evaluated, however on the basis of route of administration (transdermal) the product is not being evaluated.
GDG6 4.6.13	No new declarations of interest	None
GDG7 8.7.13	No new declarations of interest	None
GDG8 9.7.13	No new declarations of interest	None
GDG9 18.09.13	**Personal pecuniary interest: 1)** Honoraria for speaking at Satellite Symposia in South Africa, Australia and Amsterdam for Servier. **Personal pecuniary interest: 2)** Honoraria for speaking at Satellite Symposia in Amsterdam and Marseille, and press conference in Amsterdam, for Novartis. Zero hour contract with NICE for the Scientific Advisory Programme. **Non-personal pecuniary interest: 3)** Zero hour contract with NICE for the Scientific Advisory Programme	1. Declare and withdraw from diuretics 2. Declare and participate (see above). 3.declare and participate
GDG10 25.11.13	No new declarations of interest	None
GDG11 26.11.13	No new declarations of interest	None
GDG12 23.01.14	No new declarations of interest	None
GDG13 24.01.14	No new declarations of interest	None
GDG14 26.02.14	No new declarations of interest	None

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B.3 Suzanna Hardman

GDG meeting	Declaration of Interests	Action taken
Original DoI	**Personal pecuniary interest**: I have limited share holdings with 1. Glaxo-Welcome. 2. Astra Zeneca	Declare and withdraw from ACE and betablockers - conflict with AstraZeneca
	Personal family interest: My husband has ments with Glaxo-Welcome. **Non-personal pecuniary interest**: I am current Chair to the British Society for Heart Failure since May 2011. The BSH is a registered charity and its activities in turn are heavily dependent upon funding from Industry. Funds have been received from June 2011 from the following companies: Alere, Biotronik, Edwards Lifesciences, GE Healthcare, Heartware, Medtronic, Pfizer, Servier, St Jude Medical, Takeda, Thoratec and Vifor Pharma. Boston Scientific, British Heart Foundation, Gambro Lundia, NHS Improvement, Novartis, ResMed, Roche Diagnostics and Wisepress	Declare and participate Glaxo-welcome do not manufacture or own products under evaluation. Declare and participate
GDG1 31.10.12	No new declarations of interest	None
GDG2 11.12.12	**Personal non-pecuniary interest**: I have given a number of interviews to publicise the National Heart Failure Audit data for 2011/12.	Declare and participate
GDG3 16.1.13	No new declarations of interest	None
GDG4 20.3.13	No new declarations of interest	None

GDG5 30.4.13	I no longer hold any shares in either Glaxo-Wellcome or Astra- Zeneca	Declare and participate for ACEi and beta-blockers. COI no longer exists
GDG6 4.6.13	No new declarations of interest	None
GDG7 8.7.13	No new declarations of interest	None
GDG8 9.7.13	No new declarations of interest	None
GDG9 18.09.13	No new declarations of interest	None
GDG10 25.11.13	No new declarations of interest	None
GDG11 26.11.13	No new declarations of interest	None
GDG12 23.01.14	No new declarations of interest	None
GDG13 24.01.14	No new declarations of interest	None
GDG14 26.02.14	No new declarations of interest	None

B.4 John McMurray

GDG meeting	Declaration of Interests	Action taken
	• Novartis - chairing a satellite symposium at the Heart Failure Association of the European Society of Cardiology annual congress - May 2011. • Thermo Fisher diagnostics - advisory board at the European Society of Cardiology annual congress - Sept 2011. • E.Merck KG - lecture at meeting on heart failure - Shanghai, Sept 2011.	Declare and participate Nile Pharma, Pharmaceutical product development Inc and Astellas do not manufacture or own product under evaluation

	• Mitsubishi - lecture at symposium at European Society of Cardiology annual congress - Sept 2011. • • Nile Pharma - advisory board at American Heart Association meeting - Nov 2011. Pharmaceutical Product Development Inc. - paid for endpoint committee work. • Astellas - will be paid for endpoint committee work. **Non-personal pecuniary interest**: Glasgow University is paid for my time spent on committees of clinical trials (Amgen, Astellas, Bayer AG, BMS-Pfizer, Guidant Europe, Merck, Novartis, Reata Pharma, Roche, Sanofi-Aventis). In 2012, Glasgow University has or will be paid for my occasional attendance at advisory boards, talks and chairing of meetings (Servier, Daiichi Sankyo Europe, Pfizer and Novartis).	
GDG1 31.10.12	No new declarations of interest	None
GDG2 11.12.12	No new declarations of interest	None
GDG3 16.1.13	No new declarations of interest	None
GDG4 20.3.13	No new declarations of interest	None
GDG5 30.4.13	No new declarations of interest	None
GDG6 4.6.13	**Non-personal pecuniary interest**: I spoke at a satellite symposium at the ESC Heart Failure Congress in Lisbon in May 2013 for which a payment was made to my employer, Glasgow University.	Declare and participate
GDG7 8.7.13	No new declarations of interest	None
GDG8 9.7.13	No new declarations of interest	None
GDG9 18.09.13	No new declarations of interest	None
GDG10 25.11.13	No new declarations of interest	None
GDG11	No new declarations of interest	None

26.11.13		
GDG12 23.01.14	No new declarations of interest	None
GDG13 24.01.14	No new declarations of interest	None
GDG14 26.02.14	No new declarations of interest	None

B.5 Jason Kendall

GDG meeting	Declaration of Interests	Action taken
Original DoI	**Personal non-pecuniary interest**: Principal Investigator for 3CPO Trial at Frenchay Hospital . A multicentre randomised controlled trial of the use of continuous positive airway pressure and non-invasive positive pressure ventilation in the early treatment of patients presenting to the emergency department with severe acute cardiogenic pulmonary oedema: the 3CPO trial.Published : Gray AJ, Goodacre S, Newby DE, Masson MA, Sampson F, Dixon S, et al., on behalf of the 3CPO study investigators. Health Technology Assess 2009;13(33).	Reviewed and decision made by Chair to declare and participate
GDG1 31.10.12	No new declarations of interest	None
GDG2 11.12.12	No new declarations of interest	None
GDG3 16.1.13	No new declarations of interest	None
GDG4 20.3.13	No new declarations of interest	None
GDG5 30.4.13	No new declarations of interest	None
GDG6 4.6.13	No new declarations of interest	None
GDG7 8.7.13	No new declarations of interest	None
GDG8 9.7.13	No new declarations of interest	None
GDG9 18.09.13	No new declarations of interest	None
GDG10 25.11.13	No new declarations of interest	None
GDG11	No new declarations of interest	None

26.11.13		
GDG12 23.01.14	No new declarations of interest	None
GDG13 24.01.14	No new declarations of interest	None
GDG14 26.02.14	No new declarations of interest	None

B.6 Nicholas Ioannou

GDG meeting	Declaration of Interests	Action taken
Original DoI	None	None
GDG1 31.10.12	No new declarations of interest	None
GDG2 11.12.12	No new declarations of interest	None
GDG3 16.1.13	No new declarations of interest	None
GDG4 20.3.13	No new declarations of interest	None
GDG5 30.4.13	No new declarations of interest	None
GDG6 4.6.13	No new declarations of interest	None
GDG7 8.7.13	No new declarations of interest	None
GDG8 9.7.13	No new declarations of interest	None
GDG9 18.09.13	No new declarations of interest	None
GDG10 25.11.13	No new declarations of interest	None
GDG11 26.11.13	No new declarations of interest	None
GDG12 23.01.14	No new declarations of interest	None
GDG13 24.01.14	No new declarations of interest	None
GDG14 26.02.14	No new declarations of interest	None

B.7 Tanzeem Raza

GDG meeting	Declaration of Interests	Action taken
Original DoI	None	None
GDG1 31.10.12	No new declarations of interest	None
GDG2 11.12.12	No new declarations of interest	None
GDG3 16.1.13	No new declarations of interest	None
GDG4 20.3.13	No new declarations of interest	None
GDG5 30.4.13	No new declarations of interest	None
GDG6 4.6.13	No new declarations of interest	None
GDG7 8.7.13	No new declarations of interest	None
GDG8 9.7.13	No new declarations of interest	None
GDG9 18.09.13	No new declarations of interest	None
GDG10 25.11.13	No new declarations of interest	None
GDG11 26.11.13	No new declarations of interest	None
GDG12 23.01.14	No new declarations of interest	None
GDG13 24.01.14	No new declarations of interest	None
GDG14 26.02.14	No new declarations of interest	None

B.8 Jayne Masters

GDG meeting	Declaration of Interests	Action taken
Original DoI	None	None

GDG1 31.10.12	No new declarations of interest	None
GDG2 11.12.12	No new declarations of interest	None
GDG3 16.1.13	No new declarations of interest	None
GDG4 20.3.13	No new declarations of interest	None
GDG5 30.4.13	No new declarations of interest	None
GDG6 4.6.13	No new declarations of interest	None
GDG7 8.7.13	Non-personal pecuniary interest Participation in an educational steering group sponsored by Novartis. There is a sum of money attached which I have elected to have paid into the Heart Failure Unit Education fund. This starts in July 2013.	Declare and participate
GDG8 9.7.13	No new declarations of interest	None
GDG9 18.09.13	No new declarations of interest	None
GDG10 25.11.13	No new declarations of interest	None
GDG11 26.11.13	No new declarations of interest	None
GDG12 23.01.14	No new declarations of interest	None
GDG13 24.01.14	No new declarations of interest	None
GDG14 26.02.14	No new declarations of interest	None

B.9 Jane Butler

GDG meeting	Declaration of Interests	Action taken
Original DoI	None	None
GDG1 31.10.12	No new declarations of interest	None
GDG2	No new declarations of interest	None

11.12.12		
GDG3 16.1.13	No new declarations of interest	None
GDG4 20.3.13	**Personal pecuniary interest**: Speaker or advisory honoraria from Novartis, Pfizer and Servier. Travel bursaries from Servier.	Novartis - declare and participate. Pfizer and Servier - declare and withdraw from diuretics, MRAs and ACEi
GDG5 30.4.13	No new declarations of interest	None
GDG6 4.6.13	No new declarations of interest	None
GDG7 8.7.13	No new declarations of interest	None
GDG8 9.7.13	No new declarations of interest	None
GDG9 18.09.13	No new declarations of interest	None
GDG10 25.11.13	No new declarations of interest	None
GDG11 26.11.13	No new declarations of interest	None
GDG12 23.01.14	No new declarations of interest	None
GDG13 24.01.14	No new declarations of interest	None
GDG14 26.02.14	No new declarations of interest	None

B.10 Christopher Jones

GDG meeting	Declaration of Interests	Action taken
Original DoI	None	None
GDG1 31.10.12	No new declarations of interest	None
GDG2	No new declarations of interest	None

11.12.12		
GDG3 16.1.13	No new declarations of interest	None
GDG4 20.3.13	No new declarations of interest	None
GDG5 30.4.13	No new declarations of interest	None
GDG6 4.6.13	No new declarations of interest	None
GDG7 8.7.13	No new declarations of interest	None
GDG8 9.7.13	No new declarations of interest	None
GDG9 18.09.13	No new declarations of interest	None
GDG10 25.11.13	No new declarations of interest	None
GDG11 26.11.13	No new declarations of interest	None
GDG12 23.01.14	No new declarations of interest	None
GDG13 24.01.14	No new declarations of interest	None

B.11 Peter Bolton

GDG meeting	Declaration of Interests	Action taken
Original DoI	None	None
GDG1 31.10.12	No new declarations of interest	None
GDG2 11.12.12	No new declarations of interest	None
GDG3 16.1.13	No new declarations of interest	None
GDG4 20.3.13	No new declarations of interest	None
GDG5 30.4.13	No new declarations of interest	None
GDG6 4.6.13	No new declarations of interest	None

GDG7 8.7.13	No new declarations of interest	None
GDG8 9.7.13	No new declarations of interest	None
GDG9 18.09.13	No new declarations of interest	None
GDG10 25.11.13	No new declarations of interest	None
GDG11 26.11.13	No new declarations of interest	None
GDG12 23.01.14	No new declarations of interest	None
GDG13 24.01.14	No new declarations of interest	None
GDG14 26.02.14	No new declarations of interest	None

B.12 Co-optee Alison Warren

GDG meeting	Declaration of Interests	Action taken
Original DoI	**Personal pecuniary interest**: Pharmacy advisory board Bayer meeting (March 2012 – one off meeting) The product discussed was not in the heart failure field. **Non-personal pecuniary interest:** Application in process for a grant from Servier (to be paid to the cardiac department at Brighton and Sussex university Hospitals NHS Trust) to sponsor a pharmacist post 1day/week for a 1 year period to implement and develop a pharmacy led heart failure medication up-titration clinic. The terms of the grant comply with ABPI regulations for NHS and industry working. There is no requirement within the grant for the prescription of Servier products.	no action required
GDG1 31.10.12	N/A	None
GDG2 11.12.12	No new declarations of interest	None
GDG3 16.1.13	No new declarations of interest	None
GDG4 20.3.13	No new declarations of interest	None
GDG5 30.4.13	N/A	None
GDG6	N/A	None

4.6.13		
GDG7 8.7.13	N/A	None
GDG8 9.7.13	N/A	None
GDG9 18.09.13	No new declarations of interest	None
GDG10 25.11.13	N/A	None
GDG11 26.11.13	N/A	None
GDG12 23.01.14	No new declarations of interest	None
GDG13 24.01.14	N/A	None
GDG14 26.02.14	N/A	None

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2 B.13 Co-optee Paul Collinson

GDG meeting	Declaration of Interests	Action taken
Original DoI	None	None
GDG1 31.10.12	N/A	None
GDG2 11.12.12	N/A	None
GDG3 16.1.13	N/A	None
GDG4 20.3.13	N/A	None
GDG5 30.4.13	N/A	None
GDG6 4.6.13	No new declarations of interest	None
GDG7 8.7.13	N/A	None
GDG8 9.7.13	N/A	None
GDG9 18.09.13	N/A	None
GDG10	N/A	None

25.11.13		
GDG11 26.11.13	N/A	None
GDG12 23.01.14	N/A	None
GDG13 24.01.14	N/A	None
GDG14 26.02.14	N/A	None

B.14 Co-opteeStephen Westaby

GDG meeting	Declaration of Interests	Action taken
Original DoI	**Personal pecuniary interest**: Shareholder in Calon Cardiotechnology Ltd - a university based blood pump bioengineering group. I am medical director for this development project - unpaid. **Personal non-pecuniary interest**: I have pioneered the role of mechanical circulatory support in severe heart failure.	Declare and participate
GDG1 31.10.12	N/A	None
GDG2 11.12.12	N/A	None
GDG3 16.1.13	N/A	None
GDG4 20.3.13	N/A	None
GDG5 30.4.13	N/A	None
GDG6 4.6.13	N/A	None
GDG7 8.7.13	N/A	None
GDG8 9.7.13	No new declarations of interest	None
GDG9 18.09.13	N/A	None
GDG10 25.11.13	N/A	None
GDG11 26.11.13	No new declarations of interest	None

GDG12 23.01.14	N/A	None
GDG13 24.01.14	N/A	None
GDG14 26.02.14	N/A	None

B.15 Co-optee Ahmed Fuat

GDG meeting	Declaration of Interests	Action taken
Original DoI 4.11.12	None	None
GDG1 31.10.12	N/A	None
GDG2 11.12.12	N/A	None
GDG3 16.1.13	N/A	None
GDG4 20.3.13	N/A	None
GDG5 30.4.13	N/A	None
GDG6 4.6.13	N/A	None
GDG7 8.7.13	N/A	None
GDG8 9.7.13	N/A	None
GDG9 18.09.13	N/A	None
GDG10 25.11.13	N/A	None
GDG11 26.11.13	N/A	None
GDG12 23.01.14	N/A	None
GDG13 24.01.14	N/A	None
GDG14 26.02.14	No new declarations of interest	None

1 ## B.16 Co-optee Mark Devonald

2

GDG meeting	Declaration of Interests	Action taken
Original DoI 23.11.12	**Non-personal pecuniary**: I am currently in discussion with MSD, Amgen and Fresenius representatives about sponsorship of an educational meeting on acute kidney injury which I am organizing, to be held in or near Nottingham on 20 April 2013. No fee will be paid to me personally. **Personal non-pecuniary**: I have published in the field of acute kidney injury and lead a research group which has developed an electronic alert system for acute kidney injury..	Declare and participate
GDG1 31.10.12	N/A	None
GDG2 11.12.12	N/A	None
GDG3 16.1.13	N/A	None
GDG4 20.3.13	N/A	None
GDG5 30.4.13	No new declarations of interest	None
GDG6 4.6.13	N/A	None
GDG7 8.7.13	N/A	None
GDG8 9.7.13	N/A	None
GDG9 18.09.13	N/A	None
GDG10 25.11.13	N/A	None
GDG11 26.11.13	N/A	None
GDG12 23.01.14	N/A	None
GDG13 24.01.14	N/A	None
GDG14 26.02.14	N/A	None

B.17 Marie McKenniff

GDG meeting	Declaration of Interests	Action taken
Original DoI 10.6.13	None	None
GDG1 31.10.12	N/A	None
GDG2 11.12.12	N/A	None
GDG3 16.1.13	N/A	None
GDG4 20.3.13	N/A	None
GDG5 30.4.13	N/A	None
GDG6 4.6.13	N/A	None
GDG7 8.7.13	No new declarations of interest	None
GDG8 9.7.13	N/A	None
GDG9 18.09.13	N/A	None
GDG10 25.11.13	N/A	None
GDG11 26.11.13	N/A	None
GDG12 23.01.14	N/A	None
GDG13 24.01.14	N/A	None
GDG14 26.02.14	N/A	None

B.18 Andrew Ludman

GDG meeting	Declaration of Interests	Action taken
Original DoI 6.8.12	None	None

GDG1 31.10.12	No new declarations of interest	None
GDG2 11.12.12	No new declarations of interest	None
GDG3 16.1.13	No new declarations of interest	None
GDG4 20.3.13	No new declarations of interest	None
GDG5 30.4.13	No new declarations of interest	None
GDG6 4.6.13	**Personal pecuniary interest:** Educational grant from Servier of £600 to cover part of the reasonable travel costs of attending the European Society of Cardiology Heart Failure congress- May 2013.	Declare and participate
GDG7 8.7.13	No new declarations of interest	None
GDG8 9.7.13	No new declarations of interest	None
GDG9 18.09.13	No new declarations of interest	None
GDG10 25.11.13	No new declarations of interest	None
GDG11 26.11.13	No new declarations of interest	None
GDG12 23.01.14	No new declarations of interest	None
GDG13 24.01.14	No new declarations of interest	None
GDG14 26.02.14	No new declarations of interest	None

B.19 NCGC Staff

GDG meeting	Declaration of Interests	Action taken
GDG1 31.10.12	In receipt of NICE commissions.	None
GDG2 11.12.12	No new declarations of interest	None
GDG3 16.1.13	No new declarations of interest	None
GDG4	**Edward Griffin personal pecuniary interest**: Previously	Declare and

20.3.13	employed in the biotechnology industry for Amgen Ltd (up to December 2012). I worked on denosumab in oncology. The company also promote in the UK in anaemia, osteoporosis and idiopathic thrombocytopenia.	participate. Amgen do not make any cardiology drugs so no COI exists.
GDG5 30.4.13	No new declarations of interest	None
GDG6 4.6.13	No new declarations of interest	None
GDG7 8.7.13	No new declarations of interest	None
GDG8 9.7.13	No new declarations of interest	None
GDG9 18.09.13	No new declarations of interest	None
GDG10 25.11.13	No new declarations of interest	None
GDG11 26.11.13	No new declarations of interest	None
GDG12 23.01.14	No new declarations of interest	None
GDG13 24.01.14	No new declarations of interest	None
GDG14 26.02.14	No new declarations of interest	None

Appendix C: Review protocols

C.1 Natriuretic peptides

Table 1: Clinical review protocol: Natriuretic peptides

Component	Description
Review question	In people with suspected (or under investigation for) acute heart failure, is the addition of natriuretic peptides to the standard initial investigations (using ECG, chest x-ray and blood tests) more accurate compared to standard initial investigations, clinical judgement and each other?
Objectives	Improve speed and accuracy of acute heart failure diagnosis
Population / Target condition	All adults with suspected (under investigation for) acute heart failure those presenting in an acute care (non-primary care) setting. Definition of condition:

	Rapid worsening or onset of signs and symptoms of heart failure. This is characterised by symptoms such as breathlessness, ankle swelling and fatigue) and signs (elevated jugular venous pressure, pulmonary crackles and displaced apex beat) resulting from an abnormality of cardiac structure or function.
Subgroups	Stratified by groups of patients with pulmonary oedema, cardiogenic shock, acute right-sided heart failure or acute decompensated heart failure.
Index test	Natriuretic peptides: BNP NT-proBNP ANP NT-proANP mid regional-proANP As a diagnostic accuracy with or without cut off Blood concentration of natriuretic peptides
Comparator tests	N/A
Reference standard	Using ECG, chest X-ray and blood tests plus clinical judgement
Outcomes	• Specificity • Sensitivity • Negative predictive value • Positive predictive value • Positive likelihood ratio • Negative likelihood ratio • Most accurate threshold (for instance the European guideline mentions a threshold of 100 pg/mL) • ROC curve • Destination of care May want to discuss consequences of false positive and false negative outcome. e.g. Mortality
Study design	Cross sectional studies, retrospective or prospective case reviews and cohort studies.
Exclusion	Non acute care (Primary care and community) settings Case-control studies Urinary natriuretic peptides Screening for left or right ventricular dysfunction Use of natriuretic peptides in diagnosis of pleural effusions of unknown aetiology
Setting	Are there particular settings in which this test is carried out and does the setting affect the interpretation of test results?
Equalities	Check any equalities identified in the scope equality form. Is this test available in rural areas as much as in urban hospitals? Levels are different in men and women
Review Strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using a modified version of the QUADAS-II checklist. Synthesis of data • Diagnostic meta-analysis will be conducted where appropriate.

1

1 **Table 2: Appended economic review protocol: Natriuretic peptides**

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 F.
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 [(a)] • foreign language articles **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.

(a) Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.

C.2 Echocardiography

Table 3: Clinical review protocol: Echocardiography

Review question	In adults with suspected acute heart failure does echocardiography early compared to later echocardiography in addition to standard investigations (using ECG, chest x-ray and blood tests) improve outcome?
Objectives	To estimate the clinical and cost effectiveness of early access to echocardiography.
Criteria	Population Adults with suspected (or under investigation for) acute heart failure excluding primary care and community settings Intervention and comparison Early echocardiography vs. later echocardiography Outcomes • Mortality • Major adverse events • Length of hospital stay and re-admission rates • Quality of Life
Search	The databases to be searched are Medline, EMBASE and the Cochrane Library. Randomised controlled trials and non-randomised studies will be considered (no particular year or sample size restrictions) Studies will be restricted to English language only
Review strategy	Stratification • Acute heart failure with pulmonary oedema • Cardiogenic shock • Acute right-sided heart failure • Acute decompensated chronic heart failure

Table 4: Health economic review protocol: Echocardiography

Review question	All questions – health economic evidence
Objectives	To identify economic evaluations relevant to the review questions set out above.
Criteria	• Populations, interventions and comparators must be as specified in the individual review protocols above. • Studies must be of a relevant economic study design (cost–utility analysis, cost–benefit analysis, cost-effectiveness analysis, cost–consequence analysis, comparative cost analysis). • Studies must not be an abstract only, a letter, editorial or commentary, or a review of economic evaluations.**(a)** Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search	An economic study search will be undertaken using population-specific terms and an economic

strategy	study filter – see Appendix F.
Review strategy	Each study fulfilling the criteria above will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in Appendix G of the NICE guidelines manual (2012).[118] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. An economic evidence table will be completed and it will be included in the economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then an economic evidence table will not be completed and it will not be included in the economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will 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 is to include studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the GDG if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation as excluded economic studies in Appendix L. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden) • OECD countries with predominantly private health insurance systems (for example, 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. • Studies that are based on resource use and unit costs from more than 10 years ago will be downgraded in terms of applicability. *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 outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

C.3 Invasive monitoring

Table 5: Clinical review protocol: Invasive monitoring

Review question	Is the addition of invasive monitoring more clinically/cost-effective over and above non-invasive monitoring to improve outcome?
Objectives	To estimate the clinical and cost-effectiveness of invasive monitoring.
Criteria	Population Adults with acute heart failure Intervention Invasive monitoring with arterial lines, central venous pressure lines or pulmonary artery catheters (PACs) Comparison All those who are not invasively monitored including those with non-invasive monitoring Outcomes • Mortality • Major cardiovascular events • Length of hospital stay • Re-admission rates • Number of patients proceeding to invasive ventilation • Measures of renal function (e.g. eGFR or serum creatinine) • Quality of life (as well as reported anxiety and pain) • Adverse events (cardiovascular)
Search	The databases to be searched are Medline, Embase, The Cochrane Library Randomised controlled trials (RCTs) and cohort studies will be considered (no particular year or sample size restrictions) Studies will be restricted to English language only
Review strategy	Stratification • Acute heart failure with pulmonary oedema • Cardiogenic shock • Acute right-sided heart failure • Acute decompensated chronic heart failure

Table 6: Health economic review protocol: Invasive monitoring

Review question	All questions – health economic evidence
Objectives	To identify economic evaluations relevant to the review questions set out above.
Criteria	• Populations, interventions and comparators must be as specified in the individual review protocols above. • Studies must be of a relevant economic study design (cost-utility analysis, cost-benefit analysis, cost-effectiveness analysis, cost-consequence analysis, comparative cost analysis). • Studies must not be an abstract only, a letter, editorial or commentary, or a review of economic evaluations.[(a)] Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	An economic study search will be undertaken using population-specific terms and an economic study filter – see Appendix F.
Review strategy	Each study fulfilling the criteria above will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in Appendix G of

	the NICE guidelines manual (2012).[118] Inclusion and exclusion criteria • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. An economic evidence table will be completed and it will be included in the economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then an economic evidence table will not be completed and it will not be included in the economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. Where there is discretion The health economist will 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 is to include studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the GDG if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation as excluded economic studies in Appendix M. The health economist will 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. • Studies that are based on resource use and unit costs from more than [10] years ago will be downgraded in terms of applicability. *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 outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

(a) Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.

C.4 Opiates

Table 7: Clinical review protocol: Opiates

Review question	**In patients with acute heart failure are opiates as an adjunct to other first line therapies more clinically or cost effective compared to placebo and to other treatments alone?**

Objectives	To estimate the effectiveness and cost-effectiveness of opiates as an adjunct to therapy in acute heart failure.
Criteria	Population Adults with acute heart failure Intervention Morphine or diamorphine Comparison Standard medical care or placebo Outcome • Mortality • Major cardiovascular events • Length of hospital stay and re-admission rates • Number of patients proceeding to invasive ventilation • Measures of dyspnoea (breathing rate or breathlessness scales) • Quality of life (as well as reported anxiety and pain) • Adverse events (particularly respiratory arrest and nausea)
Search	The databases to be searched are Medline, Embase, The Cochrane Library. Systematic reviews (SRs), randomised controlled trials (RCTs) (no particular year or sample size restrictions) and observational studies will be considered Studies will be restricted to English language only
Review strategy	Stratification • Acute heart failure with pulmonary oedema • Cardiogenic shock • Acute right-sided heart failure • Acute decompensated chronic heart failure

Table 8: Appended economic review protocol: Opiates

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 F.
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 <u>Where there is discretion</u> 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.

(b) Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.

C.5 Diuretic administration

Table 9: Review protocol: Diuretic administration strategy in acute heart failure

Review question	In patients with acute heart failure which diuretic administration strategy is the most clinically/cost-effective to improve outcome?
Objectives	To estimate the clinical and cost-effectiveness of differing administration strategies of diuretic therapy in adults with acute heart failure
Criteria	<u>Population</u> Adults with acute heart failure <u>Interventions</u> One of - using one mode of administration: • Furosemide (Oral, IV Bolus or IV infusion) • Bumetanide (Oral, IV Bolus or IV infusion)

	• Torasemide (Oral, IV Bolus or IV infusion) • Amiloride (Oral only) • Bendroflumethiazide (Oral only) • Metolazone (Oral only) • Hydrochlorothiazide (Oral only) • Indapamide (Oral only) Plus any IV strategy using adjunctive hypertonic saline solution (HSS) <u>Comparisons</u> Any of the interventions listed above <u>Outcomes</u> • Mortality • Dyspnoea • Urine output • Weight loss • Length of hospital stay and re-admission rates • Quality of life • Serum creatinine level (or other measure of renal function for example eGFR) • Adverse events (particularly renal adverse events and ototoxicity)
Search	The databases to be searched are Medline, Embase, The Cochrane Library, Only systematic reviews and randomised controlled trials (RCTs) will be considered (no particular year or sample size restrictions) Studies will be restricted to English language only
Review strategy	<u>Stratification</u> • Acute heart failure with pulmonary oedema • Cardiogenic shock • Acute right-sided heart failure • Acute decompensated chronic heart failure

Table 10: Appended economic review protocol: Diuretic administration strategy in acute heart failure

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 F.
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 **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.

(c) Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.

C.6 Vasodilators

Table 11: Clinical review protocol: Vasodilators

Review question	In patients with acute heart failure are vasodilators more clinically/cost-effective than placebo to improve clinical outcomes?
Objectives	To estimate the effectiveness and cost effectiveness of vasodilator therapy in acute heart

	failure
Criteria	Population Adults with acute heart failure Interventions • Glyceryl trinitrate(GTN)/Nitroglycerin/e • Isosorbide dinitrate • Sodium nitroprusside Comparison • Placebo (medical care) Outcomes • Mortality • Major cardiovascular events • Length of hospital stay and readmission rates • Quality of life • Dyspnoea • Haemodynamic outcomes: e.g. pulmonary capillary wedge pressure (PCWP), cardiac index • Discontinuation of therapy • Adverse events (particularly headache and hypotension)
Search	The databases to be searched are Medline, Embase, The Cochrane Library, Only systematic reviews and randomised controlled trials (RCTs) will be considered (no particular year or sample size restrictions) Studies will be restricted to English language only
Review strategy	Stratification • Acute heart failure with pulmonary oedema • Cardiogenic shock • Acute right-sided heart failure • Acute decompensated chronic heart failure Subgroups • Acute heart failure with known aortic stenosis • Acute heart failure with ischaemia or infarction

Table 12: Appended economic review protocol: Vasodilators

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 F.
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[(a)] • foreign language articles **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.

(d) Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.

C.7 Inotropes and vasopressors

Table 13: Review protocol: Inotropes/vasopressors

Review question	• In patients with acute heart failure are inotropes safe and clinically/cost effective compared to placebo to improve outcome • In patients with acute heart failure are vasopressors safe and clinically/cost effective compared to placebo to improve outcome? • In patients with acute heart failure are inotropes safe and clinically/cost effective compared to vasopressors to improve outcome? These three comparisons were combined into one review question:

	In patients with acute heart failure are inotropes or vasopressors safe and clinically / cost effective compared to medical care or each other to improve outcome?
Objectives	To estimate the effectiveness and cost-effectiveness of inotropes or vasopressors compared to usual care or each other in the treatment of acute heart failure.
Criteria	Population Adults with acute heart failure and cardiogenic pulmonary oedema Intervention and comparison Inotropes (milrinone, enoximone, dobutamine, dopamine) or vasopressors (adrenaline, noradrenaline/norepinephrine, vasopressin) compared with each other, or with standard medical care generally coupled with placebo Outcomes • Mortality • Major cardiovascular events • Length of hospital stay and readmission rates • Quality of life • Dyspnoea • Discontinuation of therapy • Adverse events
Search	The databases to be searched are Medline, Embase, The Cochrane Library, Only systematic reviews and randomised controlled trials (RCTs) will be considered (no particular year or sample size restrictions) Studies will be restricted to English language only
Review strategy	Stratification • Acute heart failure with pulmonary oedema • Cardiogenic shock • Acute right-sided heart failure • Acute decompensated chronic heart failure

Table 14: Appended economic review protocol: : Inotropes/vasopressors

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 F.
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 <u>Where there is discretion</u> 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.

(e) Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.

C.8 Non-invasive ventilation

Table 13: Review protocol: Non-invasive ventilation

Review question	**In people with confirmed acute heart failure and cardiogenic pulmonary oedema is non-invasive positive pressure ventilation (CPAP and/or BiPAP) more clinical and cost effective than standard medical care alone to improve outcome?**
Objectives	To estimate the effectiveness and cost-effectiveness of non-invasive ventilation compared to medical care in the treatment of acute heart failure with cardiogenic pulmonary oedema.
Criteria	<u>Population</u> Adults with acute heart failure and cardiogenic pulmonary oedema <u>Intervention and comparison</u> Continuous positive airway pressure (CPAP) and bilevel ventilation (BiPAP) vs. medical care

	(any form of medical care, such as oxygen by face mask, diuretics or nitrates, provided for the management of cardiogenic pulmonary oedema, excluding non-invasive positive pressure ventilation (NIPPV) and alternative methods of ventilatory support). Outcomes • Mortaliy • Intubation rates • Myocardial infarction • Quality of life
Search	The databases to be searched are Medline, Embase and the Cochrane Library. Only systematic reviews and randomised controlled trials will be considered (no particular year or sample size restrictions). Studies will be restricted to English language only.
Review strategy	Subgroups Setting / follow-up times

1 **Table 14: Appended economic review protocol: Non-invasive ventilation**

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 F.
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(a) • foreign language articles **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.

(a) Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.

C.9 Mechanical Ventilation

Table 15: Review protocol: Mechanical Ventilation

Review question	What are the predictors of outcome in mechanically ventilated acute heart failure patients?
Objectives	To determine the predictors of outcome in mechanically ventilated acute heart failure patients
Criteria	**Population:** Adults with acute heart failure who are mechanically ventilated **Prognostic Factors:** Any **Potential prognostic factors identified by the GDG:** • Age • Aetiology of heart failure • BNP • Blood pressure • Killip Class • LV ejection fraction • Hyponatraemia • Renal disease • Body mass index • Inotropic / vasopressor support • Urinary output • Infection (particularly ventilator associated pneumonia) • APACHE score • Organ failure score **Outcomes:** • Mortality

	• Length of mechanical ventilation • Major cardiovascular events • Length of hospital stay • Re-admission rates • Admission to critical care units • Quality of life • Adverse events (organ failure)
Search	The databases to be searched are Medline, Embase, The Cochrane Library Systematic reviews, randomised controlled trials (RCTs) and observational studies will be considered (no particular year or sample size restrictions) Studies will be restricted to English language only
Review strategy	Studies using only univariate analysis will be excluded

1 **Table 16: Appended economic review protocol: Mechanical Ventilation**

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 F.
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[(a)] • foreign language articles **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.

(a) Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.

C.10 Ultrafiltration

Table 17: Review protocol: Ultrafiltration

Review question	In patients with acute heart failure is ultrafiltration more clinically/cost-effective than diuretic therapy alone or in addition to diuretic therapy to improve outcome?
Objectives	To estimate the clinical effectiveness and cost effectiveness of ultrafiltration as a management strategy in acute heart failure, and its optimal timing and duration
Criteria	Population - Adults (18 years and above) with AHF Intervention: • - Ultrafiltration • - Ultrafiltration in addition to diuretic therapy Comparison: • - Medical care with diuretics Outcomes: • - Mortality • - Major cardiovascular events • - Length of hospital stay and re-admission rates • - Dyspnoea • - Weight Loss • - Quality of life • - Change in renal function • Adverse events (particularly renal and cardiovascular events)
Search	The databases to be searched are Medline, Embase, The Cochrane Library, Only systematic reviews and randomised controlled trials (RCTs) will be considered (no particular year or sample size restrictions) Studies will be restricted to English language only
Review strategy	Stratification: • Acute heart failure with pulmonary oedema,

	• Cardiogenic shock, • Acute right-sided heart failure, • Acute decompensated chronic heart failure

1 **Table 18: Appended economic review protocol: Ultrafiltration**

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 F.
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 [(a)] • foreign language articles **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.

(a) Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.

C.11 Beta-blockers

Table 19: Clinical review protocol: Commencing Beta-blocker therapy

Review question	For people with confirmed acute heart failure not already on beta-blocker therapy, should beta-blocker therapy commence in hospital or following discharge?
Objectives	To estimate the clinical and cost effectiveness of Beta-blocker therapy when commenced in hospital compared to following discharge.
Criteria	Population: Adults with acute heart failure not already receiving beta-blocker treatment. Intervention and comparison: Commencing Beta-blocker therapy in hospital vs. commencing Beta-blocker therapy after discharge Outcomes: • Mortality • Major cardiovascular events • Length of hospital stay • Re-admission rates and readmission to critical care units • Quality of Life • Change in renal function • Adverse events (hyperkalaemia, cough, symptomatic hypotension)
Search	The databases to be searched are Medline, Embase, The Cochrane Library. Systematic reviews (SRs), randomised controlled trials (RCTs) (no particular year or sample size restrictions) and observational studies (n>2000) will be considered Studies will be restricted to English language only Studies restricted to univariate analyses will be excluded
Review strategy	Stratification: • Acute heart failure with pulmonary oedema, • Cardiogenic shock, • Acute right-sided heart failure, • Acute decompensated chronic heart failure

Table 20: Clinical review protocol: Continuing Beta-blocker therapy

Review question	In people with acute heart failure already on beta-blocker therapy should beta-blockers be reduced or discontinued, and if so should they be reinstated in hospital after stabilisation?
Objectives	To estimate the clinical and cost effectiveness of Beta-blocker therapy when commenced in hospital compared to following discharge.
Criteria	Population: Adults with acute heart failure who are already on beta-blocker treatment on admission to hospital Intervention and comparison: Continuing Beta-blocker therapy in hospital vs. discontinuing or reducing beta-blocker therapy Outcomes:

	Mortality Major cardiovascular events Length of hospital stay Re-admission rates and readmission to critical care units Quality of Life Change in renal function Adverse events (hyperkalaemia, cough, symptomatic hypotension)
Search	The databases to be searched are Medline, Embase, The Cochrane Library. Systematic reviews (SRs), randomised controlled trials (RCTs) (no particular year or sample size restrictions) and observational studies (n>2000) will be considered Studies will be restricted to English language only Studies restricted to univariate analyses will be excluded
Review strategy	Stratification: Acute heart failure with pulmonary oedema, Cardiogenic shock, Acute right-sided heart failure, Acute decompensated chronic heart failure

Table 21: Appended economic review protocol: Beta-blocker therapy

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
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 (a) • foreign language articles

	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.

(a) Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.

C.12 ACE inhibitors

Table 22: Clinical review protocol: Timing of ACE inhibitor therapy

Review question	For people with confirmed acute heart failure not already on angiotensin converting enzyme (ACE)-inhibitor therapy, should ACEI therapy commence in hospital or following discharge?
Objectives	To estimate the clinical and cost effectiveness of ACE inhibitor therapy when commenced in hospital compared to following discharge.
Criteria	Population: Adults with acute heart failure Intervention and comparison: Commencing ACE inhibitor therapy in hospital vs. commencing ACE inhibitor therapy after discharge Outcomes: • Mortality • Major cardiovascular events • Length of hospital stay • Re-admission rates and readmission to critical care units • Quality of Life • Change in renal function • Adverse events (hyperkalaemia, cough, symptomatic hypotension)
Search	The databases to be searched are Medline, Embase, The Cochrane Library. Systematic reviews (SRs), randomised controlled trials (RCTs) (no particular year or sample size restrictions) and observational studies (n>2000) will be considered Studies will be restricted to English language only Studies restricted to univariate analyses will be excluded
Review strategy	Stratification: • Acute heart failure with pulmonary oedema,

	• Cardiogenic shock, • Acute right-sided heart failure, • Acute decompensated chronic heart failure

1 **Table 23: Appended economic review protocol: Timing of ACE inhibitor therapy**

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 F.
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(a) • foreign language articles **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.

(a) Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.

C.13 MRA

Table 24: Clinical review protocol: Timing of MRAs therapy

Review question	For people with confirmed acute heart failure not already on angiotensin converting enzyme (ACE)-inhibitor therapy, should ACEI therapy commence in hospital or following discharge?
Objectives	To estimate the clinical and cost effectiveness of MRAs therapy when commenced in hospital compared to following discharge.
Criteria	Population: Adults with acute heart failure Intervention and comparison: Commencing MRAs therapy in hospital vs. commencing MRAs therapy after discharge Outcomes: • Mortality • Major cardiovascular events • Length of hospital stay • Re-admission rates and readmission to critical care units • Quality of Life • Change in renal function • Adverse events (hyperkalaemia, cough, symptomatic hypotension)
Search	The databases to be searched are Medline, Embase, The Cochrane Library. Systematic reviews (SRs), randomised controlled trials (RCTs) (no particular year or sample size restrictions) and observational studies (n>2000) will be considered Studies will be restricted to English language only Studies restricted to univariate analyses will be excluded
Review strategy	Stratification: • Acute heart failure with pulmonary oedema, • Cardiogenic shock, • Acute right-sided heart failure, • Acute decompensated chronic heart failure

Table 25: Appended economic review protocol: Timing of MRAs therapy

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	An economic study search was undertaken using population specific terms and an economic

strategy	study filter – see Appendix F.
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**Error! Reference source not found.** • foreign language articles **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.

(b) Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.

C.14 Aortic stenosis

Table 26: Clinical review protocol: aortic stenosis

Review question	• For people with the clinical syndrome of heart failure secondary to aortic stenosis is surgical valvular intervention more clinically or cost effective compared to medical care? • For people with the clinical syndrome of heart failure secondary to aortic stenosis is percutaneous valvular intervention more clinically or cost effective compared to medical care? • For people with the clinical syndrome of heart failure secondary to aortic stenosis is surgical valvular intervention more clinically or cost effective compared to percutaneous valvular intervention? These three comparisons were combined into one review question: **For people with the clinical syndrome of heart failure secondary to aortic stenosis are surgical valvular or percutaneous interventions more clinically or cost effective compared to best medical therapy or each other?**
Objectives	Surgical vs. percutaneous treatment for aortic stenosis
Criteria	Population: Adults with heart failure secondary to aortic stenosis Intervention: Aortic valvular surgery Intervention: Aortic valve percutaneous interventions Or Medical treatment Outcomes: • Mortality • Major cardiovascular events (MI, CVA) • Dyspnoea • Echo Criteria: Valve gradient, Ejection Fraction • Length of index hospital stay and re-admission rates including critical care units • Quality of life • Adverse events (periprocedural vascular complications, Arrhythmia)
Search	The databases to be searched are Medline, Embase, The Cochrane Library Only randomised controlled trials (RCT) will be considered (no particular year or sample size restrictions) Studies will be restricted to English language only
Review strategy	Special consideration will be placed on short and long term outcomes Subgroup analyses may include device type

Table 27: Appended economic review protocol: aortic stenosis

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 F.
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

Review question	All questions – health economic evidence
	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(a) foreign language articles 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.

(a) Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.

C.15 Mitral regurgitation

Table 28: Clinical review protocol: Mitral regurgitation

Review question	• For people with the clinical syndrome of heart failure secondary to mitral regurgitation is surgical valvular intervention more clinically or cost effective compared to medical care? • For people with the clinical syndrome of heart failure secondary to mitral regurgitation is percutaneous valvular intervention more clinically or cost effective compared to medical care?

	• For people with the clinical syndrome of heart failure secondary to mitral regurgitation is surgical valvular intervention more clinically or cost effective compared to percutaneous valvular intervention? These three comparisons were combined into one review question: **For people with heart failure with mitral regurgitation are surgical valvular or percutaneous interventions more clinically or cost effective compared to best medical therapy or each other?**
Objectives	To assess clinical and cost-effectiveness of percutaneous or surgical treatment of mitral regurgitation.
Criteria	Population Adults with heart failure secondary to mitral regurgitation Interventions Mitral valve percutaneous treatment Comparison Surgery or medical treatment Outcomes • Mortality • Major cardiovascular events (myocardial infarction) • Dyspnoea • Echocardiographic Criteria: venocontractor regurgitant jet, ejection fraction • length of index hospital stay and re-admission rates including critical care units • Quality of life • Adverse events (perioperative vascular events)
Search	The databases to be searched are Medline, Embase, The Cochrane Library Only randomised controlled trials (RCT) will be considered (no particular year or sample size restrictions) Studies will be restricted to English language only
Review strategy	Subgroup by type of mitral regurgitation: functional, mitral valve prolapse, ischaemic

Table 29: Appended economic review protocol: Mitral regurgitation

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 F
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[(a)] • foreign language articles **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.

(a) Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.

C.16 Mechanical assist devices

Table 30: Clinical review protocol: mechanical assist devices

Review question	• For people with acute heart failure is intra-aortic balloon counterpulsation more clinically / cost effective compared to medical care alone? • For people with acute heart failure are ventricular assist devices more clinically / cost effective compared to medical care (including IABP) alone These two comparisons were combined into one review question: **For people with acute heart failure is intra-aortic balloon counterpulsation more clinically or cost effective (IABP) compared to left ventricular assist devices (LVAD), medical care alone or with each other?**

Objectives	To compare the clinical and cost effectiveness of IABP, LVAD and medical care.
Criteria	Study designs Systematic reviews (SRs) and randomised controlled trials (RCTs) only Population Adults with acute heart failure Intervention Any IABPs and any LVADs Comparator Medical care alone or each other Outcomes • Mortality • Length of hospital stay • Re-admission rates • Admission to critical care units • Number of patients requiring invasive ventilation • Quality of life • Adverse events
Search	Databases MEDLINE, EMBASE, The Cochrane Library Restriction • English language only • RCTs or SRs only • No restrictions on publication date or sample size
Review strategy	Stratifications • Acute heart failure with pulmonary oedema • Cardiogenic shock • Acute right-sided heart failure • Acute decompensated chronic heart failure Divide by: • Follow-up periods Subgroup: • Type of device (e.g. first / second generation)

Table 31: Health economic review protocol: mechanical assist devices

Review question	All questions – health economic evidence
Objectives	To identify economic evaluations relevant to the review questions set out above.
Criteria	• Populations, interventions and comparators must be as specified in the individual review protocols above. • Studies must be of a relevant economic study design (cost–utility analysis, cost–benefit analysis, cost-effectiveness analysis, cost–consequence analysis, comparative cost analysis). • Studies must not be an abstract only, a letter, editorial or commentary, or a review of economic evaluations.[(a)] Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	An economic study search will be undertaken using population-specific terms and an economic study filter – see Appendix F.
Review	Each study fulfilling the criteria above will be assessed for applicability and methodological

strategy	limitations using the NICE economic evaluation checklist which can be found in Appendix G of the NICE guidelines manual (2012). **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. An economic evidence table will be completed and it will be included in the economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then an economic evidence table will not be completed and it will not be included in the economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will 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 is to include studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the GDG if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation as excluded economic studies in Appendix L. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden) • OECD countries with predominantly private health insurance systems (for example, 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. • Studies that are based on resource use and unit costs from more than 10 years ago will be downgraded in terms of applicability. *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 outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

(a) Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.

C.17 Specialist management units

Table 32: Clinical review protocol: Specialist management units

Review question	For people with suspected or confirmed acute heart failure is a specialist management unit more clinically / cost effective than general medical hospital care?
Objectives	To assess clinical and cost effectiveness of specialist management care for people with suspected or confirmed acute heart failure

Criteria	Population: Adults with suspected or confirmed acute heart failure Intervention: Specialist management units or treatment by a cardiologist or cardiology team: Definition – staff expertise / training, dedicated environment with specialist equipment for the diagnosis, treatment and monitoring of cardiac conditions treatment in a specialist management unit of non-geographical design (MDT, multi professional team, specialist care, specialist team) treatment in a specialist management unit of geographical design (heart failure unit, cardiology unit Comparison: Treatment in a general medical ward or by generalists without a specific specialty in heart failure or cardiology Other wards: e.g. surgical wards, care of the elderly wards, other wards Outcomes: • Mortality • Major cardiovascular events • Length of hospital stay and re-admission rates including length of stay and readmission to critical care to critical care units • Quality of life / patient satisfaction • Adverse events
Search	Studies published since 1999
Review strategy	Only studies with multivariate analyses will be included Studies restrictued to specialist nursing will be excluded. Stratification: • Acute heart failure with pulmonary oedema, • Cardiogenic shock, • Acute right-sided heart failure, • Acute decompensated chronic heart failure

1 **Table 33: Appended economic review protocol: Specialist management units**

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 F.
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

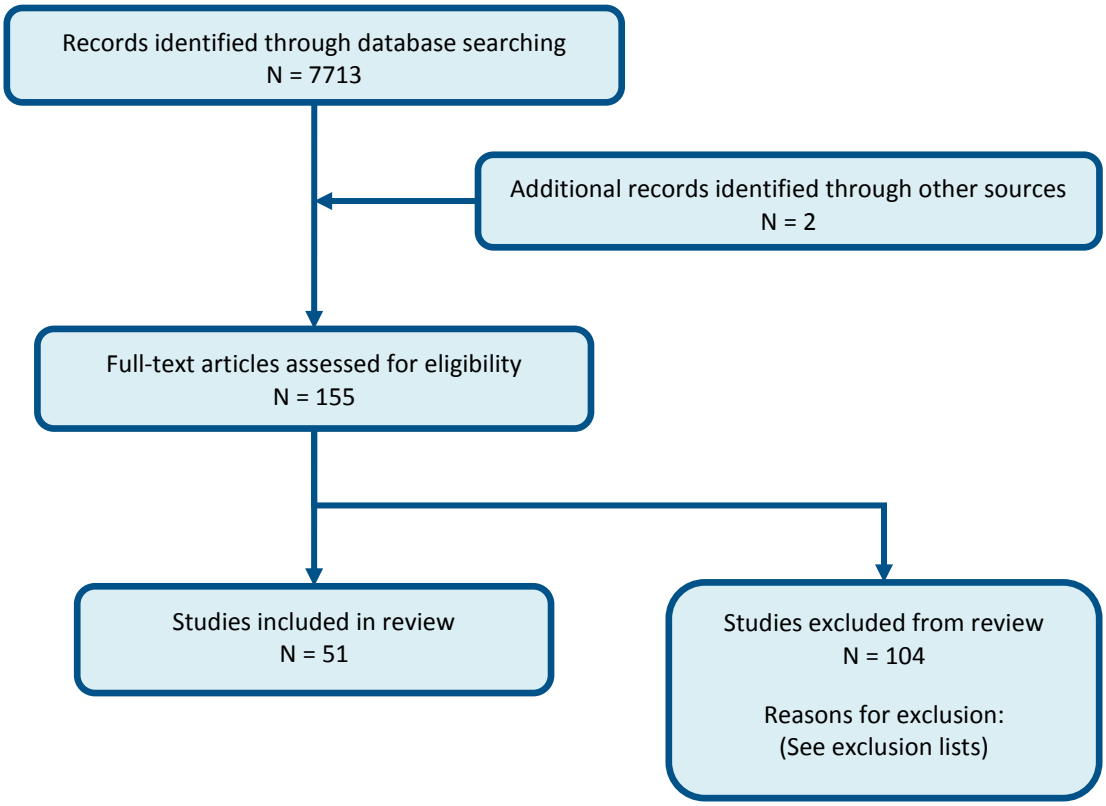
	exclusions occur on this basis, this should be noted in the relevant section of the guideline with references. Also exclude: • unpublished reports unless submitted as part of a call for evidence • abstract-only studies • letters • editorials • reviews of economic evaluations[(a)] • foreign language articles **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.

(a) Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.

Appendix D: Clinical article selection

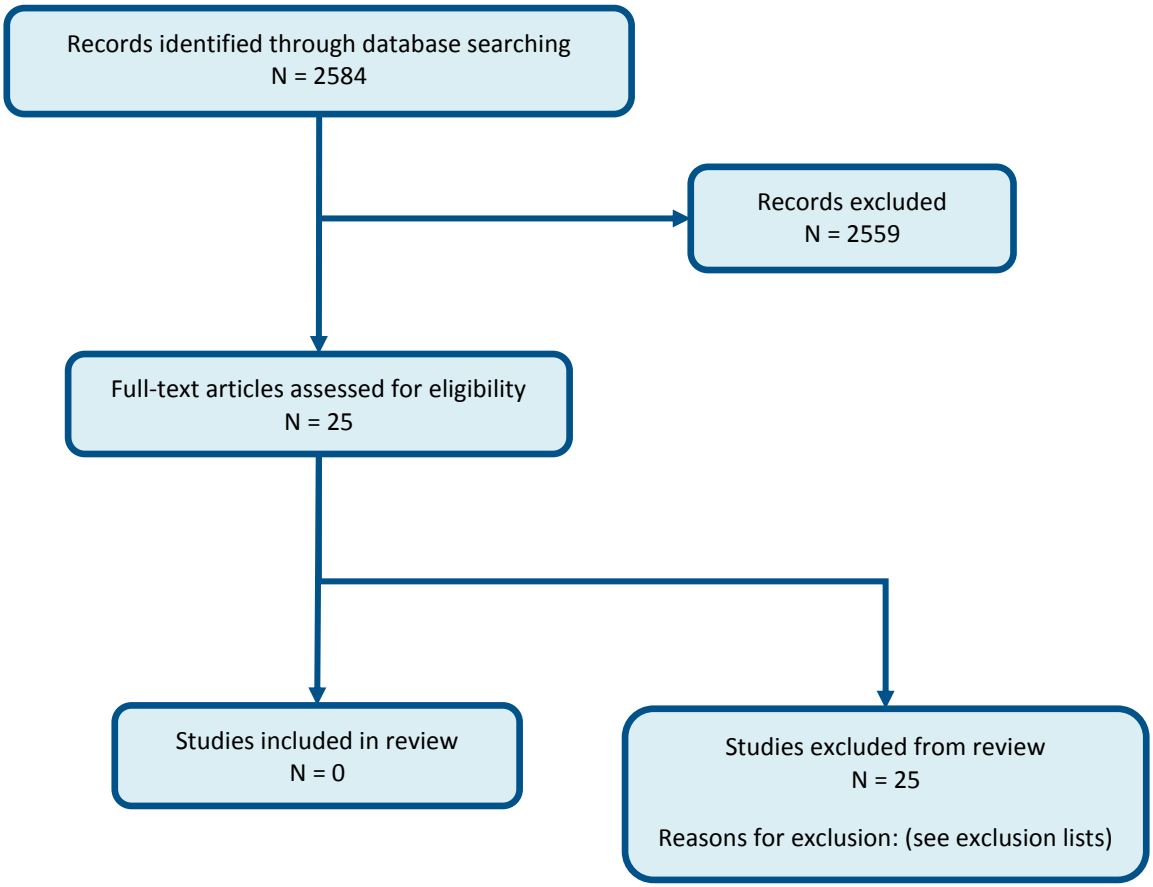
D.1 Natriuretic peptides

Figure 1: Flow diagram of clinical article selection for natriuretic peptides review



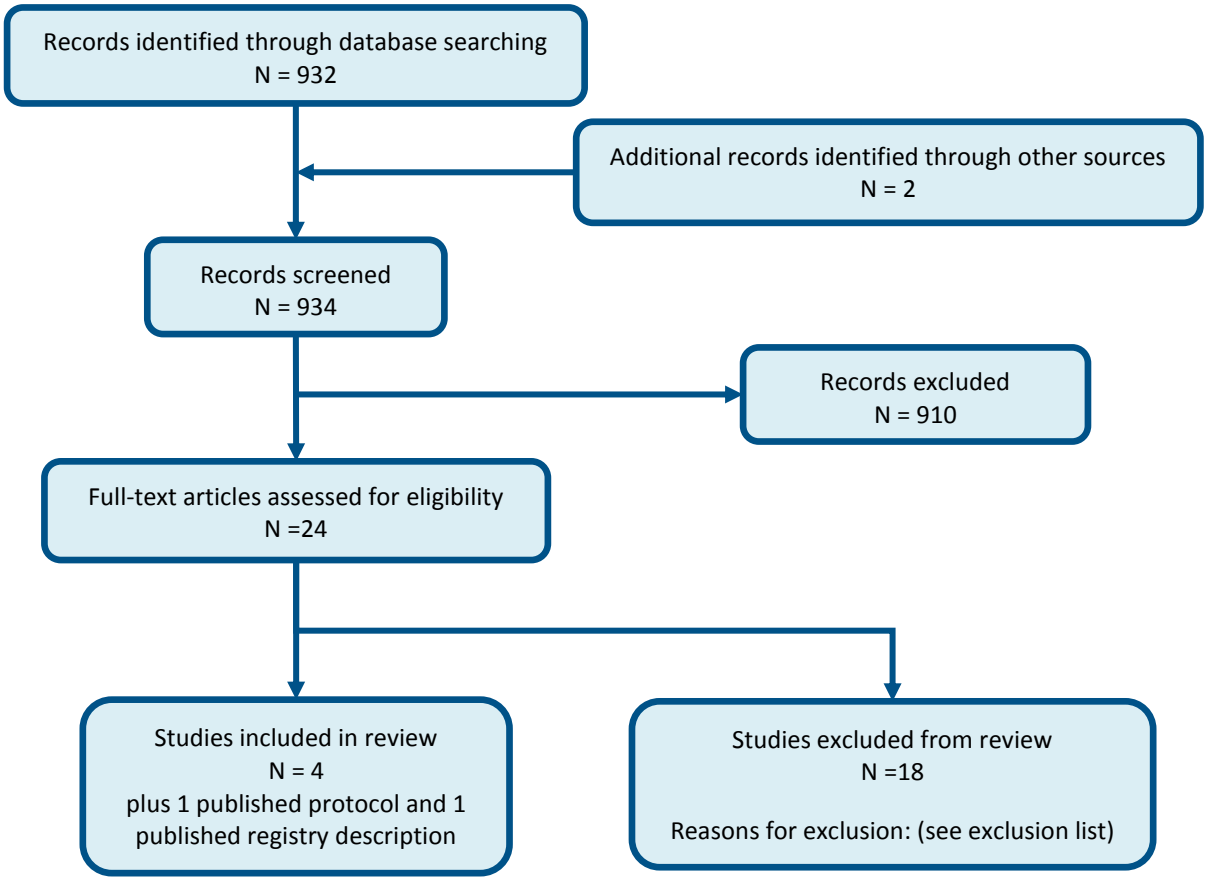
D.2 Echocardiography

Figure 2: Flow diagram of article selection for timing of echocardiography review



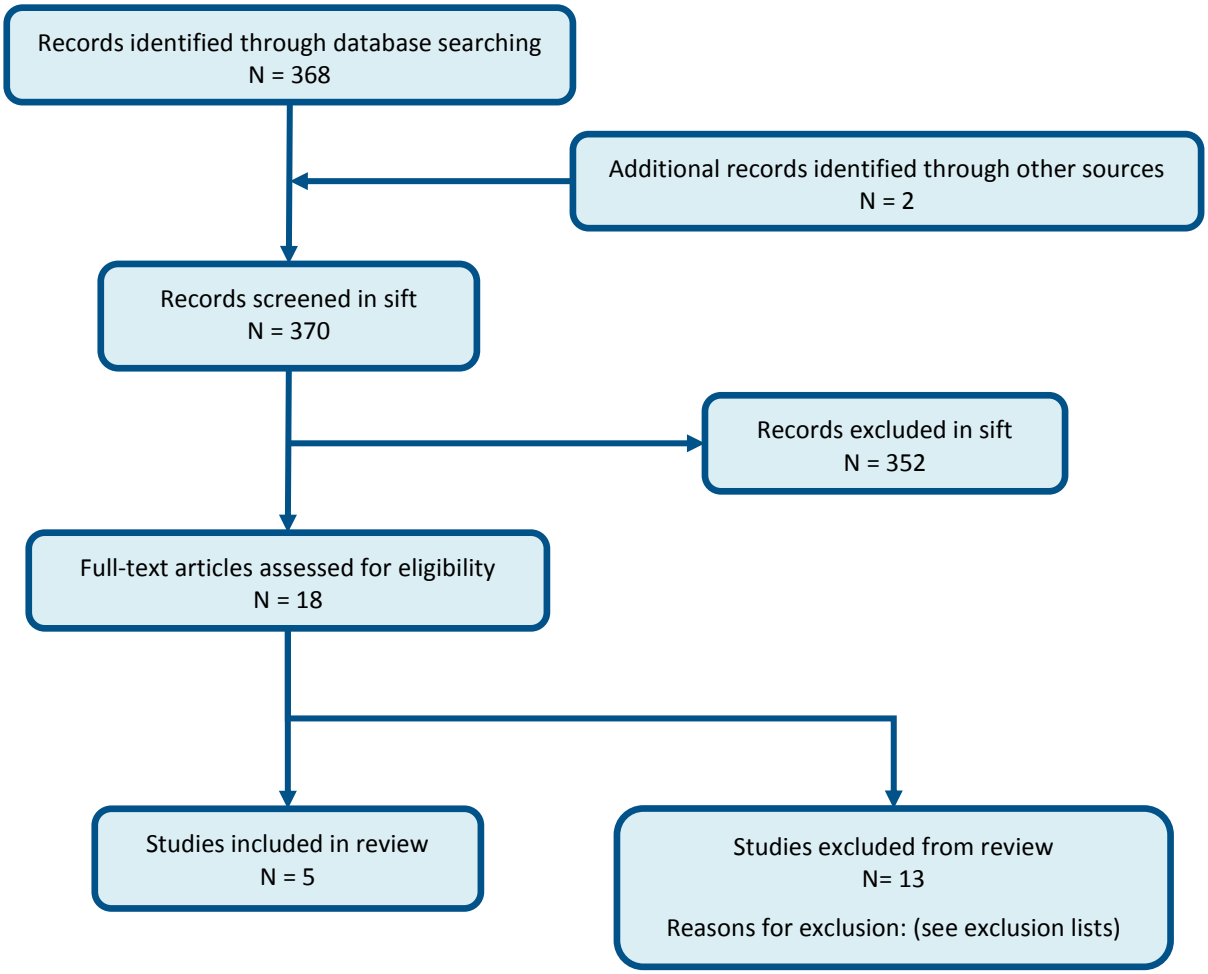
D.3 Invasive monitoring

Figure 3: Flow diagram of article selection for the review of invasive monitoring



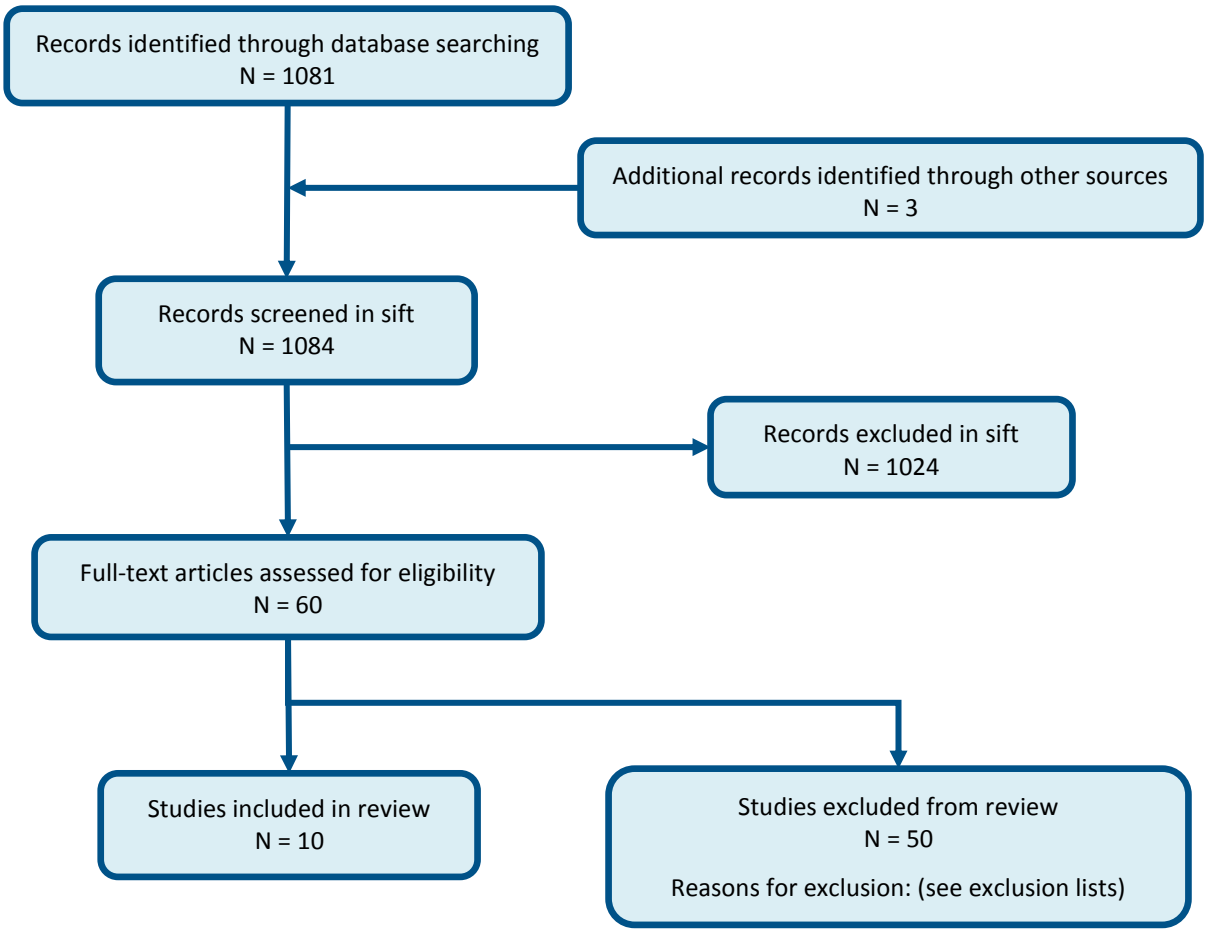
D.4 Opiates

Figure 4: Flow diagram of clinical article selection for Opiates in Acute Heart Failure



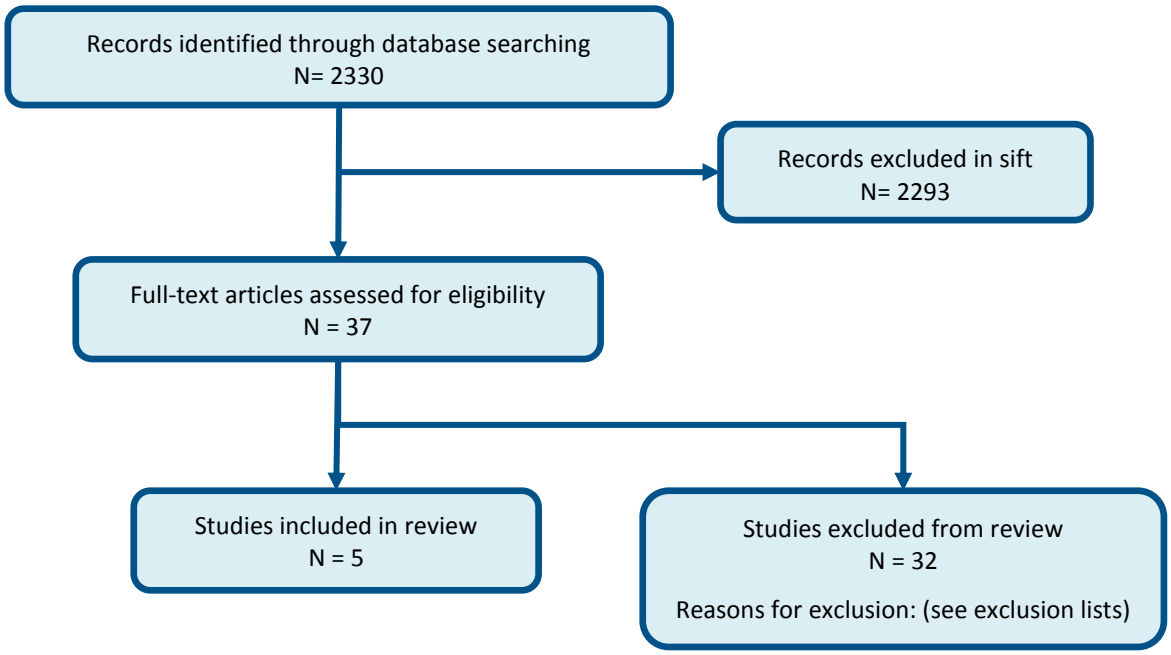
D.5 Diuretic administration

Figure 5: Flow diagram of clinical article selection for method of diuretic administration review



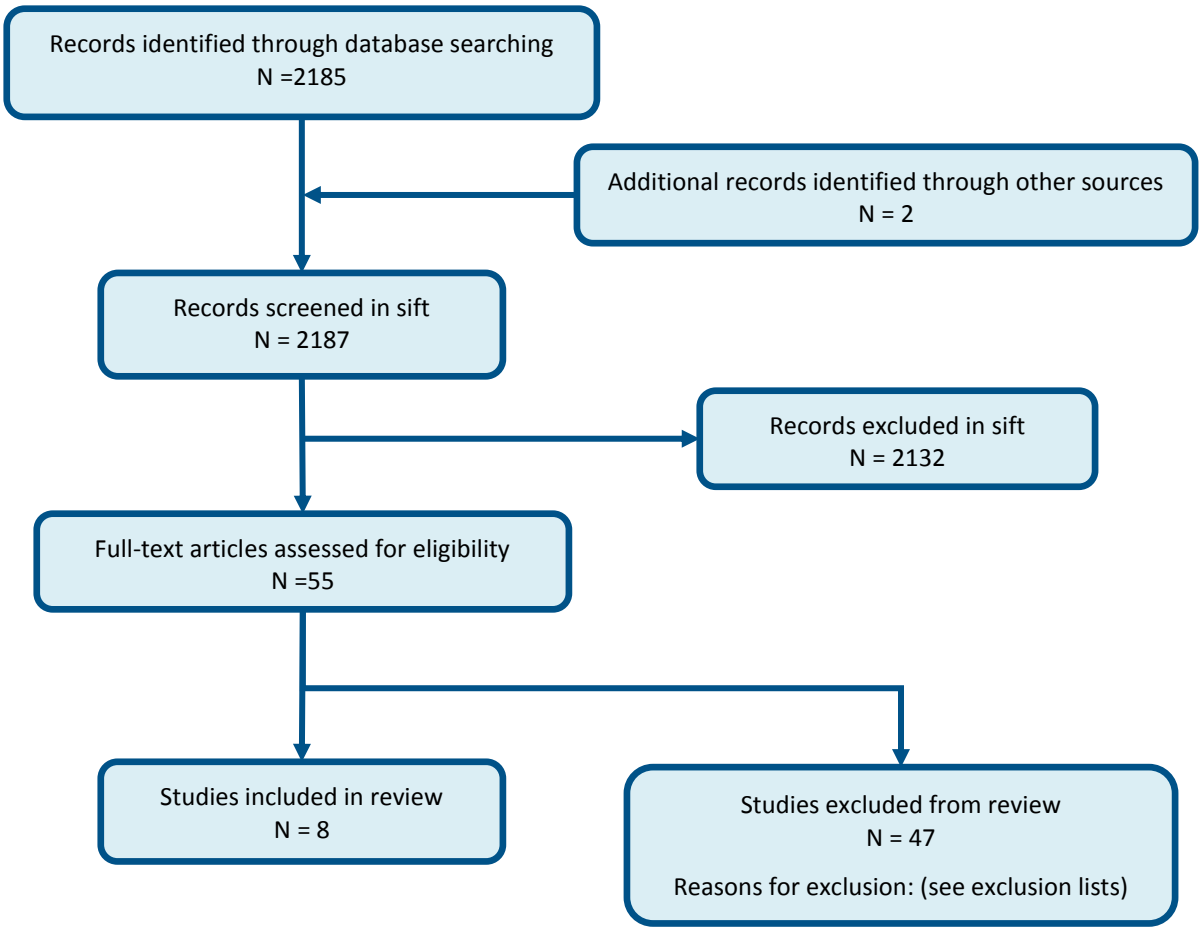
D.6 Vasodilators

Figure 6: Flow diagram of clinical article selection for vasodilators review



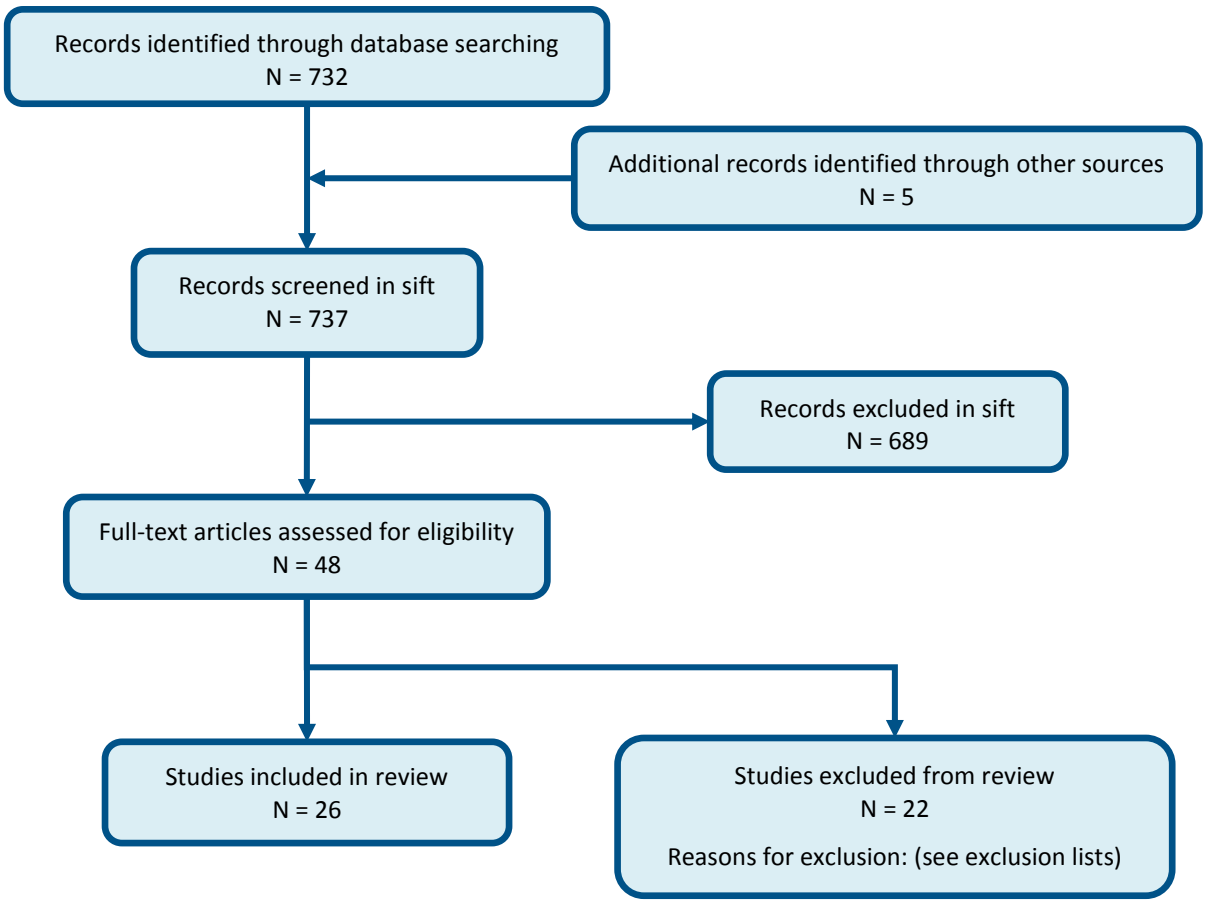
D.7 Inotropes and vasopressors

Figure 7: Flow diagram of clinical article selection for inotrope/vasopressor review



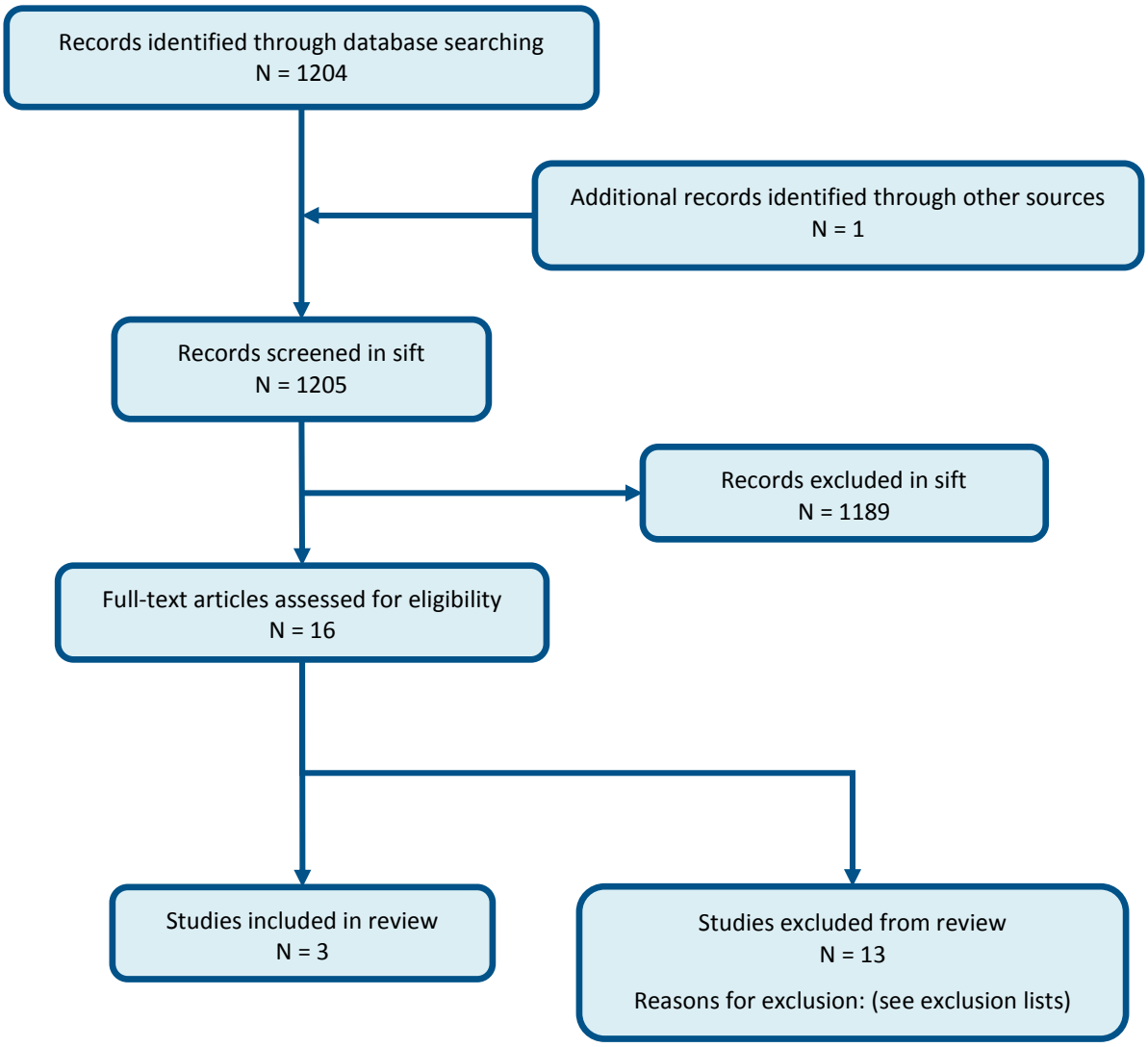
D.8 Non-invasive ventilation

Figure 8: Flow diagram of clinical article selection for non-invasive ventilation review



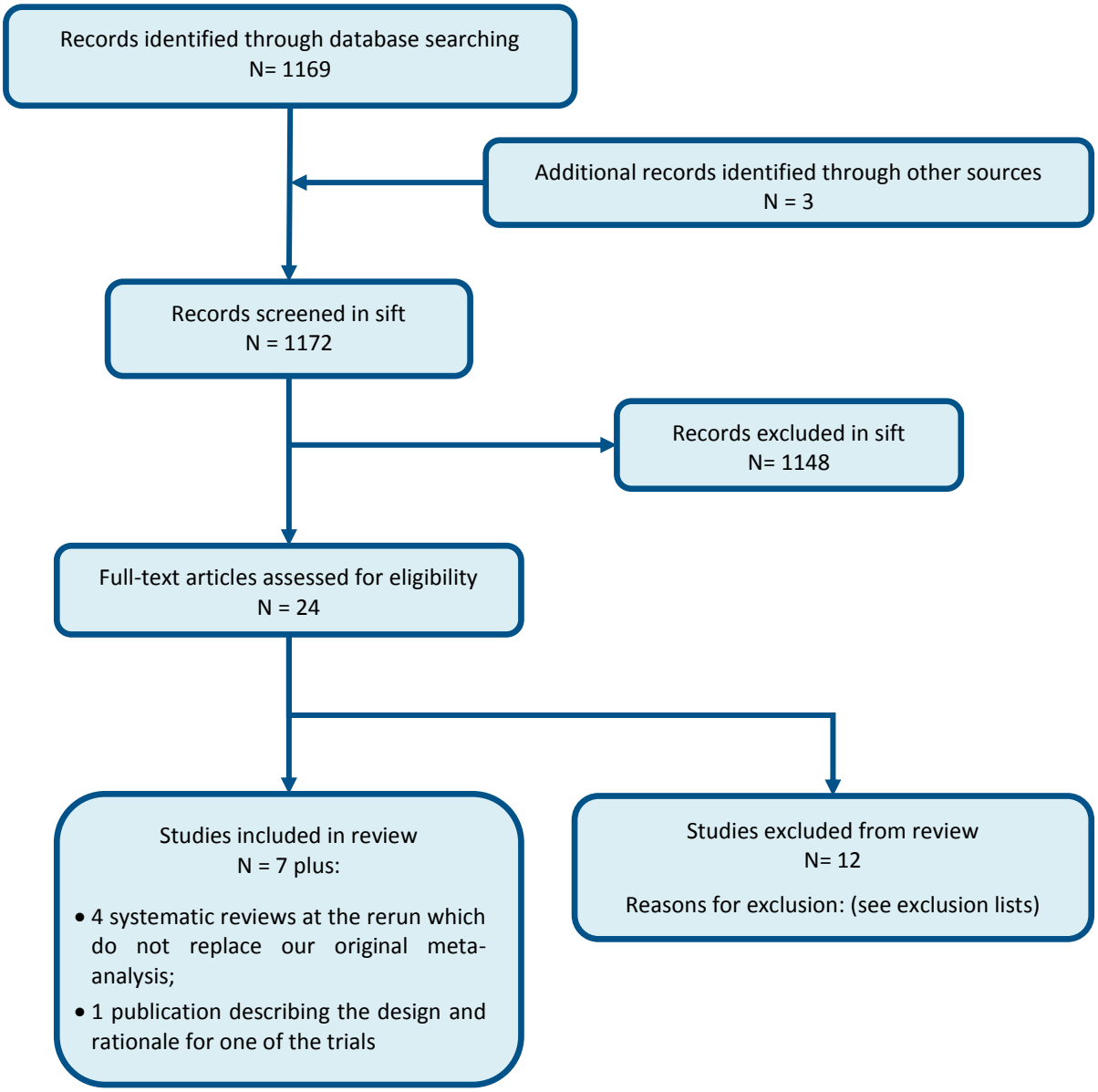
D.9 Mechanical ventilation

Figure 9: Flow diagram of clinical article selection for mechanical ventilation review



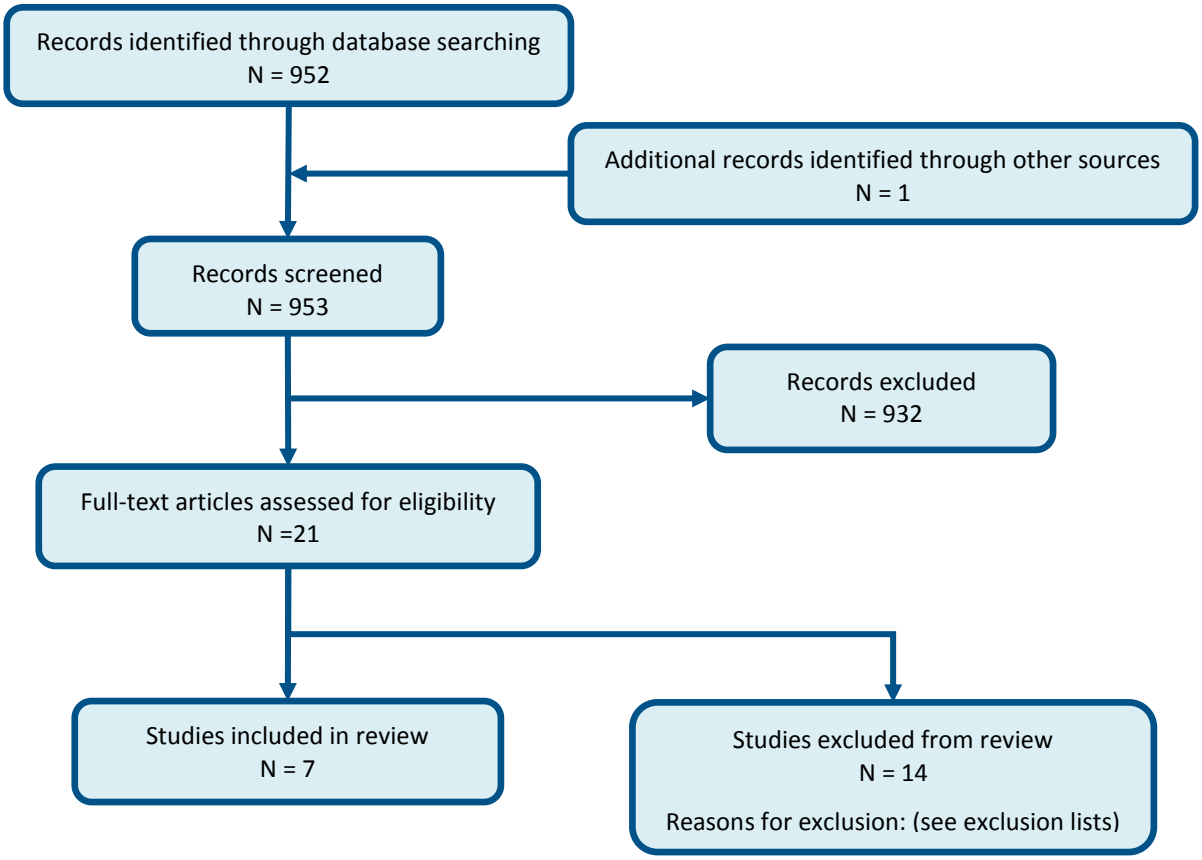
D.10 Ultrafiltration

Figure 10: Flow diagram of clinical article selection for ultrafiltration review



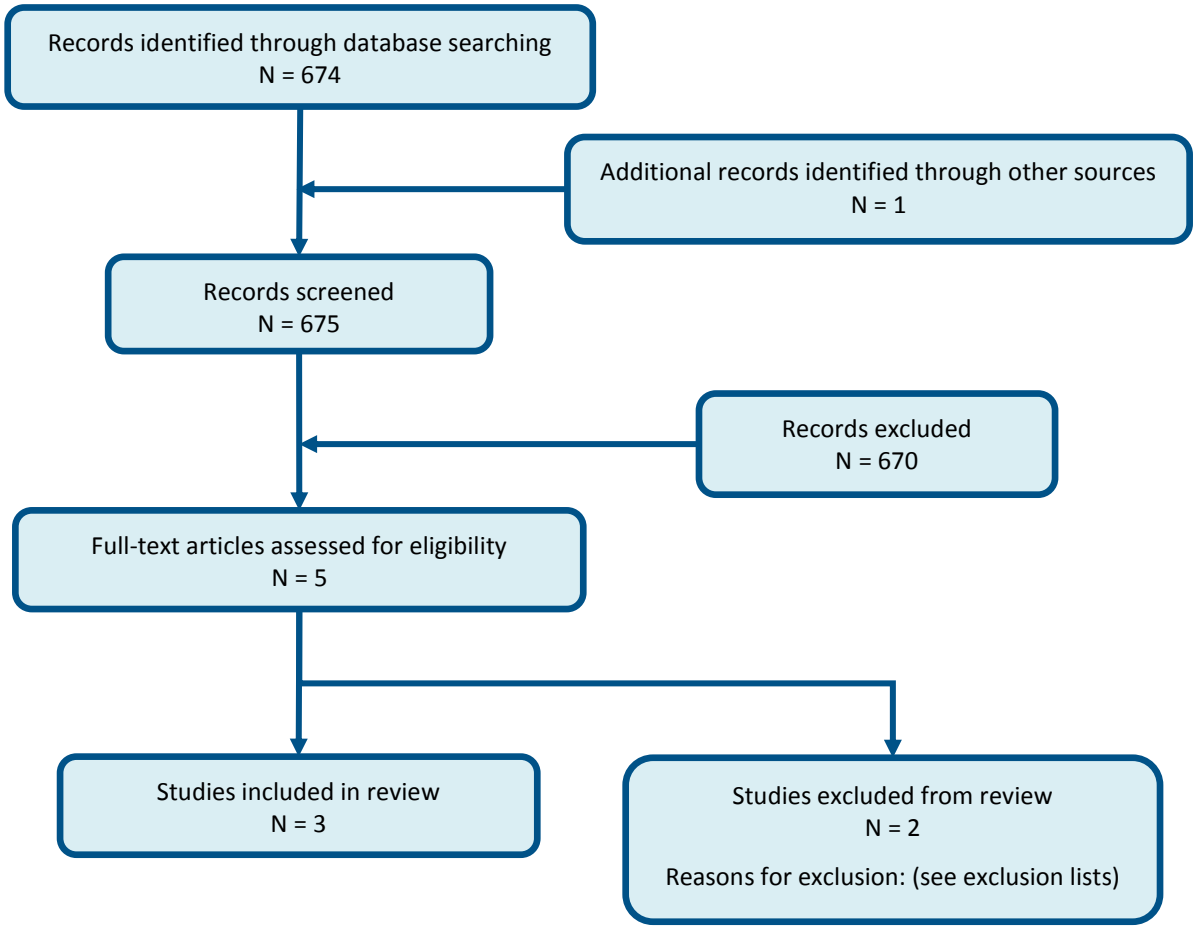
D.11 Beta-blocker

Figure 11: Flow diagram of clinical article selection for timing of beta-blocker review (2 review questions covered by one search)



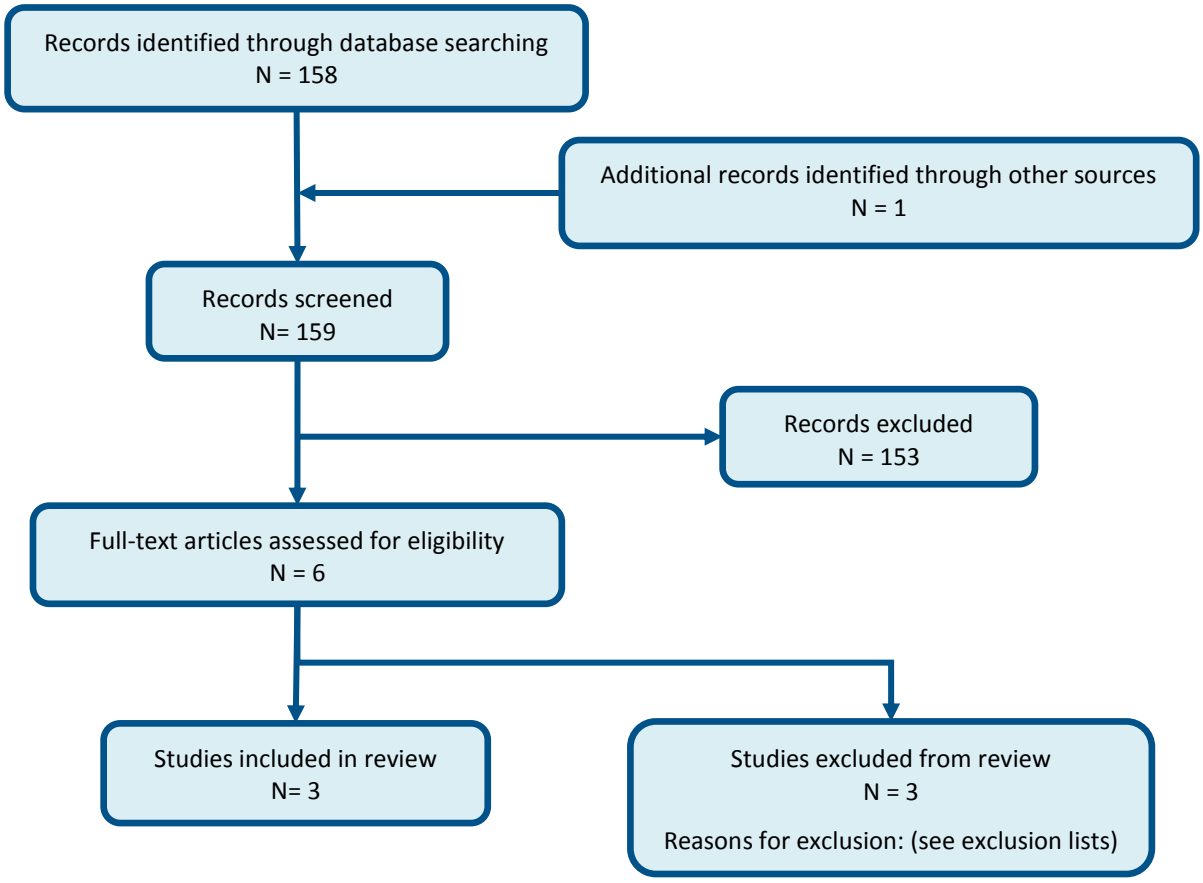
D.12 ACE inhibitors

Figure 12: Flow diagram of clinical article selection for timing of ACEi review



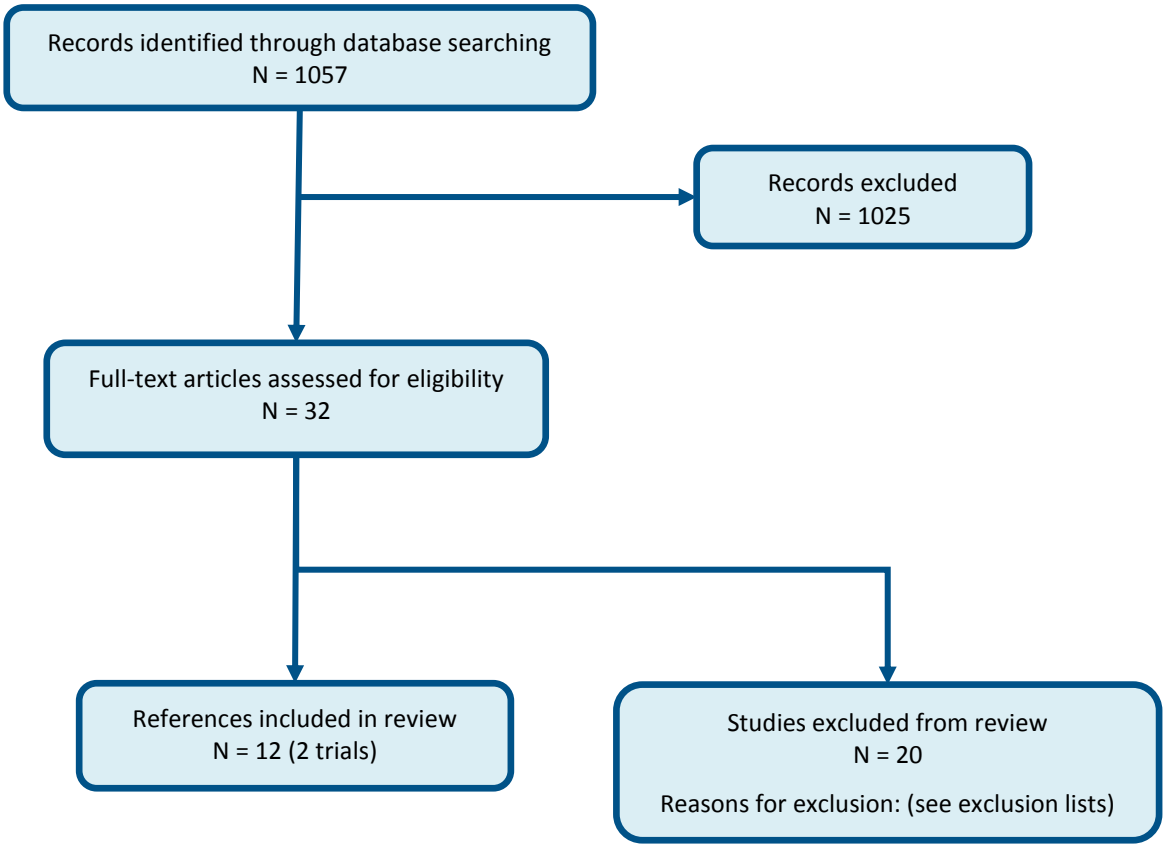
D.13 MRA aldosterone antagonist

Figure 13: Flow diagram of clinical article selection for timing of MRA aldosterone antagonist review



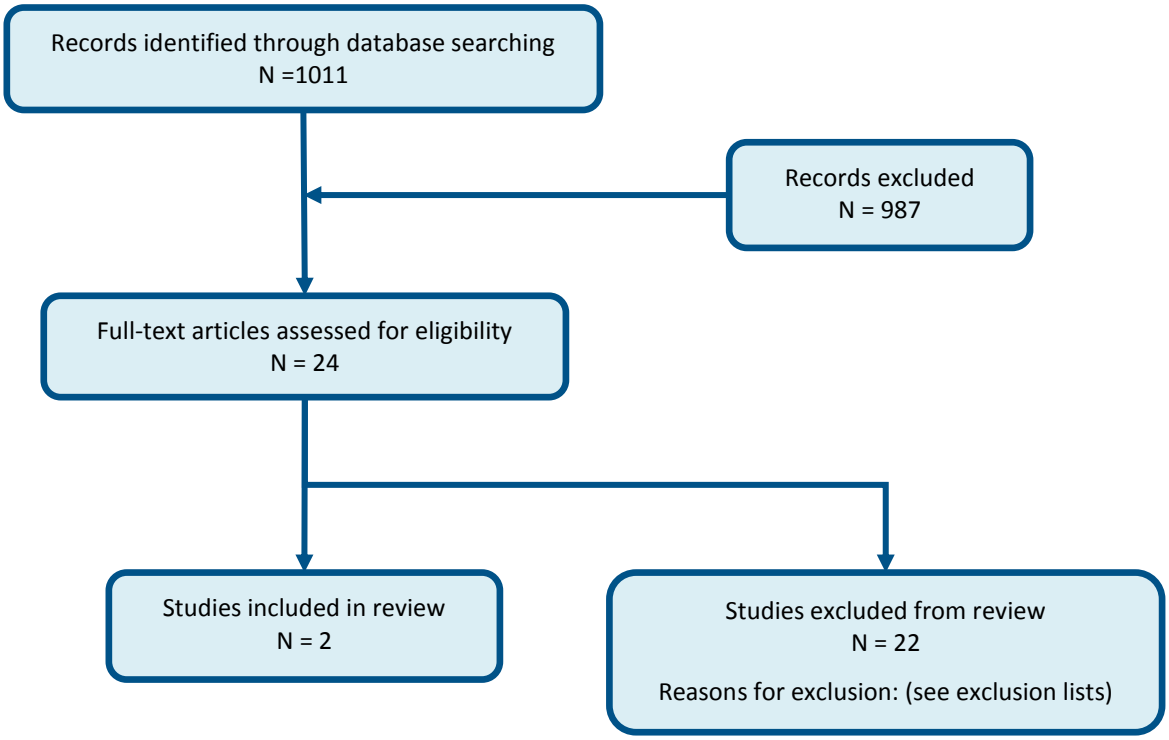
D.14 Aortic stenosis

Figure 14: Flow diagram of clinical article selection for aortic stenosis review



D.15 Mitral regurgitation

Figure 15: Flow diagram of clinical article selection for mitral regurgitation review



D.16 Mechanical assist devices

Figure 16: Flow diagram of clinical article selection for the review of IABP vs. Control

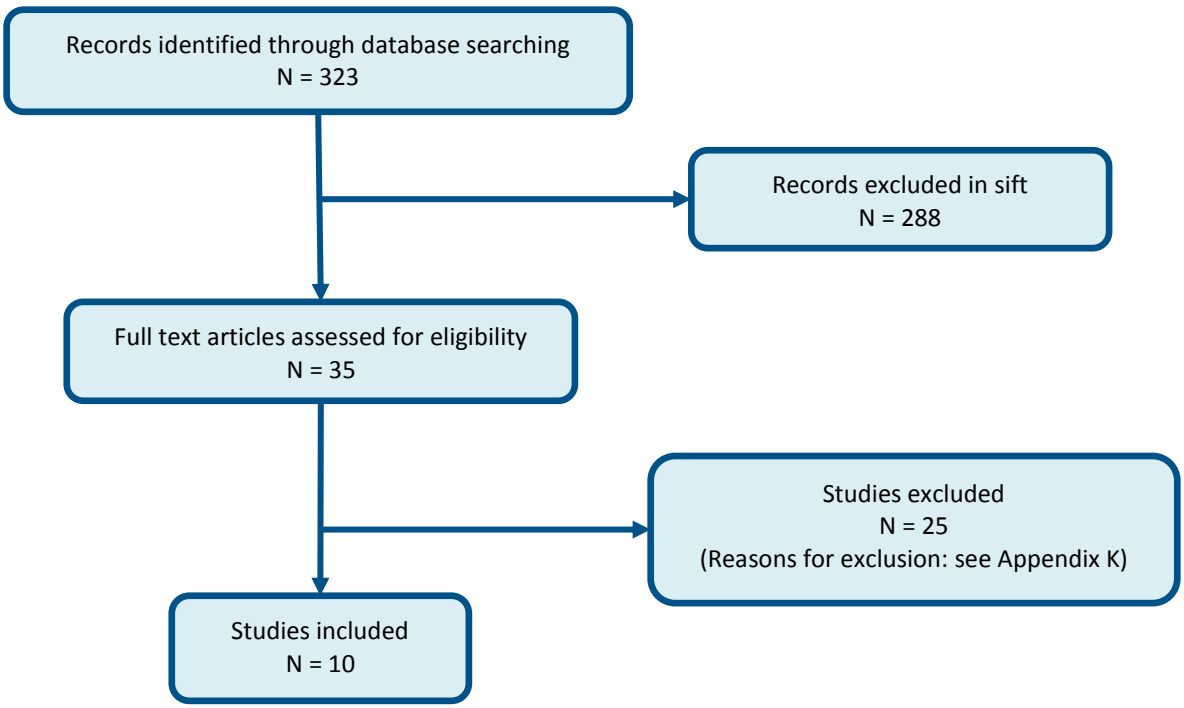
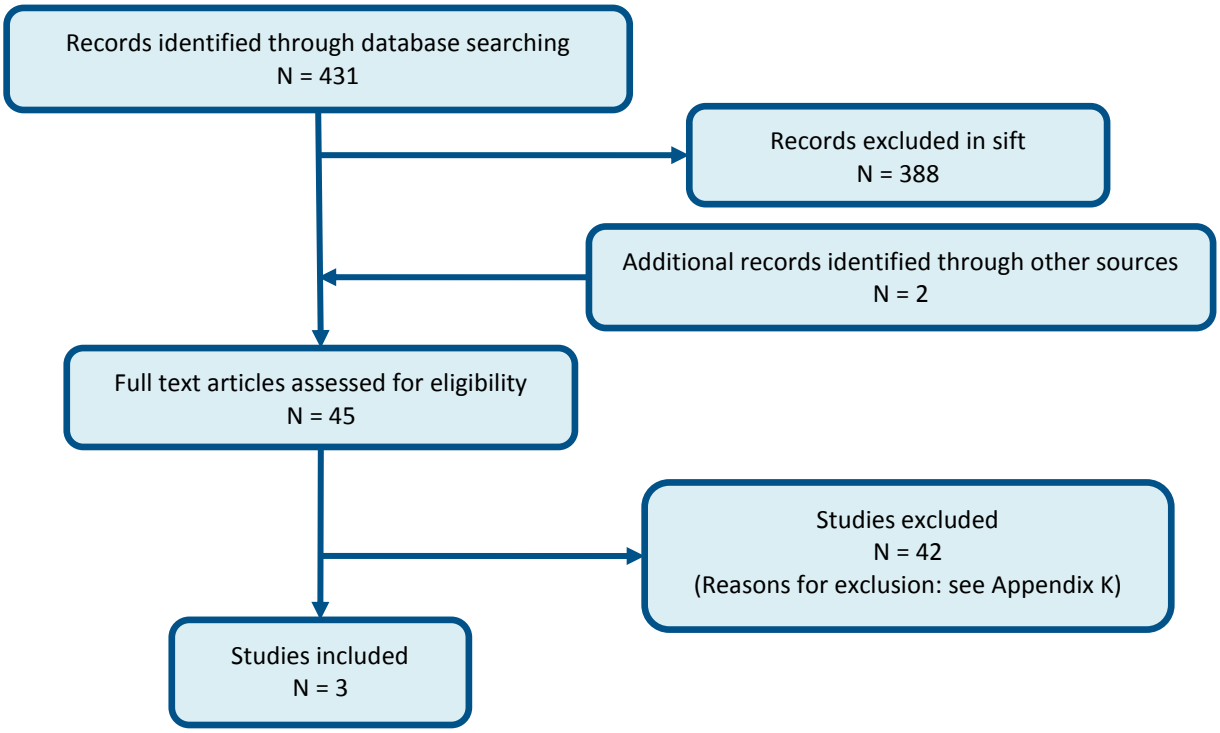
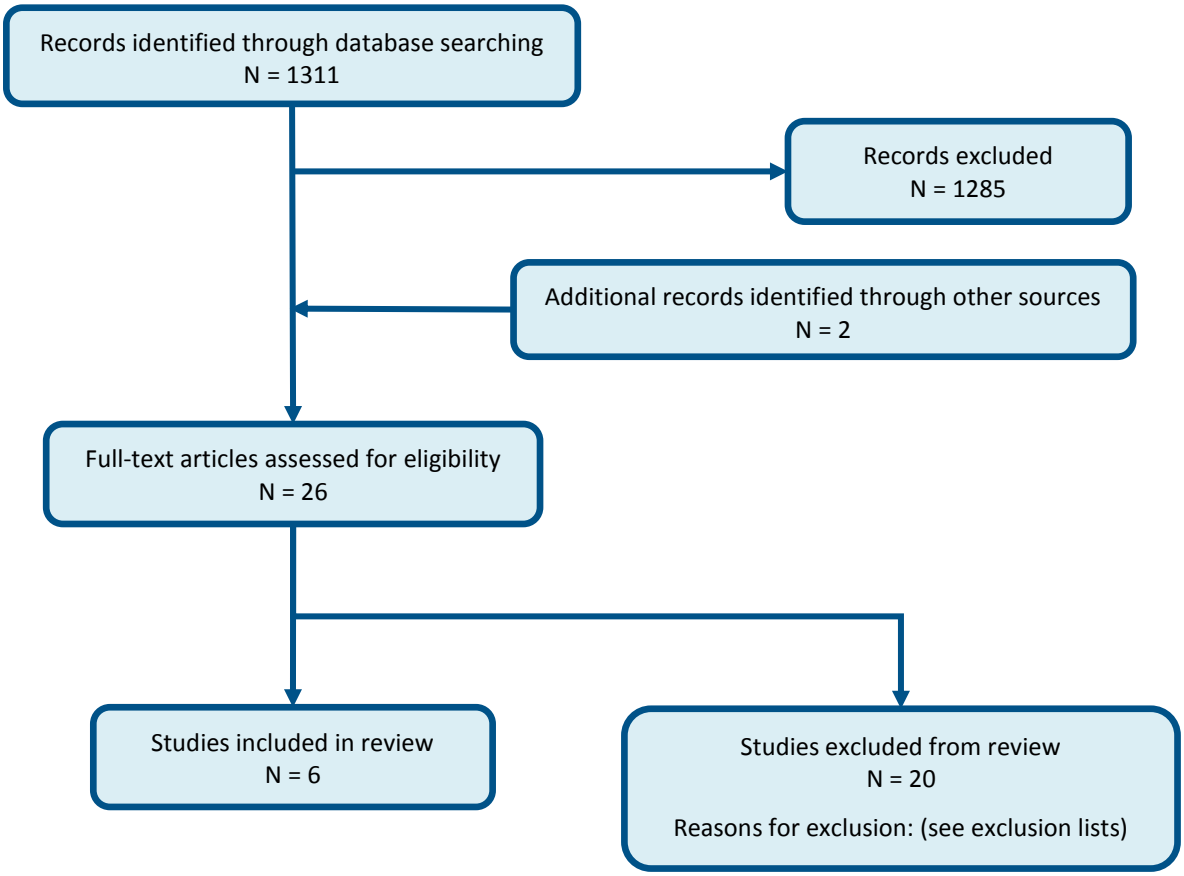


Figure 2: Flow diagram of clinical article selection for the review of LVAD vs. Control



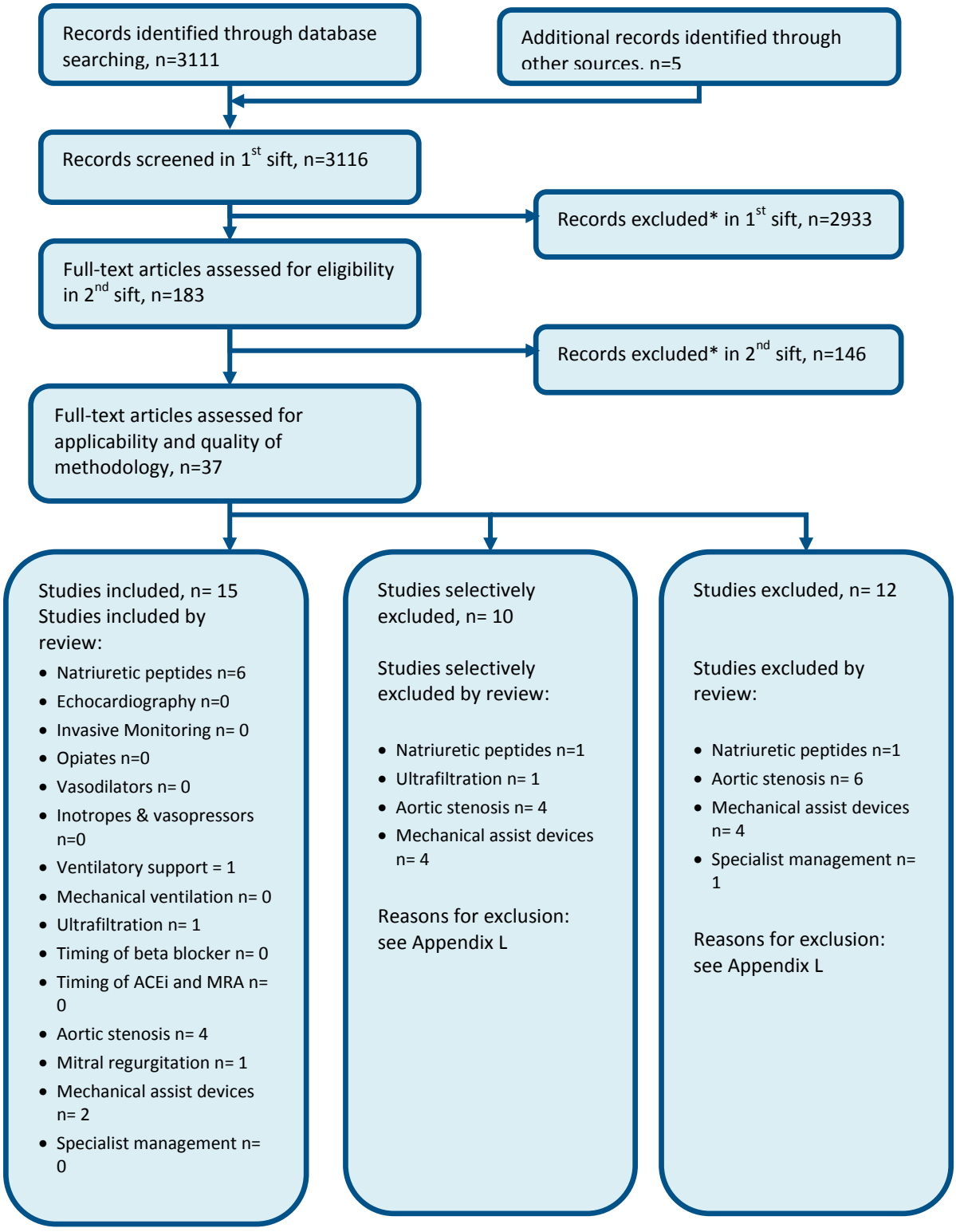
D.17 Specialist management units

Figure 17: Flow diagram of clinical article selection for specialist management units review



Appendix E: Economic article selection

Figure 18: Flow chart of economic article selection for the guideline



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

Appendix F: Literature search strategies

Contents

Introduction	**Search methodology**
Section A.1	**Standard population search strategy** This population was used for all search questions unless stated
A.1.1	Acute heart failure
A.1.2	Pulmonary oedema
A.1.3	Dyspnea
Section A.2	**Study filter terms**
A.2.1	Systematic reviews (SR)
A.2.2	Randomized controlled trials (RCT)
A.2.3	Observational studies (OBS)
A.2.4	Prognostic studies (PROG)
A.2.5	Health economic studies (HE)
A.2.6	Quality of life studies (QOL)
A.2.7	Excluded study designs and publication types
Section A.3	**Searches for specific questions with intervention**
	Diagnosis, assessment and monitoring
A.3.1	Echocardiography
A.3.2	Natriuretic peptides
A.3.3	Invasive monitoring
	Treatment before stabilisation
A.3.4	Mechanical ventilation
A.3.5	Non-invasive ventilation
A.3.6	Diuretics and ultrafiltration
A.3.7	Inotropic agents and vasopressors
A.3.8	Opiates
A.3.9	Vasodilators
	Treatment after stabilisation
A.3.10	Angiotensin converting enzyme (ACE) inhibitors
A.3.11	Beta-blockers
A.3.12	Mineralocorticoid receptor antagonists (MRA)
A.3.13	Aortic stenosis
A.3.14	Mitral regurgitation
A.3.15	Intra-aortic balloon counterpulsation
A.3.16	Ventricular assist devices

	Organisation of care
A.3.17	Specialist management units
Section A.4	**Health Economic searches**
A.4.1	Acute heart failure
A.4.2	Valvular surgery
A.4.3	Quality of life
Section A.5	**References**

Search strategies used for the acute heart failure guideline are outlined below and were run in accordance with the methodology in the NICE Guidelines Manual 2012.[118]

All searches were run up to 28th January 2014 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.

Table 34: Database date parameters

Database	Dates searched
Medline	1946 – 28th January 2014
Embase	1980 – January 2014 (week 4)
The Cochrane Library	Cochrane Reviews to 2014 Issue 1 of 12 CENTRAL to 2013 Issue 12 of 12 DARE, HTA and NHSEED to 2013 Issue 4 of 4

Clinical searches

Searches for the **clinical reviews** were run in Medline (OVID), Embase (OVID) and the Cochrane Library (Wiley). Additional searches were run in HMIC (OVID) for one question. 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.

Health economics searches

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). 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. An additional search on valvular surgery was run using only intervention terms (A.4.2).

Searches for **quality of life** data were run in Medline (OVID) and Embase (OVID) by adding the filter in section A.2.5 to the population terms.

F.1 Population search strategies

The same population was used throughout the guideline with the following exceptions:

- the questions on valvular surgery (A.3.13 & A.3.14) where no population was used
- the questions on non-invasive ventilation, diuretics and ultrafiltration and opiates (A3.5, A3.6 & A.3.8) and health economics searches where the population was expanded to include pulmonary oedema
- the question on natriuretic peptides (A.3.2) where the population was expanded to include dyspnea

F.1.1 Acute heart failure population

Medline search terms

1.	exp heart failure/
2.	cardiomyopathy, dilated/
3.	shock, cardiogenic/
4.	exp ventricular dysfunction/
5.	cardiac output, low/
6.	((heart or cardiac or myocardial) adj2 (failure or decompensation)).ti.
7.	((congestive or acute or decompensat*) adj2 "heart failure").ti,ab.
8.	((dilated or congestive) adj2 cardiomyopath*).ti.
9.	"cardiogenic shock".ti.
10.	((ventricular or ventricle*) adj2 (failure or insufficien* or dysfunction*)).ti.
11.	(("left ventricular" or "left ventricle") adj2 (failure or insufficien* or dysfunction*)).ti,ab.
12.	lvsd.ti,ab.
13.	or/1-12

Embase search terms

1.	*heart failure/ or acute heart failure/ or *cardiogenic shock/ or *diastolic dysfunction/ or *forward heart failure/ or *high output heart failure/ or *systolic dysfunction/
2.	*congestive cardiomyopathy/ or exp *congestive heart failure/
3.	exp *heart ventricle failure/
4.	((heart or cardiac or myocardial) adj2 (failure or decompensation)).ti.
5.	((congestive or acute or decompensat*) adj2 "heart failure").ti,ab.
6.	((dilated or congestive) adj2 cardiomyopath*).ti.
7.	"cardiogenic shock".ti.
8.	((ventricular or ventricle*) adj2 (failure or insufficien* or dysfunction*)).ti.
9.	(("left ventricular" or "left ventricle") adj2 (failure or insufficien* or dysfunction*)).ti,ab.
10.	lvsd.ti,ab.
11.	or/1-10

Cochrane search terms

#1.	MeSH descriptor: [Heart Failure] explode all trees
#2.	MeSH descriptor: [Cardiomyopathy, Dilated] explode all trees
#3.	MeSH descriptor: [Shock, Cardiogenic] explode all trees
#4.	MeSH descriptor: [Ventricular Dysfunction] explode all trees
#5.	MeSH descriptor: [Cardiac Output, Low] explode all trees

#6.	(heart or cardiac or myocardial) near/2 (failure or decompensation):ti
#7.	((congestive or acute or decompensat*) near/2 "heart failure"):ti,ab
#8.	(dilated or congestive) near/2 cardiomyopath*:ti
#9.	cardiogenic shock:ti
#10.	(ventricular or ventricle*) near/2 (failure or insufficien* or dysfunction*):ti
#11.	(("left ventricle" or "left ventricular") near/2 (failure or insufficienc* or dysfunction*)):ti,ab
#12.	lvsd:ti,ab
#13.	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12

HMIC search terms

1.	exp cardiogenic shock/
2.	exp cardiac output/
3.	((heart or cardiac or myocardial) adj2 (failure or decompensation)).ti.
4.	((congestive or acute or decompensat*) adj2 "heart failure").ti,ab.
5.	((dilated or congestive) adj2 cardiomyopath*).ti.
6.	"cardiogenic shock".ti.
7.	((ventricular or ventricle*) adj2 (failure or insufficien* or dysfunction*)).ti.
8.	(("left ventricular" or "left ventricle") adj2 (failure or insufficien* or dysfunction*)).ti,ab.
9.	lvsd.ti,ab.
10.	or/1-9

F.1.2 Pulmonary oedema search terms

This population was used for the diuretics, ultrafiltration (A.3.6) and opiates (A.3.8) questions, and with a modification in the non-invasive ventilation question (A.3.5) see footnote.

Medline search terms

1.	*pulmonary edema/
2.	(cardiogenic adj2 (pulmonary oedema or pulmonary edema or lung edema or lung oedema)).ti,ab.[a]
3.	or/1-2

Embase search terms

1.	*lung edema/
2.	(cardiogenic adj2 (pulmonary edema or pulmonary oedema or lung edema or lung oedema)).ti,ab.[a]
3.	or/1-2

Cochrane search terms

#1	MeSH descriptor: [Pulmonary Edema] this term only
#2	cardiogenic near/2 ("pulmonary edema" or "pulmonary oedema" or "lung edema" or "lung oedema"):ti,ab[a]
#3	#1 or #2

[a] For the non-invasive ventilation question line 2 was replaced by this for Medline and Embase: (pulmonary oedema or pulmonary edema or lung edema or lung oedema).ti,ab. and by this for Cochrane: ("pulmonary edema" or "pulmonary oedema" or "lung edema" or "lung oedema"):ti,ab

F.1.3 Dyspnea population terms

Medline search terms

1.	dyspnea/di
2.	dyspnea/et
3.	((cadiac or cardio* or cardiac-related) adj3 dyspnea).ti,ab.
4.	or/1-3

Embase search terms

1.	dyspnea/di
2.	dyspnea/et
3.	((cadiac or cardio* or cardiac-related) adj3 dyspnea).ti,ab.
4.	or/1-3

Cochrane search terms

#1	MeSH descriptor: [Dyspnea] explode all trees and with qualifiers: [Diagnosis - DI]
#2	MeSH descriptor: [Dyspnea] explode all trees and with qualifiers: [Etiology - ET]
#3	(cadiac or cardio* or cardiac-related) near/3 dyspnea:ti,ab
#4	#1 or #2 or #3

F.2 Study filter search terms

F.2.1 Systematic review (SR) search terms

Medline search terms

1.	meta-analysis/
2.	meta-analysis as topic/
3.	(meta analy* or metanaly* or metaanaly* or meta regression).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.	((multiple treatment* or 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* or meta regression).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.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
11.	or/1-10

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.	double blind procedure/
8.	single blind procedure/
9.	randomized controlled trial/
10.	or/1-9

F.2.3 Observational studies (OBS) 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 Prognostic (PROG) studies search terms

Medline search terms

1.	predict.ti.
2.	(validat* or rule*).ti,ab.
3.	(predict* and (outcome* or risk* or model*)).ti,ab.
4.	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).ti,ab.
5.	decision*.ti,ab. and logistic models/
6.	(decision* and (model* or clinical*)).ti,ab.
7.	(prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).ti,ab.
8.	(stratification or discrimination or discriminate or c statistic or "area under the curve" or AUC or calibration or indices or algorithm or multivariable).ti,ab.
9.	ROC curve/
10.	or/1-9

Embase search terms

1.	predict.ti.
2.	(validat* or rule*).ti,ab.
3.	(predict* and (outcome* or risk* or model*)).ti,ab.
4.	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).ti,ab.
5.	decision*.ti,ab. and statistical model/
6.	(decision* and (model* or clinical*)).ti,ab.
7.	(prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).ti,ab.
8.	(stratification or discrimination or discriminate or c statistic or "area under the curve" or AUC or calibration or indices or algorithm or multivariable).ti,ab.
9.	receiver operating characteristic/
10.	or/1-9

F.2.5 Health economics (HE) 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 (QOL) 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 5d*).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*).ti,ab.
10.	(hui or hui1 or hui2 or hui3).ti,ab.
11.	health* year* equivalent*.ti,ab.
12.	(hye or hyes).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 5d*).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*).ti,ab.
12.	(hui or hui1 or hui2 or hui3).ti,ab.
13.	health* year* equivalent*.ti,ab.
14.	(hye or hyes).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.2.7 Excluded studies search terms

The following study designs and publication types were removed from retrieved results using the NOT operator.

Medline search terms

1.	letter/
2.	editorial/
3.	news/

4.	exp historical article/
5.	anecdotes as topic/
6.	comment/
7.	case report/
8.	(letter or comment*).ti.
9.	or/1-8
10.	randomized controlled trial/ or random*.ti,ab.
11.	9 not 10
12.	animals/ not humans/
13.	exp animals, laboratory/
14.	exp animal experimentation/
15.	exp models, animal/
16.	exp rodentia/
17.	(rat or rats or mouse or mice).ti.
18.	or/11-17

Embase search terms

1.	letter.pt. or letter/
2.	note.pt.
3.	editorial.pt.
4.	case report/ or case study/
5.	(letter or comment*).ti.
6.	or/1-5
7.	randomized controlled trial/ or random*.ti,ab.
8.	6 not 7
9.	exp animal/ not human/
10.	nonhuman/
11.	exp experimental animal/
12.	exp animal experiment/
13.	exp animal model/
14.	exp rodent/
15.	(rat or rats or mouse or mice).ti.
16.	or/8-15

F.3 Searches by specific questions

Diagnosis, assessment and monitoring

F.3.1 Echocardiography

In adults with suspected acute heart failure does echocardiography early compared to later echocardiography in addition to standard investigations (using ECG, chest x-ray and blood tests) improve outcome?

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

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Adults (aged 18	Echocardiography	Standard	None	See Table 1

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
years or older) who have a diagnosis of acute heart failure, or have possible acute heart failure, or are being investigated for acute heart failure.		investigations		

1 Medline search terms

1.	*echocardiography/ or exp echocardiography, doppler/ or exp echocardiography, three-dimensional/ or exp myocardial perfusion imaging/ or exp radionuclide ventriculography/
2.	echocardiograph*.ti,ab.
3.	angiograph*.ti,ab.
4.	*angiography/ or *angiocardiography/ or *angiography, digital subtraction/ or *aortography/ or *cineangiography/ or *coronary angiography/
5.	(angiograph* or angiocardiograph* or aortograph* or cineangiograph*).ti,ab.
6.	((cardiac or doppler) adj ultrasound).ti,ab.
7.	sonogram*.ti,ab.
8.	or/1-7
9.	*electrocardiography, ambulatory/ or *electrocardiography/
10.	(ECG or EKG).ti,ab.
11.	(("12" or twelve) adj2 lead).ti,ab.
12.	*radiography, thoracic/ or *mass chest x-ray/
13.	((chest or thoracic) adj (xray* or x-ray*)).ti,ab.
14.	(roentogra* or roentenogra* or roentnogra*).ti,ab.
15.	*hematologic tests/ or exp blood cell count/
16.	troponin/
17.	exp electrolytes/
18.	((cell or erythrocyte or reticulocyte or leukocyte or lymphocyte or platelet) adj (count or test)).ti,ab.
19.	((copeptin or troponin) adj test*).ti,ab.
20.	((electrolyte* or sodium or potassium or chloride or bicarbonate or urea or "creatinine anion gap" or glucose or "CKMB") adj2 test*).ti,ab.
21.	or/9-20
22.	8 and 21

2 **Embase search terms**

1.	exp doppler echocardiography/ or exp three dimensional echocardiography/ or *echocardiography/
2.	exp myocardial perfusion imaging/
3.	exp radioisotope ventriculography/
4.	echocardiograph*.ti,ab.
5.	angiograph*.ti,ab.
6.	*angiography/ or *digital subtraction angiography/
7.	*angiocardiography/
8.	*aortography/

9.	*cineangiography/
10.	(angiograph* or angiocardiograph* or aortograph* or cineangiograph*).ti,ab.
11.	((cardiac or doppler) adj ultrasound).ti,ab.
12.	sonogram*.ti,ab.
13.	or/1-12
14.	*electrocardiography monitoring/ or *electrocardiography/ or *electrocardiogram/ or *ambulatory monitoring/
15.	(ECG or EKG).ti,ab.
16.	(("12" or twelve) adj2 lead).ti,ab.
17.	*thorax radiography/
18.	((chest or thoracic) adj (xray* or x-ray*)).ti,ab.
19.	(roentogra* or roentenogra* or roentnogra*).ti,ab.
20.	*blood examination/
21.	*blood cell count/
22.	exp *troponin/
23.	exp electrolyte/
24.	((cell or erythrocyte or reticulocyte or leukocyte or lymphocyte or platelet) adj (count or test)).ti,ab.
25.	((copeptin or troponin) adj test*).ti,ab.
26.	((electrolyte* or sodium or potassium or chloride or bicarbonate or urea or "creatinine anion gap" or glucose or "CKMB") adj2 test*).ti,ab.
27.	or/14-26
28.	13 and 27

Cochrane search terms

#1.	MeSH descriptor: [Echocardiography] explode all trees
#2.	MeSH descriptor: [Echocardiography, Doppler] explode all trees
#3.	MeSH descriptor: [Echocardiography, Three-Dimensional] explode all trees
#4.	MeSH descriptor: [Myocardial Perfusion Imaging] explode all trees
#5.	MeSH descriptor: [Radionuclide Ventriculography] explode all trees
#6.	echocardiograph*:ti,ab
#7.	angiograph*:ti,ab
#8.	MeSH descriptor: [Angiography] explode all trees
#9.	MeSH descriptor: [Angiocardiography] explode all trees
#10.	MeSH descriptor: [Angiography, Digital Subtraction] explode all trees
#11.	MeSH descriptor: [Aortography] explode all trees
#12.	MeSH descriptor: [Cineangiography] explode all trees
#13.	MeSH descriptor: [Coronary Angiography] explode all trees
#14.	(angiograph* or angiocardiograph* or aortograph* or cineangiograph*):ti,ab
#15.	((cardiac or doppler) next ultrasound):ti,ab
#16.	sonogram*:ti,ab
#17.	#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
#18.	MeSH descriptor: [Electrocardiography] explode all trees
#19.	MeSH descriptor: [Electrocardiography, Ambulatory] explode all trees
#20.	(ECG or EKG):ti,ab

#21.	(("12" or twelve) near/2 lead):ti,ab
#22.	MeSH descriptor: [Radiography, Thoracic] explode all trees
#23.	MeSH descriptor: [Mass Chest X-Ray] explode all trees
#24.	((chest or thoracic) next (xray* or x-ray*)):ti,ab
#25.	(roentogra* or roentenogra* or roentnogra*):ti,ab
#26.	MeSH descriptor: [Hematologic Tests] explode all trees
#27.	MeSH descriptor: [Blood Cell Count] explode all trees
#28.	MeSH descriptor: [Troponin] explode all trees
#29.	MeSH descriptor: [Electrolytes] explode all trees
#30.	((cell or erythrocyte or reticulocyte or leukocyte or lymphocyte or platelet) next (count or test)):ti,ab
#31.	((copeptin or troponin) next test*):ti,ab
#32.	((electrolyte* or sodium or potassium or chloride or bicarbonate or urea or "creatinine anion gap" or glucose or "CKMB") near/2 test*):ti,ab
#33.	#18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32
#34.	#17 and #33

F.3.2 Natriuretic peptides

In people with suspected (or under investigation for) acute heart failure, is the addition of natriuretic peptides to the standard initial investigations (using ECG, chest x-ray and blood tests) more accurate compared to standard initial investigations, clinical judgement and each other?

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

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Adults (aged 18 years or older) who have a diagnosis of acute heart failure, or have possible acute heart failure, or are being investigated for acute heart failure or people with dyspnea.	Natriuretic peptides	n/a	None	See Table 1

Medline search terms

1.	exp *natriuretic peptides/
2.	(natriuretic adj2 peptide*).ti,ab.
3.	(natriuretic adj2 factor*).ti,ab.
4.	(BNP or ANP or pro-BNP or pro-ANP or pro BNP or pro ANP).ti,ab.
5.	or/1-4

Embase search terms

1.	exp *natriuretic factor/
2.	(natriuretic adj2 peptide*).ti,ab.
3.	(natriuretic adj2 factor*).ti,ab.
4.	(BNP or ANP or pro-BNP or pro-ANP or pro BNP or pro ANP).ti,ab.

5.	or/1-4

Cochrane search terms

#1.	MeSH descriptor: [Natriuretic Peptides] explode all trees
#2.	(natriuretic near/2 peptide*):ti,ab
#3.	(natriuretic near/2 factor*):ti,ab
#4.	(BNP or ANP or pro-BNP or pro-ANP or pro BNP or pro ANP):ti,ab
#5.	#1 or #2 or #3 or #4

F.3.3 Invasive monitoring

Is the addition of invasive monitoring more clinically/cost-effective over and above non-invasive monitoring to improve outcome?

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

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Adults (aged 18 years or older) who have a diagnosis of acute heart failure, or have possible acute heart failure, or are being investigated for acute heart failure.	Invasive monitoring procedures	n/a	The following filters were used in Medline and Embase only: OBS, RCT, SR	See Table 1

Medline search terms

1.	exp *cardiac catheterization/
2.	catheterization, central venous/
3.	catheterization, swan-ganz/
4.	*pulmonary wedge pressure/
5.	(pulmonary arter* adj (catheter* or cannula* or line*)).ti,ab.
6.	swan-ganz*.ti,ab.
7.	(central venous adj3 (catheter* or cannula* or line*)).ti,ab.
8.	(internal jugular adj3 (catheter* or cannula* or line*)).ti,ab.
9.	(peripherally inserted central adj (catheter* or cannula* or line*)).ti,ab.
10.	((intra-arterial or intra arterial) adj (catheter* or cannula* or line*)).ti,ab.
11.	or/1-10

Embase search terms

1.	exp pulmonary artery catheter/
2.	*lung wedge pressure/
3.	exp *central venous catheter/
4.	*heart catheterization/
5.	swan-ganz*.ti,ab.
6.	(pulmonary arter* adj (catheter* or cannula* or line*)).ti,ab.
7.	(central venous adj3 (catheter* or cannula* or line*)).ti,ab.
8.	(internal jugular adj3 (catheter* or cannula* or line*)).ti,ab.
9.	(peripherally inserted central adj (catheter* or cannula* or line*)).ti,ab.

10.	((intra-arterial or intra arterial) adj (catheter* or cannula* or line*)).ti,ab.
11.	or/1-10

Cochrane search terms

#1.	MeSH descriptor: [Catheterization, Swan-Ganz] explode all trees
#2.	MeSH descriptor: [Cardiac Catheterization] explode all trees
#3.	MeSH descriptor: [Catheterization, Central Venous] explode all trees
#4.	MeSH descriptor: [Pulmonary Wedge Pressure] explode all trees
#5.	swan next ganz*:ti,ab
#6.	(pulmonary arter* next (catheter* or cannula* or line*)):ti,ab
#7.	(central venous near/3 (catheter* or cannula* or line*)):ti,ab
#8.	(internal jugular near/3 (catheter* or cannula* or line*)):ti,ab
#9.	(internal jugular near/3 (catheter* or cannula* or line*)):ti,ab
#10.	((intra-arterial or intra arterial) next (catheter* or cannula* or line*)):ti,ab
#11.	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10

Treatment before stabilisation

F.3.4 Mechanical ventilation

What are the predictors of outcome in mechanically ventilated acute heart failure patients?

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

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Adults (aged 18 years or older) who have a diagnosis of acute heart failure, or have possible acute heart failure, or are being investigated for acute heart failure.	Mechanical ventilation	n/a	The following filters were used in Medline and Embase only: PROG, RCT, SR	See Table 1

Medline search terms

1.	exp respiration, artificial/
2.	exp ventilators, mechanical/
3.	exp intubation, intratracheal/
4.	exp respiratory insufficiency/
5.	(artificial adj2 (respir* or ventil*)).ti,ab.
6.	(ventil* adj2 (mechanical or assisted)).ti,ab.
7.	respiratory failure.ti,ab.
8.	high-frequency ventil*.ti,ab.
9.	negative-pressure ventil*.ti,ab.
10.	Intratracheal intub*.ti,ab.
11.	invasive ventil*.ti,ab.
12.	or/1-11
13.	((child* or adolescen* or school* or infant* or teen* or paediatric* or pediatric* or youth*) not adult*).ti.

14.	12 not 13

Embase search terms

1.	exp *artificial ventilation/
2.	exp *endotracheal intubation/
3.	exp *respiratory failure/
4.	(artificial adj2 (respir* or ventil*)).ti,ab.
5.	(ventil* adj2 (mechanical or assisted)).ti,ab.
6.	respiratory failure.ti,ab.
7.	high-frequency ventil*.ti,ab.
8.	negative-pressure ventil*.ti,ab.
9.	invasive ventil*.ti,ab.
10.	endotracheal intub*.ti,ab.
11.	or/1-10
12.	((child* or adolescen* or school* or infant* or teen* or paediatric* or pediatric* or youth*) not adult*).ti.
13.	11 not 12

Cochrane search terms

#1.	MeSH descriptor: [Respiration, Artificial] explode all trees
#2.	MeSH descriptor: [Ventilators, Mechanical] explode all trees
#3.	MeSH descriptor: [Intubation, Intratracheal] explode all trees
#4.	MeSH descriptor: [Respiratory Insufficiency] explode all trees
#5.	(artificial near/2 (respir* or ventil*)):ti,ab
#6.	(ventil* near/2 (mechanical or assisted)):ti,ab
#7.	respiratory failure:ti,ab
#8.	high frequency ventil*:ti,ab
#9.	negative pressure ventil*:ti,ab
#10.	Intratracheal intub*:ti,ab
#11.	endotracheal intub*:ti,ab
#12.	invasive ventil*:ti,ab
#13.	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12

F.3.5 Non-invasive ventilation

In people with confirmed acute heart failure and cardiogenic pulmonary oedema is non-invasive positive pressure ventilation (CPAP and/or bilevel NIPPV) more clinical and cost effective than standard medical care alone to improve outcome?

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

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Adults (aged 18 years or older) who have a diagnosis of acute heart failure, or have possible acute heart failure, or are being investigated for	Non-invasive ventilation	n/a	The following filters were used in Medline and Embase only: RCT, SR	See Table 1

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
acute heart failure or pulmonary oedema.				

1 **Medline search terms**

1.	exp respiration, artificial/
2.	exp ventilators, mechanical/
3.	mechanical ventilation.ti,ab.
4.	assisted ventilation.ti,ab.
5.	artificial respiration.ti,ab.
6.	artificial ventilation.ti,ab.
7.	(respirator or respirators).ti,ab.
8.	(bipap or nippv or nppv or niv or niav or cpap or aprv or ippb or ippv or peep).ti,ab.
9.	positive pressure ventilation.ti,ab.
10.	pulmonary ventilation.ti,ab.
11.	non invasive ventilation.ti,ab.
12.	noninvasive ventilation.ti,ab.
13.	pressure support ventilation.ti,ab.
14.	positive end expiratory pressure.ti,ab.
15.	bi-level positive airway pressure.ti,ab.
16.	bilevel positive airway pressure.ti,ab.
17.	or/1-16

2 **Embase search terms**

1.	mechanical ventilation.ti,ab.
2.	assisted ventilation.ti,ab.
3.	artificial respiration.ti,ab.
4.	artificial ventilation.ti,ab.
5.	(respirator or respirators).ti,ab.
6.	(bipap or nippv or nppv or niv or niav or cpap or aprv or ippb or ippv or peep).ti,ab.
7.	positive pressure ventilation.ti,ab.
8.	pulmonary ventilation.ti,ab.
9.	non invasive ventilation.ti,ab.
10.	noninvasive ventilation.ti,ab.
11.	pressure support ventilation.ti,ab.
12.	positive end expiratory pressure.ti,ab.
13.	bi-level positive airway pressure.ti,ab.
14.	bilevel positive airway pressure.ti,ab.
15.	or/1-14

3 **Cochrane search terms**

#1.	respiration artificial
#2.	ventilators mechanical
#3.	(mechanical next ventilation)
#4.	(artificial next ventilation)

#5.	(assisted next ventilation)
#6.	(artificial next respiration)
#7.	(positive next pressure next ventilation)
#8.	(pulmonary next ventilat*)
#9.	respirator or respirators
#10.	(non next invasive next ventilation)
#11.	(noninvasive next ventilation)
#12.	(non-invasive next ventilation)
#13.	(pressure next support next ventilation)
#14.	(inspiratory next positive next pressure next ventilation)
#15.	(positive next end next expiratory next pressure)
#16.	(bi-level next positive next airway next pressure)
#17.	(bilevel next positive next airway next pressure)
#18.	bipap or nippv or nppv or niv or niav or cpap or aprv or ippb or ippv or peep
#19.	(mask next ventilation)
#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

F.3.6 Diuretics and ultrafiltration

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

- In patients with acute heart failure which diuretic administration strategy is the most clinically/cost-effective to improve outcome?
- In patients with acute heart failure is ultrafiltration more clinically/cost-effective than diuretic therapy alone or in addition to diuretic therapy to improve outcome?

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

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Adults (aged 18 years or older) who have a diagnosis of acute heart failure, or have possible acute heart failure, or are being investigated for acute heart failure or pulmonary oedema.	Diuretic therapy or ultrafiltration	n/a	The following filters were used in Medline and Embase only: RCT, SR	See Table 1

Medline search terms

1.	*diuretics/ or diuretics/ad or metolazone/ or amiloride/ or bendroflumethiazide/ or bumetanide/ or furosemide/ or hydrochlorothiazide/ or indapamide/
2.	diuretic*.ti.
3.	(metolazone or amiloride or bendroflumethiazide or bumetanide or furosemide or hydrochlorothiazide or indapamide or torasemide).ti,ab.
4.	exp *ultrafiltration/
5.	(ultrafilt* or hemofiltr* or aquapher*).ti,ab.
6.	or/1-5

Embase search terms

1.	*diuretic agent/
2.	diuretic agent/ad, po
3.	*metolazone/ or *thiazide diuretic agent/ or thiazide diuretic agent/ad, po
4.	*amiloride/ or *amiloride plus hydrochlorothiazide/ or *potassium sparing diuretic agent/ or potassium sparing diuretic agent/ad, po
5.	*bendroflumethiazide/
6.	*bumetanide/ or *loop diuretic agent/ or loop diuretic agent/ad, po
7.	*furosemide/
8.	*hydrochlorothiazide/
9.	*indapamide/
10.	*torasemide/
11.	diuretic.ti.
12.	(metolazone or amiloride or bendroflumethiazide or bumetanide or furosemide or hydrochlorothiazide or indapamide or torasemide).ti,ab.
13.	exp *ultrafiltration/
14.	exp *hemofiltration/
15.	modified ultrafiltration/ or slow continuous ulfrafiltration/ or continuous hemofiltration/
16.	(ultrafilt* or hemofiltr* or aquapher*).ti,ab.
17.	or/1-16

Cochrane search terms

#1.	MeSH descriptor: [Diuretics] this term only and with qualifiers: [Administration & dosage - AD]
#2.	MeSH descriptor: [Metolazone] this term only
#3.	MeSH descriptor: [Amiloride] this term only
#4.	MeSH descriptor: [Bendroflumethiazide] this term only
#5.	MeSH descriptor: [Bumetanide] this term only
#6.	MeSH descriptor: [Furosemide] this term only
#7.	MeSH descriptor: [Hydrochlorothiazide] explode all trees
#8.	MeSH descriptor: [Indapamide] this term only
#9.	diuretic*:ti
#10.	(metolazone or amiloride or bendroflumethiazide or bumetanide or furosemide or hydrochlorothiazide or indapamide or torasemide):ti
#11.	((metolazone or amiloride or bendroflumethiazide or bumetanide or furosemide or hydrochlorothiazide or indapamide or torasemide or diuretic*) near/3 (oral or intravenous or bolus or infusion)):ti,ab
#12.	MeSH descriptor: [Ultrafiltration] explode all trees
#13.	(ultrafilt* or hemofiltr* or aquapher*):ti,ab
#14.	#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

F.3.7 Inotropic agents and vasopressors

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

- In patients with acute heart failure are inotropes more clinically/cost-effective than placebo to improve clinical outcomes?
- In patients with acute heart failure are vasopressors more clinically/cost-effective than placebo to improve clinical outcomes?

- In patients with acute heart failure are inotropes safe and clinically / cost effective compared to vasopressors to improve outcome?

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

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Adults (aged 18 years or older) who have a diagnosis of acute heart failure, or have possible acute heart failure, or are being investigated for acute heart failure.	Inotropic agents or vasopressors	n/a	The following filters were used in Medline and Embase only: RCT, SR	See Table 1

Medline search terms

1.	inotrope*.ti,ab.
2.	inotropic*.ti,ab.
3.	exp milrinone/
4.	exp enoximone/
5.	exp dobutamine/
6.	exp dopamine/
7.	(milrinone or primacor).ti,ab.
8.	(enoximone or perfan).ti,ab.
9.	(dobutamine or dopamine).ti,ab.
10.	(dopexamine or isoprenaline or dopacard).ti,ab.
11.	exp *epinephrine/
12.	exp *norepinephrine/
13.	exp *vasopressins/
14.	(adrenalin or epinephrine or anapen or epipen or jext).ti,ab.
15.	(noradrenaline or norepinephrine).ti,ab.
16.	(vasopressin* or pitressin).ti,ab.
17.	or/1-16

Embase search terms

1.	inotrope*.ti,ab.
2.	inotropic*.ti,ab.
3.	exp milrinone/
4.	exp enoximone/
5.	exp dobutamine/
6.	exp dopamine/
7.	(milrinone or primacor).ti,ab.
8.	(enoximone or perfan).ti,ab.
9.	(dobutamine or dopamine).ti,ab.
10.	(dopexamine or dopacard or isoprenaline).ti,ab.
11.	*adrenalin/
12.	*noradrenalin/
13.	*vasopressin/

14.	(adrenalin or epinephrine or anapen or epipen or jext).ti,ab.
15.	(noradrenaline or norepinephrine).ti,ab.
16.	(vasopressin* or pitressin).ti,ab.
17.	or/1-16

Cochrane search terms

#1.	MeSH descriptor: [Milrinone] explode all trees
#2.	MeSH descriptor: [Enoximone] explode all trees
#3.	MeSH descriptor: [Dobutamine] explode all trees
#4.	(milrinone or primacor):ti,ab
#5.	(enoximone or perfan):ti,ab
#6.	(dobutamine or dopamine):ti,ab
#7.	(dopexamine or isoprenaline or dopacard):ti,ab
#8.	(inotrope* or inotropic*):ti,ab
#9.	MeSH descriptor: [Epinephrine] explode all trees
#10.	MeSH descriptor: [Norepinephrine] explode all trees
#11.	MeSH descriptor: [Vasopressins] explode all trees
#12.	(adrenalin or epinephrine or anapen or epipen or jext):ti,ab
#13.	(noradrenaline or norepinephrine):ti,ab
#14.	(vasopressin* or pitressin) .ti,ab.
#15.	#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.3.8 Opiates

In patients with acute heart failure are opiates as an adjunct to other first line therapies more clinically / cost effective compared to placebo and to other treatments alone?

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

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Adults (aged 18 years or older) who have a diagnosis of acute heart failure, or have possible acute heart failure, or are being investigated for acute heart failure or pulmonary oedema.	Opiates	n/a	None	See Table 1

Medline search terms

1.	exp morphine/
2.	(morphine* or diamorphine or opiate* or oramorph or duramorph or heroin or diamorf or diacetylmorphine).ti,ab.
3.	or/1-2

Embase search terms

1.	*morphine/ or *morphine sulfate/
2.	*diamorphine/

3.	(morphine* or diamorphine or opiate* or oramorph or duramorph or heroin or diamorf or diacetylmorphine).ti,ab.
4.	or/1-3

Cochrane search terms

#1.	MeSH descriptor: [Morphine] explode all trees
#2.	(morphine* or diamorphine or opiate* or oramorph or duramorph or heroin or diamorf or diacetylmorphine):ti,ab
#3.	#1 or #2

F.3.9 Vasodilators

In patients with acute heart failure are vasodilators more clinically/cost-effective than placebo to improve clinical outcomes?

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

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Adults (aged 18 years or older) who have a diagnosis of acute heart failure, or have possible acute heart failure, or are being investigated for acute heart failure.	Vasodilators	n/a	The following filters were used in Medline and Embase only: RCT, SR	See Table 1

Medline search terms

1.	exp *vasodilator agents/
2.	*nitroglycerin/
3.	*isosorbide dinitrate/
4.	*sodium nitroprusside/
5.	("glyceryl trinitrate" or nitroglycerin or "isosorbide dinitrate" or nitroprusside).ti,ab.
6.	(coro-nitro or glytrin or "GTN 300" or "GTN 400" or nitrolingual or nitromin or suscard or nitrocine or nitronel or deponit or minitran or nitro-dur or percutol or transiderm-nitro).ti,ab.
7.	(cecodard or angitak or isoket).ti,ab.
8.	nesiritide.ti,ab.
9.	(vasoactiv* or vasodilat* or vasorelax*).ti,ab.
10.	or/1-9

Embase search terms

1.	exp *coronary vasodilating agent/
2.	exp *glyceryl trinitrate/
3.	exp *isosorbide dinitrate/
4.	exp *nitroprusside sodium/
5.	("glyceryl trinitrate" or "isosorbide dinitrate" or nitroprusside).ti,ab.
6.	(coro-nitro or glytrin or "GTN 300" or "GTN 400" or nitrolingual or nitromin or suscard or nitrocine or nitronel or deponit or minitran or nitro-dur or percutol or transiderm-nitro).ti,ab.
7.	(cecodard or angitak or isoket).ti,ab.
8.	(vasoactiv* or vasodilat* or vasorelax*).ti,ab.

9.	nitroglycerin.ti,ab.
10.	nesiritide.ti,ab.
11.	or/1-10

Cochrane search terms

#1.	MeSH descriptor: [Vasodilator Agents] explode all trees
#2.	MeSH descriptor: [Nitroglycerin] explode all trees
#3.	MeSH descriptor: [Isosorbide Dinitrate] explode all trees
#4.	MeSH descriptor: [Nitroprusside] explode all trees
#5.	("glyceryl trinitrate" or nitroglycerin or "isosorbide dinitrate" or nitroprusside):ti,ab
#6.	(coro-nitro or glytrin or "GTN 300" or "GTN 400" or nitrolingual or nitromin or suscard or nitrocine or nitronel or deponit or minitran or nitro-dur or percutol or transiderm-nitro):ti,ab
#7.	(cecodard or angitak or isoket):ti,ab
#8.	nesiritide:ti,ab
#9.	(vasoactiv* or vasodilat* or vasorelax*):ti,ab
#10.	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9

Treatment after stabilisation

F.3.10 Angiotensin converting enzyme (ACE) inhibitors

For people with confirmed acute heart failure not already on angiotensin converting enzyme (ACE)-inhibitor therapy should ACEi therapy commence in hospital or following discharge?

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

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Adults (aged 18 years or older) who have a diagnosis of acute heart failure, or have possible acute heart failure, or are being investigated for acute heart failure.	ACE inhibitor therapy	n/a	The following filters were used in Medline and Embase only: OBS, RCT, SR	See Table 1

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.	or/1-3
5.	time factors/
6.	exp drug administration schedule/
7.	((time or timing or early or earlier or late or later) adj2 (initiat* or start* or treat* or therap* or administ*)).ti,ab.

8.	((commenc* or start* or initiat*) adj2 treat*).ti,ab.
9.	or/5-8
10.	4 and 9

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.	or/1-3
5.	*time/
6.	exp *drug administration/
7.	((time or timing or early or earlier or late or later) adj2 (initiat* or start* or treat* or therap* or administ*)).ti,ab.
8.	((commenc* or start* or initiat*) adj2 treat*).ti,ab.
9.	or/5-8
10.	1 and 9

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.	#1 or #2 or #3
#5.	MeSH descriptor: [Time Factors] explode all trees
#6.	MeSH descriptor: [Drug Administration Schedule] explode all trees
#7.	((time or timing or early or earlier or late or later) near/2 (initiat* or start* or treat* or therap* or administ*)):ti,ab
#8.	((commenc* or start* or initiat*) near/2 treat*):ti,ab
#9.	#5 or #6 or #7 or #8
#10.	#4 and #9

F.3.11 Beta-blockers

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

- In people with acute heart failure already on beta-blocker therapy should beta-blockers be reduced or discontinued, and if so should they be reinstated in hospital after stabilisation?
- For people with confirmed acute heart failure not already on beta-blocker therapy should beta-blocker treatment commence in hospital after stabilisation or following discharge?

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

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Adults (aged 18 years or older) who have a diagnosis of acute heart failure, or have possible acute heart failure, or are being investigated for acute heart failure.	Beta blocker therapy	n/a	The following filters were used in Medline and Embase only: OBS, RCT, SR	See Table 1

1 **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.	((beta-adrenoceptor or b-adrenoceptor or beta-adrenergic) adj3 (blockade or blocker*or blocking or antagonist*)).ti,ab.
7.	or/1-6
8.	exp time factors/
9.	exp drug administration schedule/
10.	(continu* or discontinu* or stop* or halt* or ceas* or cessation).ti,ab.
11.	((time or timing or early or earlier or late or later) adj2 (initiat* or start* or treat* or therap* or administ*)).ti,ab.
12.	((commenc* or start* or initiat*) adj2 treat*).ti,ab.
13.	or/8-12
14.	7 and 13

2 **Embase search terms**

1.	exp *beta adrenergic receptor blocking agent/
2.	exp *bisoprolol/ or exp *bisoprolol fumarate/ or exp *bisoprolol fumarate plus hydrochlorothiazide/ or exp *carvedilol/ or exp *metoprolol/ or exp*metoprolol fumarate/ or exp *metoprolol succinate/ or exp *metoprolol tartrate/ or exp *nebivolol/
3.	(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.
4.	(beta adj3 block*).ti,ab.
5.	(b adj3 block*).ti,ab.
6.	(beta adj2 antagonist*).ti,ab.
7.	((beta-adrenoceptor or b-adrenoceptor or beta-adrenergic) adj3 (blockade or blocker* or blocking or antagonist*)).ti,ab.

8.	or/1-7
9.	*time/
10.	exp *drug administration/
11.	(continu* or discontinu* or stop* or halt* or ceas* or cessation).ti,ab.
12.	((time or timing or early or earlier or late or later) adj2 (initiat* or start* or treat* or therap* or administ*)).ti,ab.
13.	((commenc* or start* or initiat*) adj2 treat*).ti,ab.
14.	or/9-13
15.	8 and 14

Cochrane search terms

#1.	MeSH descriptor: [Adrenergic beta-Antagonists] explode all trees
#2.	MeSH descriptor: [Bisoprolol] explode all trees
#3.	MeSH descriptor: [Metoprolol] explode all trees
#4.	(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
#5.	(beta near/3 block*):ti,ab
#6.	(b near/3 block*):ti,ab
#7.	(beta near/2 antagonist*):ti,ab
#8.	((beta-adrenoceptor or b-adrenoceptor or beta-adrenergic) next (block* or antagonist*)):ti,ab
#9.	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10.	MeSH descriptor: [Time Factors] explode all trees
#11.	MeSH descriptor: [Drug Administration Schedule] explode all trees
#12.	(continu* or discontinu* or stop* or halt* or ceas* or cessation):ti,ab
#13.	((time or timing or early or earlier or late or later) near/2 (initiat* or start* or treat* or therap* or administ*)):ti,ab
#14.	((commenc* or start* or initiat*) near/2 treat*):ti,ab
#15.	#10 or #11 or #12 or #13 or #14
#16.	#9 and #15

F.3.12 Mineralocorticoid receptor antagonists (MRA)

For people with confirmed acute heart failure not already on mineralocorticoid receptor antagonists (MRAs) should MRA therapy commence in hospital or following discharge?

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

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Adults (aged 18 years or older) who have a diagnosis of acute heart failure, or have possible acute heart failure, or are being investigated for	MRA therapy	n/a	The following filters were used in Medline and Embase only: OBS, RCT, SR	See Table 1

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
acute heart failure.				

1 **Medline search terms**

1.	exp mineralocorticoid receptor antagonists/
2.	exp triamterene/
3.	((mra or ((mineralocorticoid adj receptor*) or aldosterone)) adj2 (inhibit* or antagonist*)).ti,ab.
4.	(spironolactone or aldactone or lasilctone or co-flumactone or aldactide or eplerenone or inspra or triamterene or dytac or frusene or co-triamterzide or triam-co or dyazide or kalspare).ti,ab.
5.	or/1-4
6.	time factors/
7.	exp drug administration schedule/
8.	((time or timing or early or earlier or late or later) adj2 (initiat* or start* or treat* or therap* or administ*)).ti,ab.
9.	((commenc* or start* or initiat*) adj2 treat*).ti,ab.
10.	or/6-9
11.	5 and 10

2 **Embase search terms**

1.	exp *mineralocorticoid antagonist/
2.	exp *triamterene/
3.	exp *aldosterone antagonist/ or exp *aldosterone/
4.	exp *eplerenone/
5.	exp *spironolactone/
6.	((mra or ((mineralocorticoid adj receptor*) or aldosterone)) adj2 (inhibit* or antagonist*)).ti,ab.
7.	(spironolactone or aldactone or lasilctone or co-flumactone or aldactide or eplerenone or inspra or triamterene or dytac or frusene or co-triamterzide or triam-co or dyazide or kalspare).ti,ab.
8.	or/1-7
9.	time factors/
10.	exp drug administration schedule/
11.	((time or timing or early or earlier or late or later) adj2 (initiat* or start* or treat* or therap* or administ*)).ti,ab.
12.	((commenc* or start* or initiat*) adj2 treat*).ti,ab.
13.	or/9-12
14.	8 and 13

3 **Cochrane search terms**

#1.	MeSH descriptor: [Mineralocorticoid Receptor Antagonists] explode all trees
#2.	MeSH descriptor: [Triamterene] explode all trees
#3.	MeSH descriptor: [Spironolactone] explode all trees
#4.	((mra or ((mineralocorticoid next receptor*) or aldosterone)) near/2 (inhibit* or antagonist*)):ti,ab
#5.	(spironolactone or aldactone or lasilctone or co-flumactone or aldactide or eplerenone or inspra or triamterene or dytac or frusene or co-triamterzide or triam-co or dyazide or

	kalspare):ti,ab
#6.	#1 or #2 or #3 or #4 or #5
#7.	MeSH descriptor: [Time Factors] explode all trees
#8.	MeSH descriptor: [Drug Administration Schedule] explode all trees
#9.	((time or timing or early or earlier or late or later) near/2 (initiat* or start* or treat* or therap* or administ*)):ti,ab
#10.	((commenc* or start* or initiat*) near/2 treat*):ti,ab
#11.	#7 or #8 or #9 or #10
#12.	#6 and #11

F.3.13 Aortic stenosis

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

- For people with acute heart failure accompanied by aortic stenosis is surgical valvular intervention more clinically or cost effective compared to standard medical care?
- For people with acute heart failure accompanied by aortic stenosis is percutaneous valvular intervention more clinically or cost effective compared to standard medical care?
- For people with acute heart failure accompanied by aortic stenosis is surgical valvular intervention more clinically or cost effective compared to percutaneous valvular intervention?

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

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
None	Aortic valve surgery	n/a	The following filters were used in Medline and Embase only: RCT, SR	See Table 1

Medline search terms

1.	exp *aortic valve stenosis/
2.	(aort* adj2 stenos*).ti,ab.
3.	(aort* adj2 scleros*).ti,ab.
4.	or/1-3

Embase search terms

1.	exp *aorta valve stenosis/
2.	(aort* adj2 stenos*).ti,ab.
3.	(aort* adj2 scleros*).ti,ab.
4.	or/1-3

Cochrane search terms

#1.	MeSH descriptor: [Aortic Valve Stenosis] explode all trees
#2.	(aort* near/2 stenos*):ti,ab
#3.	(aort* near/2 scleros*):ti,ab
#4.	#1 or #2 or #3

F.3.14 Mitral regurgitation

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

- For people with acute heart failure accompanied by mitral regurgitation is surgical valvular intervention more clinically or cost effective compared to standard medical care?
- For people with acute heart failure accompanied by mitral regurgitation is percutaneous valvular intervention more clinically or cost effective compared to standard medical care?
- For people with acute heart failure accompanied by mitral regurgitation is surgical valvular intervention more clinically or cost effective compared to percutaneous valvular intervention?

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

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
None	Mitral valve surgery	n/a	The following filters were used in Medline and Embase only:	See Table 1

Medline search terms

1.	exp *mitral valve insufficiency/
2.	(mitral adj2 (regurgit* or incompet* or insufficien* or prolapse*)).ti,ab.
3.	1 or 2

Embase search terms

1.	exp *mitral valve regurgitation/
2.	(mitral adj2 (regurgit* or incompet* or insufficien* or prolapse*)).ti,ab.
3.	1 or 2

Cochrane search terms

#1.	MeSH descriptor: [Mitral Valve Insufficiency] explode all trees
#2.	(mitral near/2 (regurgit* or incompet* or insufficien* or prolapse*)):ti,ab
#3.	#1 or #2

F.3.15 Intra-aortic balloon counterpulsation

For people with acute heart failure is intra-aortic balloon counterpulsation (IABP) more clinically / cost effective compared to standard medical care alone?

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

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Adults (aged 18 years or older) who have a diagnosis of acute heart failure, or have possible acute heart failure, or are being investigated for acute heart failure.	IABP	n/a	The following filters were used in Medline and Embase only: RCT, SR	See Table 1

Medline search terms

1.	*heart-assist devices/
2.	intra-aortic balloon pumping/
3.	counterpulsation/
4.	counterpulsation.ti,ab.
5.	(intra-aortic balloon* or intraaortic balloon* or iabp).ti,ab.
6.	assist* circulation.ti,ab.
7.	((intra-aort* or intraaort* or aort*) adj2 counterpulsation).ti,ab.
8.	((intra-aort* or intraaort* or aort*) adj2 pump*).ti,ab.
9.	((intra-aort* or intraaort* or aort*) adj2 balloon*).ti,ab.
10.	or/1-9

Embase search terms

1.	*heart assist device/
2.	aorta balloon/
3.	intraaortic balloon pump/
4.	counterpulsation/
5.	counterpulsation.ti,ab.
6.	assist* circulation.ti,ab.
7.	(intra-aortic balloon* or intraaortic balloon* or iabp).ti,ab.
8.	((intra-aort* or intraaort* or aort*) adj2 counterpulsation).ti,ab.
9.	((intra-aort* or intraaort* or aort*) adj2 pump*).ti,ab.
10.	((intra-aort* or intraaort* or aort*) adj2 ballon*).ti,ab.
11.	or/1-10

Cochrane search terms

#1.	MeSH descriptor: [Intra-Aortic Balloon Pumping] explode all trees
#2.	MeSH descriptor: [Counterpulsation] explode all trees
#3.	MeSH descriptor: [Heart-Assist Devices] explode all trees
#4.	counterpulsation:ti,ab
#5.	assist* circulation:ti,ab
#6.	(intra-aortic balloon* or intraaortic balloon* or iabp):ti,ab
#7.	((intra-aort* or intraaort* or aort*) near/2 counterpulsation):ti,ab
#8.	((intra-aort* or intraaort* or aort*) near/2 pump*):ti,ab
#9.	((intra-aort* or intraaort* or aort*) near/2 balloon*):ti,ab
#10.	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9

F.3.16 Ventricular assist devices

For people with acute heart failure are ventricular assist devices more clinically / cost effective compared to standard medical care (including IABP) alone?

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

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Adults (aged 18 years or older) who have a diagnosis of acute heart failure, or have possible	Ventricular assist devices	n/a	The following filters were used in Medline and Embase only:	See Table 1

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
acute heart failure, or are being investigated for acute heart failure.			RCT, SR	

Medline search terms

1.	exp *heart-assist devices/
2.	ventricular assist* device*.ti,ab.
3.	(mechanical* adj2 circulatory support).ti,ab.
4.	rotary blood pump*.ti,ab.
5.	LVAD*.ti,ab.
6.	(heartware or jarvik heart or heartmate ii or berlin heart or terumo or micromed debakey vad or levitronix or thoratec or berlin excor or abiomed).ti,ab.
7.	or/1-6

Embase search terms

1.	exp *heart assist device/
2.	exp *assisted circulation/
3.	ventricular assist* device*.ti,ab.
4.	(mechanical* adj2 circulatory support).ti,ab.
5.	rotary blood pump*.ti,ab.
6.	LVAD*.ti,ab.
7.	(heartware or jarvik heart or heartmate ii or berlin heart or terumo or micromed debakey vad or levitronix or thoratec or berlin excor or abiomed).ti,ab.
8.	or/1-7

Cochrane search terms

#1.	MeSH descriptor: [Heart-Assist Devices] explode all trees
#2.	MeSH descriptor: [Assisted Circulation] explode all trees
#3.	(ventricular next assist* next device*):ti,ab
#4.	(mechanical* near/2 "circulatory support"):ti,ab
#5.	LVAD*:ti,ab
#6.	(rotary next blood next pump*):ti,ab
#7.	(heartware or jarvik heart or heartmate ii or berlin heart or terumo or micromed debakey vad or levitronix or thoratec or berlin excor or abiomed):ti,ab
#8.	#1 or #2 or #3 or #4 or #5 or #6 or #7

Organisation of care

F.3.17 Specialist management units

For people with suspected or confirmed acute heart failure is a specialist management unit more clinically / cost effective than general medical hospital care?

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

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Adults (aged 18 years or older) who	Special management units	n/a	The following filters were used in	1999-?

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
have a diagnosis of acute heart failure, or have possible acute heart failure, or are being investigated for acute heart failure.			Medline and Embase only: RCT, SR, OBS	

1 **Medline search terms**

1.	exp physician's practice patterns/
2.	exp nurse's practice patterns/
3.	exp case management/
4.	exp patient care team/
5.	exp interdisciplinary communication/
6.	(special* adj2 (team* or unit* or ward* or center* or centre* or equip* or hub* or network* or care or clinic or clinics or doctor* or physician* or nurse* or clinician*)).ti,ab.
7.	(multidisciplinar* or multiprofessional* or interdisciplinar* or interobserver*).ti,ab.
8.	((cardi* or heart failure) adj2 (ward* or unit*)).ti,ab.
9.	or/1-8

2 **Embase search terms**

1.	exp *clinical practice/
2.	exp *nursing practice/
3.	exp *case management/
4.	exp *patient care/
5.	exp *interdisciplinary communication/
6.	(special* adj2 (team* or unit* or ward* or center* or centre* or equip* or hub* or network* or care or clinic or clinics or doctor* or physician* or nurse* or clinician*)).ti,ab.
7.	(multidisciplinar* or multiprofessional* or interdisciplinar* or interobserver*).ti,ab.
8.	((cardi* or heart failure) adj2 (ward* or unit*)).ti,ab.
9.	or/1-8

3 **Cochrane search terms**

#1.	MeSH descriptor: [Physician' s Practice Patterns] explode all trees
#2.	MeSH descriptor: [Nurse's Practice Patterns] explode all trees
#3.	MeSH descriptor: [Case Management] explode all trees
#4.	MeSH descriptor: [Patient Care Team] explode all trees
#5.	MeSH descriptor: [Interdisciplinary Communication] explode all trees
#6.	(special* near/2 (team* or unit* or ward* or center* or centre* or equip* or hub* or network* or care or clinic or clinics or doctor* or physician* or nurse* or clinician*))):ti,ab
#7.	(multidisciplinar* or multiprofessional* or interdisciplinar* or interobserver*):ti,ab
#8.	((cardi* or heart failure) near/2 (ward* or unit*)):ti,ab
#9.	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8

4 **HMIC search terms**

1.	exp medical staff/
2.	exp case management/

3.	exp health care teams/
4.	exp interprofessional communication/
5.	(special* adj2 (team* or unit* or ward* or center* or centre* or equip* or hub* or network* or care or clinic or clinics or doctor* or physician* or nurse* or clinician*)).ti,ab.
6.	(multidisciplinar* or multiprofessional* or interdisciplinar* or interobserver*).ti,ab.
7.	((cardi* or heart failure) adj2 (ward* or unit*)).ti,ab.
8.	or/1-7

F.4 Health economics searches

F.4.1 Acute heart failure

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Adults (aged 18 years or older) who have a diagnosis of acute heart failure, or have possible acute heart failure, or are being investigated for acute heart failure or pulmonary oedema.			The following filters were used in Medline and Embase only: HE	Medline and Embase: 2010-28th January 2014 CRD and HEED: 1999-28th January 2014

CRD search terms

1.	MeSH descriptor heart failure explode all trees
2.	MeSH descriptor shock, cardiogenic
3.	MeSH descriptor ventricular dysfunction explode all trees
4.	MeSH descriptor cardiac output, low
5.	MeSH descriptor cardiomyopathy, dilated
6.	(lsvd) or (cardiogenic near2 shock):ti
7.	((heart or cardiac or myocardial) near2 (failure or decompensation)):ti
8.	(((congestive or acute or decompensat*) near2 (heart failure)))
9.	(((dilated or congestive) near2 (cardiomyopath*)):ti)
10.	(((left ventricle* or left ventricular) near2 (failure or insufficienc* or dysfunction*)))
11.	(((ventricle* or ventricular) near2 (failure or insufficienc* or dysfunction*)):ti)
12.	(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11)
13.	MeSH descriptor pulmonary edema explode all trees
14.	(((cardiogenic) near2 (pulmonary oedema or pulmonary edema or lung edema or lung oedema)):ti)
15.	(#12 or #13 or #14)

HEED search terms

1.	ax=heart or cardiac or myocardial
2.	ax=failure or decompensat*
3.	cs=1 and 2

4.	ax=ventricular or ventricle*
5.	ax=failure or insufficient* or dysfunction*
6.	cs=4 and 5
7.	ax=cardiomyopathy
8.	ax=cardiogenic shock
9.	ax=cardiac output
10.	ax=lvsd
11.	ax=cardiogenic
12.	ax=pulmonary oedema or pulmonary edema or lung edema or lung oedema
13.	cs=11 and 12
14.	cs=3 or 6 or 7 or 8 or 9 or 10 or 13

F.4.2 Valvular surgery

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
No population	Valvular surgery		The following filters were used in Medline and Embase only: HE	Medline and Embase: 2010-28th January 2014 CRD and HEED: 1999-28th January 2014

Medline search terms

1.	exp *aortic valve stenosis/
2.	(aort* adj2 stenos*).ti,ab.
3.	(aort* adj2 scleros*).ti,ab.
4.	exp *mitral valve insufficiency/
5.	(mitral adj2 (regurgit* or incompet* or insufficien* or prolapse*)).ti,ab.
6.	or/1-5

Embase search terms

1.	exp *aorta valve stenosis/
2.	(aort* adj2 stenos*).ti,ab.
3.	(aort* adj2 scleros*).ti,ab.
4.	exp *mitral valve regurgitation/
5.	(mitral adj2 (regurgit* or incompet* or insufficien* or prolapse*)).ti,ab.
6.	or/1-5

CRD search terms

1.	MeSH descriptor aortic valve stenosis explode all trees
2.	MeSH descriptor mitral valve insufficiency explode all trees
3.	((aort* near2 (stenos* or scleros*)))
4.	((mitral near2 (regurgit* or incompet* or insufficien* or prolapse*)))
5.	#1 or #2 or #3 or #4

HEED search terms

1.	AX=mitral or aort*

2.	AX=stenos* or scleros* or regurgit* or incompet* or insufficien* or prolapse*
3.	CS=1 AND 2

F.4.3 Quality of life

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Adults (aged 18 years or older) who have a diagnosis of acute heart failure, or have possible acute heart failure, or are being investigated for acute heart failure or pulmonary oedema.			The following filters were used in Medline and Embase only: QOL	Medline: 1946-22nd March 2013 Embase: 1974-22nd March 2013

Appendix G: Clinical evidence tables

G.1 Diagnosis, assessment and monitoring

G.1.1 Natriuretic peptides

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
Afaq 2011[4]	Natriuretic peptide/s: NTproBNP Roche Threshold/s: Results presented stratified by age related threshold. Cumulative data presented without specific threshold Study type: Retrospective cohort	N = 502 Inclusion criteria: patients presenting to the ED for evaluation of dyspnoea Exclusion criteria: Subjects with incomplete laboratory results or missing clinical data	Mean age: 71.4 (15.1) Male/Female (n): 226/276	Index test: Serum NTproBNP Reference standard: Single physician using Framingham criteria blinded to NTproBNP Time between index test and reference standard: NR Target condition: Congestive heart failure	Results presented stratified by age related threshold. Cumulative data presented without specific threshold. NPV at 300pg/mL 86% AUC:0.73 (0.69-0.77)		Source of funding: NR Limitations: Patient Selection: High Index test: Low Reference Standard: Low Flow and timing: Low Overall: High Additional data: Results presented stratified by age related threshold.

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
	Setting: Single ED in the USA						Cumulative data presented without specific threshold.

Table 35: Clinical evidence tables for Ailbay 2005[8]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures				Effect sizes		Comments
Ailbay 2005[8]	Natriuretic peptide/s: BNP Biosite (Triage) NTproBNP Roche Threshold/s: 100 and 150pg/mL BNP and 280 and 1000pg/mL NTproBNP Study type: Cross Sectional	N = 160 Inclusion criteria: Patients referred to the ED with dyspnoea Exclusion criteria: NR	Mean age: 80.1 (13.5) Male/Female (n): 76/84	Index test: Serum BNP and NTproBNP Reference standard: Retrospective review by two senior cardiologists using all available data including echocardiography and the European Society of Cardiology (ESC) guidelines. Time between index test and reference standard: NR Target condition: Acute dyspnoea due to heart failure		Ref std +	Ref std -	Total			Source of funding: NR Limitations: Patient Selection: High Index test: Low Reference Standard: Low Flow and timing: Low Overall: High Additional data: Nil
					BNP 100 +	59	53	112			
					BNP 100 -	1	47	48			
					Total	60	100	160			
					Sensitivity: 0.98 [0.91, 1.00] Specificity: 0.47 [0.37, 0.57]						
						Ref std +	Ref std -	Total			
					BNP 150 +	56	39	95			
					BNP 150 -	4	61	65			
					Total	60	100	160			

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
	Setting: Single ED in France				Sensitivity: 0.93 [0.84, 0.98] Specificity: 0.61 [0.51, 0.71]				
					AUC:0.82 (0.8-0.83)				
						Ref std +	Ref std -	Total	
					NTproBNP 280 +	60	95	155	
					NTproBNP 280 -	0	5	5	
					Total	60	100	160	
					Sensitivity: 1.00 [0.94, 1.00] Specificity: 0.05 [0.02, 0.11]				
						Ref std +	Ref std -	Total	
					NTproBNP 1000 +	58	37	95	
					NTproBNP 1000 -	2	63	65	
					Total	60	100	160	
					Sensitivity: 0.97 [0.88, 1.00] Specificity: 0.63 [0.53, 0.72]				
					AUC:0.84 (0.83-0.86)				

1

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Arques 2005[10]	Natriuretic peptide/s: BNP Biosite Threshold/s: 100pg/mL 146pg/mL Study type: Prospective cohort Setting: Single centre acute referrals in France	N = 70 Inclusion criteria: Patients referred to cardiology for acute or recently aggravated dyspnoea at rest. Exclusion criteria: EF<45%; severe mitral valve disease; arrhythmia; unstable angina; acute MI with ST elevation, complete symptom relief by time of echocardiography	Mean age: NR Male/Female (n): 35/35	Index test: Serum BNP Reference standard: 2 cardiologists and one pulmonologist retrospective review blinded to BNP and echocardiography using all information from patient stay and applying Framingham criteria Time between index test and reference standard: NR Target condition: Decompensated heart failure with preserved ejection fraction		Ref std +	Ref std -	Total	Source of funding: NR Limitations: Patient Selection: High Index test: Low Reference Standard: High Flow and timing: Low Overall: Very High Additional data: Additional thresholds
					BNP 100 +	31	14	45	
					BNP 100 -	1	24	25	
					Total	32	38	70	
					Sensitivity: 0.97 [0.84, 1.00] Specificity: 0.63 [0.46, 0.78]				
						Ref std +	Ref std -	Total	
					BNP 146 +	29	9	38	
					BNP 146 -	3	29	32	
					Total	32	38	70	
					Sensitivity: 0.91 [0.75, 0.98] Specificity: 0.76 [0.60, 0.89]				
					AUC: 0.875 (0.77-0.94)				

1

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Arques 2007[11]	Natriuretic peptide/s: BNP Triage Bisoite	N = 41 Inclusion criteria:	Mean age: HF: 84.3 (5.2) Non HF: 83.6	Index test: Serum BNP		Ref std +	Ref std -	Total	Source of funding: NR
					BNP 253 +	19	2	21	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
	Threshold/s: 253pg/mL Study type: Prospective cohort Setting: Single centre ED in France	≥ 70 years of age history of permanent non-valvular atrial fibrillation (AF) presenting to the ED with acute dyspnoea at rest and normal left ventricular (LV) ejection fraction on bedside echo Exclusion criteria: isolated dyspnoea on exertion, arrhythmias other than permanent AF, significant left sided valve disease, acute coronary syndromes and inadequate Doppler tracking	(5.1) Male/Female (n): 17/24	Reference standard: Retrospective review by two cardiologists and one respiratory physician blinded to BNP and tissue Doppler echocardiography Time between index test and reference standard: NR Target condition: Heart failure with preserved ejection fraction	BNP 253 -	3	17	20	Limitations: Patient Selection: High Index test: Low Reference Standard: Low Flow and timing: Low Overall: High Additional data: Additional thresholds
				Total	22	19	41	
				Sensitivity: 0.86 [0.65, 0.97] Specificity: 0.89 [0.67, 0.99]				
				AUC:0.928 (0.8-0.98)				

Table 36: Clinical evidence tables for Barcase 2004[14]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Barcase 2004[14]	Natriuretic peptide/s: BNP Biosite (Triage) Threshold/s:	N = 98 Inclusion criteria: Presenting to urgent care centre/ED with shortness of breath	Mean age: 65 years Male/Female(n): 	Index test: Serum BNP Reference standard: Cardiologist review of medical record blinded to haemodynamic		Ref std +	Ref std -	Total	Source of funding: Kits for BNP supplied by Biosite
					BNP 100 +	55	4	59	
					BNP 100 -	2	37	39	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
	110pg/mL extracted from figure Study type: Prospective cohort Setting: Single ED in USA	Exclusion criteria: Patients under 18 years or those receiving continuous inotrope infusions on an outpatient basis, those whose dyspnoea was clearly not secondary to CHF (trauma, tamponade)	100/0	parameters. Cardiologist had access to all information ED physician had as well as results of any further tests conducted including echocardiography Time between index test and reference standard: BNP taken within 4 hours of admission Reference after hospital trajectory known. Target condition: Acute dyspnoea secondary to CHF	Total	57	41	98	Limitations: Patient Selection: Low Index test: High Reference Standard: High Flow and timing: Low Overall: High Study looked at diagnostic of impedance echocardiography so physicians not blinded to BNP. Male/female imbalance Additional data: NR
					Sensitivity: 0.96 (0.88-1.0) Specificity: 0.90 (0.77-0.97)				
						Ref std +	Ref std -	Total	
					BNP 300 +	40	0	40	
					BNP 300 -	17	41	58	
					Total	57	41	98	
					Sensitivity: 0.70 [0.57, 0.82] Specificity: 1.00 [0.91, 1.00]				
					AUC: 0.979 (0.956-1.002)				

1

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Behnes 2009: MANPRO study[18]	Natriuretic peptide/s: NTproBNP (Dimension	N = 401 Inclusion criteria:	Mean age: 67.4	Index test: Serum NTproBNP		Ref std +	Ref std -	Total	Source of funding: Grant from University of
					NTproBNP 300	117	145	262	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
	Dade) Threshold/s: 300, 500pg/mL Study type: Prospective Cohort Setting: Single ED in Germany	Patients presenting with symptoms of acute dyspnoea and/or peripheral oedema to ED Exclusion criteria: patients with severe renal disease or anaemia; obvious traumatic cause of dyspnoea; pregnancy; a status after immediate cardiopulmonary resuscitation; participation in another clinical trial; aged <18 years	Male/Female (n): 205/196	Reference standard: Retrospective review by study physician with unrestricted access to medical records blinded to NTproBNP Time between index test and reference standard: NR Target condition: Acute heart failure (AHF)	+				Manheim, kits provided by industry Limitations: Patient Selection: Low Index test: Low Reference Standard: Low Flow and timing: Low Overall: Low Additional data: Additional thresholds
				NTproBNP 300 -	5	134	139	
				Total	122	279	401	
				Sensitivity: 0.96 [0.91, 0.99] Specificity: 0.48 [0.42, 0.54]				
					Ref std +	Ref std -	Total	
				NTpro BNP 500 +	112	112	224	
				NTpro BNP 500 -	10	167	177	
				Total	122	279	401	
				Sensitivity: 0.92 [0.85, 0.96] Specificity: 0.60 [0.54, 0.66]				
				AUC: 0.85 (0.81-0.89)				

1

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Berdague 2006[19]	Natriuretic peptide/s: NTproBNP (Roche)	N = 254 Inclusion criteria:	Mean age: 81 +/- 7	Index test: Serum NTproBNP		Ref std +	Ref std -	Total	Source of funding: NR
					NtproBNP	138	57	195	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
	Threshold/s: NTproBNP 1000 and 3000pg/mL Study type: Prospective cohort Setting: Single ED in France	Most prominent disorder acute dyspnoea. Exclusion criteria: Patients younger than 70 years; patients whose dyspnoea was clearly not due to left heart failure (e.g. trauma, tamponade); AMI; unstable angina unless main presenting symptom was dyspnoea	Male/Female (n): 123/133	Reference standard: Two cardiologists retrospective review of medical records and investigations including echocardiography aware of the Framingham criteria. Time between index test and reference standard: NR Target condition: Cardiac dyspnoea	1000 +				Limitations: Patient Selection: Low Index test: Low Reference Standard: Low Flow and timing: Low Additional data: Additional thresholds
					NTproBNP 1000 -	4	55	59	
					Total	142	112	254	
					Sensitivity: 0.97 [0.93, 0.99] Specificity: 0.49 [0.40, 0.59]				
						Ref std +	Ref std -	Total	
					NtproBNP 3000 +	124	31	155	
					NTproBNP 3000 -	18	81	99	
					Total	142	112	254	
					Sensitivity: 0.87 [0.81, 0.92] Specificity: 0.72 [0.63, 0.80]				
					AUC: 0.86(0.81-0.91)				

1

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Blonde-Cynober 2011[22]	Natriuretic peptide/s: BNP Triage	N = 64 Inclusion criteria:	Mean age: 84.3 (+/-7.4)	Index test: Serum BNP		Ref std +	Ref std -	Total	Source of funding: NR
					BNP 100 +	23	12	35	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
	Threshold/s: 100, 129, 635 pg/mL Study type: Prospective cohort Setting: Single centre inpatients of geriatric hospital in France	Suspected HF Exclusion criteria: NR	Male/Female (n): 20/44	Reference standard: Retrospective review by cardiologist and geriatrician using Framingham criteria with access to medical records and investigations including echocardiography Time between index test and reference standard: NR Target condition: Definite heart failure	BNP 100 -	3	26	29	Limitations: Patient Selection: Low Index test: Low Reference Standard: Low Flow and timing: Low Overall: Low Additional data: Additional thresholds
					Total	26	38	64	
					Sensitivity: 0.88 [0.70, 0.98] Specificity: 0.68 [0.51, 0.82]				
						Ref std +	Ref std -	Total	
					BNP 129 +	23	10	33	
					BNP 129 -	3	28	31	
					Total	26	38	64	
					Sensitivity: 0.88 [0.70, 0.98] Specificity: 0.74 [0.57, 0.87]				
						Ref std +	Ref std -	Total	
					BNP 635 +	9	0	9	
					BNP 635 -	17	38	55	
					Total	26	38	64	
					Sensitivity: 0.35 [0.17, 0.56] Specificity: 1.00 [0.91, 1.00]				
					AUC: 0.8391 (0.0536)				

Table 37: Clinical evidence tables for Chenevier- Gobeaux 2005[26]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
Chenevier - Gobeaux 2005[26] (All results without renal function stratification from Chenevier -Gobeaux 2010[27])	Natriuretic peptide/s: MRproANP (BRAHMS) NTproBNP (Roche) BNP Biosite Threshold/s: Study type: Prospective cohort Setting: Single ED in France	N = 378 Inclusion criteria: Dyspnoeic patients aged > 60 years attending the ED between the hours of 5pm and 8.30am Exclusion criteria: NR	Mean age: 78 (12) Male/Female (n): 190/188 *number of patients correctly identified by reference standard 115/381 in 2005 however missing data for 3 patients in 2010 paper, and no clarification as to how these three were classified by the reference standard. Taken 115 as number correctly classified.*	Index test: Serum MRproANP Serum NTproBNP Serum BNP Reference standard: 2 independent senior ED physicians based on findings of physical examination, medical history, ECG and CXR and blood tests. Time between index test and reference standard: NR Target condition: Cardiac related dyspnoea			Source of funding: NR Limitations: Patient Selection: High Index test: Low Reference Standard: Low Flow and timing: High Overall: High Additional data: Stratified by renal function for BNP and NTproBNP

	Ref std +	Ref std -	Total
BNP 100 +	114	155	269
BNP 100 -	1	108	109
Total	115	266	381

Sensitivity: 0.99 [0.95, 1.00]
Specificity: 0.41 [0.35, 0.47]

AUC:0.82 (0.79-0.88)

	Ref std +	Ref std -	Total
NTpro BNP 300 +	115	192	307
NTpro BNP 300 -	0	71	71
Total	115	266	381

Sensitivity: 1.00 [0.97, 1.00]
Specificity: 0.27 [0.22, 0.33]

AUC: 0.83 (0.78-0.87)

	Ref std +	Ref std -	Total
MRpro ANP	113	158	271

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
					169 +				
					MRpro ANP 169 -	2	105	107	
					Total	115	266	381	
					Sensitivity: Specificity:				
					AUC: 0.81 (0.76-0.84)				

1

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures				Effect sizes		Comments
Chung 2006[28]	Natriuretic peptide/s: BNP Triage Threshold/s: BNP 100, 400 pg/mL Study type: Prospective cohort Setting: Single ED in Australia	N = 143 Inclusion criteria: Severe dyspnoea presenting to the ED and requiring hospital admission Exclusion criteria: ACS; renal failure requiring dialysis; unable to give written consent	Mean age: 79 (+/-10) Male/Female (n): 63/80	Index test: Serum BNP Reference standard: Independent cardiologist specialising in heart failure retrospective review with access to medical records and investigation results including echocardiography not blinded to BNP Time between index test and reference standard: NR Target condition: Heart failure		Ref std +	Ref std -	Total			Source of funding: NR Limitations: Patient Selection: Low Index test: High Reference Standard: High Flow and timing: Low Overall: Very High Additional data: Nil
					BNP 100 +	72	42	114			
					BNP 100 -	0	29	29			
					Total	72	71	143			
					Sensitivity: 1.00 [0.95, 1.00] Specificity: 0.41 [0.29, 0.53]						
					AUC: 0.85 (0.78-0.91)						
						Ref std +	Ref std -	Total			
					BNP 400 +	60	17	77			
					BNP 400 -	12	54	66			

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
					Total	72	71	143	
					Sensitivity: 0.83 [0.73, 0.91] Specificity: 0.76 [0.64, 0.85]				

Table 38: Clinical evidence tables for Dao 2001[38]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Dao 2001[38]	Natriuretic peptide/s: BNP Biosite (Triage) Threshold/s: 100 pg/mL (Also reports: 80, 115, 120, 150 pg/mL) Study type: Cross-sectional Setting: Single ED in USA	N = 250 Inclusion criteria: Convenience sample. Patients presenting to ED with symptoms shortness of breath as predominant complaint. Associated symptoms could be oedema, weight gain, cough or wheeze Exclusion criteria: Patients whose dyspnoea was clearly not due to chronic heart failure (CHF) (trauma or cardiac tamponade). Patients with acute coronary	Mean age: 63 years Male/Female (n): 235/15	Index test: Serum BNP Reference standard: Retrospective review by two cardiologists of all medical records pertaining to the patients and made initial assessments as to the probability of CHF. Blinded to ED diagnosis, BNP. Access to ED reference sheets and any further information which may have become available including CXR, echocardiography measuring systolic or diastolic dysfunction and hospital course. Confirmation of high probability CHF based on Framingham criteria. Time between index test and reference standard: Serum taken at initial presentation. Reference		Ref std +	Ref std -	Total	Source of funding: Not reported (NR) Limitations: Patient Selection: HIgh Index test: Low Reference Standard: Low Flow and timing: Low Overall: High Male/Female imbalance Additional data:
					BNP 100 +	91	9	100	
					BNP 100 -	6	144	150	
					Total	97	153	250	
					Sensitivity: 0.94 (0.87-0.98) Specificity: 0.94 (0.89-0.97)				
						Ref std +	Ref std -	Total	
					BNP 150 +	84	5	89	
					BNP 150-	13	148	161	
					Total	97	153	250	
					Sensitivity: 0.87 [0.78, 0.93] Specificity: 0.97 [0.93, 0.99]				

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
		syndromes (ACS) were excluded unless predominant presentation was CHF.		after hospital trajectory known. Target condition: Congestive cardiac failure causing dyspnoea presenting to ED	AUC:0.979		Also reports: 80, 115, 120, 150 pg/mL

Table 39: Clinical evidence tables for Davis 2004[39]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Davis 2004[39]	Natriuretic peptide/s: BNP in house assay Threshold/s: Receiver-operating characteristic (ROC) curve Displayed all values of BNP 10-50 pmol/L *converted to pg/mL by NCGC*	N = 52 Inclusion criteria: Required urgent admission and treatment for acute dyspnoea Exclusion criteria: Obvious pneumonia, pulmonary embolism (PE), pneumothorax	Mean age: 74 years Male/Female (n): 21/31	Index test: Serum BNP Reference standard: Retrospective review by a committee of physicians and a radiologist according to clinical evaluation at admission and response to treatment, CXR. Time between index test and reference standard: Serum taken at initial presentation. Reference after hospital trajectory known. Target condition: Heart failure causing dyspnoea requiring admission and acute		Ref std +	Ref std -	Total	Source of funding: Health Research Council, national heart foundation of New Zealand, Canterbury Respiratory research trust Limitations: Patient Selection: Low Index test: Low Reference Standard: Low
					BNP 100 +	26	2	44	
					BNP 100 -	6	18	8	
					Total	32	20	52	
					Sensitivity:0.81 (0.64-0.93) Specificity: 0.9 (0.68-0.99)				
						Ref std +	Ref std -	Total	
					BNP 195 +	15	0	15	
					BNP 195 -	17	20	37	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
	100pg/ML extracted from ROC curve ≈ 28.8 pmol/L <u>Study type:</u> Prospective Cohort <u>Setting:</u> Single ED in New Zealand			treatment for dyspnoea	Total 32 20 52 Sensitivity: 0.47 [0.29, 0.65] Specificity: 1.00 [0.83, 1.00] AUC: NR "BNP provided higher sensitivity and specificity than ANP"		Flow and timing: Low Overall: Low <u>Additional data:</u> ANP data not extractable

1

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
Defilippi 2007[40]	<u>Natriuretic peptide/s:</u> BNP Triage Biosite NTproBNP Roche <u>Threshold/s:</u> ROC curves for renal function stratification only	N = 831 <u>Inclusion criteria:</u> Patients presenting to the ED with a complaint of dyspnoea and who underwent natriuretic peptide measurement <u>Exclusion criteria:</u> Patients < 18 years old, or in whom there	<u>Mean age:</u> eGFR <60ml/min/1.73 m^2: 69.3 (13.1) eGFR <60ml/min/1.73 m2: 63.5 (16.0) <u>Male/Female (n):</u> 380/451	<u>Index test:</u> Serum BNP Serum NTproBNP <u>Reference standard:</u> Case report forms reviewed by a cardiologist blind to NP results, with random sample validated by a second cardiologist Time between index test and reference standard: NR	Analysis conducted between groups with varying renal function stratified by eGFR (< or ≥ 60 ml/min/1.73m^2). Similar accuracy. NS difference in AUC when split by renal function for NTproBNP versus BNP.		<u>Source of funding:</u> Dade Behring Corporation, manufacturer of NTproBNP assay but not the one evaluated in the study. <u>Limitations:</u> Patient Selection: Low

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
	Study type: Prospective cohort Setting: Single centre ED in the USA	was inadequate information to assess the aetiology of dyspnoea		Target condition: Decompensated heart failure			Index test: Low Reference Standard: Low Flow and timing: Low Overall: Low Additional data: Renal stratification of patients data

Table 40: Clinical evidence tables for Dokanish 2004[43]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Dokanish 2004[43]	Natriuretic peptide/s: BNP Biosite (Triage) Threshold/s: 250 pg/mL Study type: Cross sectional	N = 122 Inclusion criteria: Consecutive inpatients referred to the cardiology consult service for suspected heart failure. Exclusion criteria: Non sinus rhythm,	Mean age: 56 (13) Male/Female (n): 62/60	Index test: Serum BNP Reference standard: Consultant cardiologist review with access to patient charts, laboratory and radiographic tests using Framingham criteria Time between index test and reference standard: NR		Ref std +	Ref std -	Total	Source of funding: NR Limitations: Patient Selection: High Index test: Low Reference Standard: Low Flow and timing: Low
					BNP 250 +	60	12	72	
					BNP 250 -	10	40	50	
					Total	70	52	122	
					Sensitivity: 0.86 [0.75, 0.93] Specificity: 0.77 [0.63, 0.87]				
					AUC: 0.87 (p<0.0001)				

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
	Setting: Inpatients in the USA	severe MR, mitral stenosis, prosthetic mitral valve, severe mitral annular calcification, unstable angina or MI		Target condition: Dyspnoea caused by heart failure			Overall: High Additional data: Nil

1

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Eckstein 2012[45] Overlap with BACH trial data. Data only extracted for NTproBNP otherwise double counting for MRproAN	Natriuretic peptide/s: NTproBNP Roche Threshold/s: 1550pg/mL Study type: Prospective Cohort Setting:	N = 632 Inclusion criteria: patients presenting to the ED with dyspnoea as the most prominent symptom Exclusion criteria: Patients < 18 years old; patients on haemodialysis; rhythms other than	Mean age: AF: 79 (9) SR: 71 (15) Male/Female (n): NR for included patients	Index test: Serum NTproBNP Reference standard: Two independent cardiologists retrospective review of medical records and investigation results including BNP and echocardiography Time between index test and reference standard: NR Target condition:		Ref std +	Ref std -	Total	Source of funding: Authors received honoraria from industry and grants Limitations: Patient Selection: Low Index test: Low Reference Standard: Low
					Ntpr oBNP 1550 +	304	35	339	
					Ntpr oBNP 1550 -	58	235	293	
					Total	362	270	632	
					Sensitivity: 0.84 [0.80, 0.88] Specificity: 0.87 [0.82, 0.91]				
					AUC: 0.92 (0.91-0.94)				

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
P	Single centre Ed in Switzerland	AF or SR		Acute heart failure			Flow and timing: Low Additional data: Analysis by rhythm AF versus SR

1

2

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
Fabian 2011[49]	Natriuretic peptide/s: NTproBNP Roche Threshold/s: ROC curve only Study type: Prospective cohort Setting: Single centre internal medicine	N = 130 Inclusion criteria: Patients aged 65 to 90 admitted to an internal medicine unit because of dyspnoea. Patients had to have grade 5 on the MRC dyspnoea scale and be using accessory muscles of respiration Exclusion criteria: Patients with	Mean age: 80 + 6 Male/Female (n): 57/75	Index test: Serum NTproBNP Reference standard: Clinical diagnosis according to European society of cardiology guidelines. Time between index test and reference standard: NR Target condition: Congestive cardiac failure	NTproBNP AUC: 0.576 (0.476-0.676)		Source of funding: NR Limitations: Patient Selection: Low Index test: High Reference Standard: High Flow and timing: Low Overall: Low Additional data:

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
	admissions in Italy	pulmonary embolism					Nil

1

2

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Fleischer 1997[54]	Natriuretic peptide/s: BNP in house assay Threshold/s: 173 pg/mL Study type: Prospective	N = 123 Inclusion criteria: Patients requiring urgent medical admission to hospital with worsening dyspnoea Exclusion criteria:	Mean age: 68 (23-90) Male/Female (n): 69/54	Index test: Serum BNP Reference standard: Clinical diagnosis based on intent to treat HF with diuretic therapy for 24 hours Time between index test and reference standard: NR		Ref std +	Ref std -	Total	Source of funding: Health research council and national heart foundation of New Zealand Limitations: Patient Selection: High
					BNP 173 +	36	4	40	
					BNP 173 -	7	76	83	
					Total	43	80	123	
					Sensitivity: 0.84 [0.69, 0.93] Specificity: 0.95 [0.88, 0.99]				

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
	Cohort Setting: Urgent medical admissions to single centre in New Zealand	NR		Target condition: Heart failure	AUC:NR		Index test: High Reference Standard: High Flow and timing: Low Overall: Very High Additional data: Nil

1

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Gargani 2008[59]	Natriuretic peptide/s: NTproBNP Roche Threshold/s: 298 pg/mL Study type: Prospective cohort Setting: Single centre in Italy;	N = 149 Inclusion criteria: Presence of dyspnoea at admission; NTproBNP taken on admission; US assessment taken on admission; no diuretic therapy before measurements Exclusion criteria: NR	Mean age: Patients with dyspnoea: 72 (11) Patients without dyspnoea: 66 (9) Male/Female (n): 98/51	Index test: Serum NTproBNP Reference standard: Retrospective review by two cardiologists blinded to NTproBNP with access to medical records and investigation results including echo Time between index test and reference standard: NR Target condition: Cardiogenic dyspnoea		Ref std +	Ref std -	Total	Source of funding: NR Limitations: Patient Selection: High Index test: Low Reference Standard: Low Flow and timing: Low Overall: High
					NTproBNP 298+	118	2	120	
					NTproBNP 298-	4	25	29	
					Total	122	27	149	
					Sensitivity: 0.97 [0.92, 0.99] Specificity: 0.93 [0.76, 0.99]				
					AUC: 0.978 (0.94-0.995)				

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
	Patients admitted to Cardiology and Pulmonology division						Additional data: Nil

1

2

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Gorissen 2007[64]	Natriuretic peptide/s: BNP Triage Biosite NTproBNP Roche Threshold/s: 225pg/mL BNP, 1550pg/mL NTproBNP Study type: Retrospective cohort Setting: Single centre	N = 80 Inclusion criteria: Presenting to the ED with dyspnoea as the primary complaint Exclusion criteria: AMI; no consensus on clinical diagnosis	Median age: 74 (43-90) Male/Female (n): 44/36	Index test: Serum BNP Serum NTproBNP Reference standard: Retrospective review by cardiologists and pulmonologist with access to hospital records and investigations Time between index test and reference standard: NR Target condition: Congestive heart failure		Ref std +	Ref std -	Total	Source of funding: NR Limitations: Patient Selection: High Index test: Low Reference Standard: Low Flow and timing: High Overall: Very High Additional data: BNP centaur assay
					BNP 225 +	31	11	42	
					BNP 225 -	9	29	38	
					Total	40	40	80	
					Sensitivity: 0.78 [0.62, 0.89] Specificity: 0.72 [0.56, 0.85]				
					AUC: 0.783				
						Ref std +	Ref std -	Total	
					NTpro BNP 1550 +	32	14	46	
					NTpro BNP	8	26	34	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
	ED in the Netherlands				1550 -				
					Total	40	40	80	
					Sensitivity: 0.80 [0.64, 0.91] Specificity: 0.65 [0.48, 0.79]				
					AUC: 0.774				

1

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Gruson 2008[69]	Natriuretic peptide/s: BNP (Access) NTproBNP (Roche) NTproANP (In house assay) Threshold/s: 8000ng/L Study type: Prospective cohort Setting: Single ED in Belgium	N = 137 Inclusion criteria: Patients presenting to the Ed with dyspnoea and/or chest pain Exclusion criteria: NR	Mean age: 69 Male/Female (n): 77/60	Index test: Serum BNP Serum NTproBNP Serum NTproANP Reference standard: Based upon clinical signs, chest radiography, echocardiography and/or radionuclide angiography and confirmed by a cardiologist blinded to all other measurements Time between index test and reference standard: NR Target condition: Congestive heart failure		Ref std +	Ref std -	Total	Source of funding: NR Limitations: Patient Selection: Low Index test: Low Reference Standard: Low Flow and timing: Low Overall: Low Additional data: 5000, 10000 ng/l thresholds
					NTproANP 8000 +	30	23	53	
					NTproANP 8000-	1	83	84	
					Total	31	106	137	
					Sensitivity: 0.97 [0.83, 1.00] Specificity: 0.78 [0.69, 0.86]				
					AUC NTproANP: 0.94 (0.89-0.98)				
					AUC BNP: 0.93 (0.87-0.96)				
					AUC NTproBNP: 0.91 (0.85-0.95)				

2

3

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
Gruson 2012[68]	Natriuretic peptide/s: BNP (Access) Beckman NTproBNP Roche Threshold/s: ROC curve only Study type: Prospective cohort Setting: Single ED in Belgium	N = 153 Inclusion criteria: Patients admitted to the ED with dyspnoea and/or chest pain Exclusion criteria: NR	Mean age: 68 +/-9 Male/Female (n): 85/71	Index test: Serum BNP Serum NTproBNP Reference standard: On the basis of clinical signs, chest x-ray, echocardiography and/or radionuclide angiography Time between index test and reference standard: NR Target condition: Congestive heart failure	BNP AUC: 0.91 (0.86-0.95) NTproBNP AUC: 0.92 (0.86-0.96)		Source of funding: NR Limitations: Patient Selection: High Index test: Low Reference Standard: High Flow and timing: Low Overall: Very High Additional data: Study primarily looking at diagnostic accuracy of $proBNP_{1-108}$ non protocol NP

1

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
Havelka 2011[73]	Natriuretic peptide/s: BNP Triage	N = 54 Inclusion criteria: Patients over the age	Mean age: NR Male/Female	Index test: Serum BNP Reference standard:	BNP AUC: 0.77 (0.59-0.95)		Source of funding: NR

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
	Threshold/s: ROC curve only Study type: Prospective cohort Setting: Single ED in the USA	of 50 presenting with a chief complaint of dyspnoea Exclusion criteria: Patients on haemodialysis	(n): 25/29	Discharge diagnosis electronic medical record for each patient, no blinding attempted. Time between index test and reference standard: NR Target condition: Congestive heart failure			Limitations: Patient Selection: Low Index test: high Reference Standard: High Flow and timing: Low Overall: Very High Additional data: Nil

Table 41: Clinical evidence tables for Januzzi 2006[78]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Januzzi 2006[78]: ICON study (comprising pooled data from Lainchbury 2003[89], Bayes Genis	Natriuretic peptide/s: NTproBNP Roche Threshold/s: 300pg/mL Study type:	N = 1256 Inclusion criteria: Dyspnoeic patients presenting to ED Exclusion criteria: NR	Mean age: 68.3 (15.9) Male/Female (n): 641/615	Index test: Serum NTproBNP Reference standard: Retrospective review utilising European society of cardiology guidelines. Suitable for pooling across studies Time between index test and		Ref std +	Ref std -	Total	Source of funding: Authors received speaking and research grants from Roche diagnostics Limitations:
					NTproBNP 300 +	713	214	927	
					NTproBNP 300 -	7	322	329	
					Total	720	536	1256	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
2004[17] and Januzzi 2005[79]: PRIDE study, and unpublished registry data)	Pooled prospective trial data Setting: Four ED departments in USA, New Zealand, Spain and the Netherlands			reference standard: NR Target condition: Acute dyspnoea due to heart failure	Sensitivity: 0.99 [0.98, 1.00] Specificity: 0.60 [0.56, 0.64] The study also stratified by age as a cut off: <50 years (n=184) 450pg/mL Sens: 97% Spec: 93% 50-75 years (n=573) 900pg/mL Sens: 90 Spec: 82 >75 years (n=535) 1800pg/mL Sens: 90 Spec: 84		Patient Selection: High Index test: Low Reference Standard: Low Flow and timing: Low Overall: High Additional data: Nil

1

2

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Karmpaliotis 2007[82]	Natriuretic peptide/s: BNP Triage Biosite Threshold/s: 1000pg/mL Study type: Prospective cohort	N = 80 (6 mixed) Inclusion criteria: Acute hypoxemic respiratory failure undergoing right heart catheterisation on the basis of diagnostic uncertainty regarding the aetiology of respiratory failure: admission to ICU	Age range: (52-85) Male/Female (n): 45/35	Index test: Serum BNP Reference standard: Two experienced attending intensivists retrospective review of medical records blinded to NPs Time between index test and reference standard: At least 10 days after enrolment		Ref std +	Ref std -	Total	Source of funding: NR Limitations: Patient Selection: High Index test: Low Reference Standard: Low Flow and timing: Low
					BNP 1000 +	13	8	21	
					BNP 1000 -	10	43	53	
					Total	23	51	74	
					Sensitivity: 0.57 [0.34, 0.77] Specificity: 0.84 [0.71, 0.93]				
					AUC: NR				

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
	Setting: Single centre ICU in the USA	with onset of respiratory failure; b8ilateral pulmonary infiltrates; known LVEF <30% Exclusion criteria: Patients undergoing RHC for non-diagnostic uncertainty reasons.		Target condition: Cardiogenic pulmonary oedema			Overall: High Additional data: Additional thresholds

1

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Klemen 2009[85]	Natriuretic peptide/s: NTproBNP Roche Threshold/s: 300, 1000, 3000 pg/mL Study type: Prospective cohort Setting: Single centre	N = 441 Inclusion criteria: Shortness of breath as primary complaint Exclusion criteria: Age <18 years old, history of renal insufficiency, trauma, severe coronary ischemia (unless predominant complaint was dyspnoea), other causes of dyspnoea	Mean age: 59.1 Male/Female (n): 271/170	Index test: Serum NTproBNP Reference standard: Final hospital diagnosis confirmed by cardiologists and or intensivists by using medical records and investigation results Time between index test and reference standard: NR Target condition: Heart failure related acute dyspnoea		Ref std +	Ref std -	Total	Source of funding: NR Limitations: Patient Selection: Low Index test: Low Reference Standard: Low Flow and timing: Low Overall: Low
					NTproBNP 300 +	236	93	329	
					BNP NTproBNP 300 -	2	110	112	
					Total	238	203	441	
					Sensitivity: 0.99 [0.97, 1.00] Specificity: 0.54 [0.47, 0.61]				
						Ref std +	Ref std -	Total	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
	pre hospital emergency setting in Slovenia	comprising pneumonia, PE, carcinoma, pneumothorax, pleural effusion, intoxication (drugs), anaphylactic reactions, upper airway obstruction, bronchial stenosis and GORD according to the history and tests available in pre hospital setting.			NTproBNP 1000 +	214	49	263	Additional data: Additional thresholds
					BNP NTproBNP 1000 -	24	154	178	
					Total	238	203	441	
					Sensitivity: 0.90 [0.85, 0.93] Specificity: 0.76 [0.69, 0.82]				
						Ref std +	Ref std -	Total	
					NTproBNP 3000 +	159	10	169	
					BNP NTproBNP 3000 -	79	193	272	
					Total	238	203	441	
					Sensitivity: 0.67 [0.60, 0.73] Specificity: 0.95 [0.91, 0.98]				
					AUC: 0.9 (0.85-0.94)				

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Table 42: Clinical evidence tables for Lainchbury 2003[89]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Lainchbury 2003[89] Only BNP results extracted. NTproBNP from pooled results in ICON study[78]	Natriuretic peptide/s: BNP Biosite Triage (plus 3 in house assays – results not shown) Threshold/s: 104 pg/mL And 346 pg/mL extracted Study type: Prospective Cohort Setting: Single ED in New Zealand	N =205 Inclusion criteria: Dyspnoea was part of the reason for presentation, and were able to give a blood sample within 8 hours of arrival in the ED Exclusion criteria: NR	Mean age: 70 years Male/Female (n): 100/105	Index test: Serum BNP Serum NTproBNP (results presented from pooled ICON analysis[78]) Reference standard: Retrospective review by two independent cardiologists with access to medical charts, all investigations including echocardiography except natriuretic peptide assays Time between index test and reference standard: NR Target condition: Cardiac dyspnoea presenting to the ED		Ref std +	Ref std -	Total	Source of funding: Health research council of New Zealand; National heart foundation of NZ. Test strips provided by industry Limitations: Patient Selection: High Index test: Low Reference Standard: Low Flow and timing: Low Overall: High Additional data: Additional thresholds
					BNP 104 +	68	69	137	
					BNP 104 -	2	66	68	
					Total	70	135	205	
					Sensitivity: 0.97 [0.90, 1.00] Specificity: 0.49 [0.40, 0.58]				
						Ref std +	Ref std -	Total	
					BNP 346 +	59	31	90	
					BNP 346 +	11	104	115	
					Total	70	135	205	
					Sensitivity: 0.84 [0.74, 0.92] Specificity: 0.77 [0.69, 0.84]				
					AUC:0.89 (CI: NR]				

Table 43: Clinical evidence tables for Logeart 2002[95]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Logeart 2002[95]	Natriuretic peptide/s: BNP Biosite (Triage) Threshold/s: 100 pg/mL and 250 pg/mL Study type: Cross-sectional Setting: Referrals to intensive care unit (ICU) in France	N =163 Inclusion criteria: All patients presenting to Ed with acute severe dyspnoea Exclusion criteria: Patients with AMI, chest injury or recent surgery	Mean age: 71 years Male/Female (n): 109/54	Index test: Serum BNP Reference standard: Retrospective review by two independent cardiologists and one pulmonologist with access to medical records including echo and pulmonary function tests Time between index test and reference standard: NR Target condition: Acute dyspnoea due to heart failure		Ref std +	Ref std -	Total	Source of funding: BNP assays free from industry Limitations: Patient Selection: High Index test: Low Reference Standard: Low Flow and timing: Low Overall: High Additional data: Additional thresholds
					BNP 100 +	110	33	143	
					BNP 100 -	5	15	20	
					Total	115	48	163	
					Sensitivity: 0.96 [0.90, 0.99] Specificity: 0.31 [0.19, 0.46]				
						Ref std +	Ref std -	Total	
					BNP 250 +	105	15	120	
					BNP 250-	10	33	43	
					Total	115	48	163	
					Sensitivity: 0.91 [0.85, 0.96] Specificity: 0.69 [0.54, 0.81]				
					AUC:0.93 [CI NR]				

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Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Lokuge 2010[96]	Natriuretic peptide/s: BNP (Abbott)	N = 612 Inclusion criteria:	Mean age: 74.5	Index test: Serum BNP		Ref std +	Ref std -	Total	Source of funding: Unrestricted grant from
					BNP 101 +	252	166	418	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
	Threshold/s: 101,265 pg/mL Study type: Retrospective cohort Setting: Multicentre EDs in Australia	Illness requiring assessment by a doctor within 30 mins of arrival with a primary presenting complaint of dyspnoea Exclusion criteria: < 40 years of age, traumatic cause of dyspnoea, cardiogenic shock, serum creatinine > 250µmol/l and patients who were transferred to another hospital within 24 hours of presentation	Male/Female (n): 328/284	Reference standard: Retrospective review by one emergency physician and one cardiologist with access to medical records and investigation results including echocardiography blinded to BNP Time between index test and reference standard: NR Target condition: Heart failure	BNP 101 -	22	172	194	Janssen Cilag. Limitations: Patient Selection: High Index test: Low Reference Standard: Low Flow and timing: Low Overall: High Additional data: Nil
				Total	274	338	612	
				Sensitivity: 0.92 [0.88, 0.95] Specificity: 0.51 [0.45, 0.56]				
					Ref std +	Ref std -	Total	
				BNP 265 +	227	64	291	
				BNP 265 -	47	274	321	
				Total	274	338	612	
				Sensitivity: 0.83 [0.78, 0.87] Specificity: 0.81 [0.76, 0.85]				
				AUC:0.8705				

Table 44: Clinical evidence tables for Maisel 2002: Breathing Not Properly Study[99]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Maisel 2002: Breathing Not Properly Study[99]	Natriuretic peptide/s: BNP Biosite (Triage) Threshold/s:	N =1586 Inclusion criteria: Shortness of breath (SOB) as the most prominent symptom;	Mean age: 64 Male/Female (n): 888/698	Index test Serum BNP Reference standard Retrospective review by two independent cardiologists of all		Ref std +	Ref std -	Total	Source of funding: Devices and meters and some financial support were
					BNP 100 +	670	202	872	
					BNP 100 -	74	640	714	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
	100 pg/mL (Also reports: 50, 80, 125, 150 pg/mL) Study type: Prospective Cohort Setting: Emergency Department (ED) in 7 hospitals: 5 USA; 1 France; 1 Norway	Aged 18 or over Exclusion criteria: Those whose dyspnoea was clearly not due to cardiac failure e.g. trauma, cardiac tamponade); acute myocardial infarction (AMI); renal failure; unstable angina unless most predominant symptom at presentation was dyspnoea		medical records, facilitated by Framingham criteria. Both were blinded to BNP result, and ED physician diagnosis. Data available were chest X-ray (CXR), medical chart not seen by ED physician, subsequent tests including echocardiography and hospital course. Time between index test and reference standard: Serum taken at initial presentation. Reference after hospital trajectory known. Target condition: Congestive cardiac failure causing dyspnoea presenting to ED	Total	744	842	1586	provided by Biosite, San Diego. Limitations: Patient Selection: Low Index test: Low Reference Standard: Low Flow and timing: Low Overall: Low Additional data: Also reports: 50, 80, 125, 150 pg/mL thresholds
					Sensitivity: 0.9 (0.88-0.92) Specificity: 0.76 (0.73-0.79)				
						Ref std +	Ref std -	Total	
					BNP 150 +	632	143	775	
					BNP 150 +	112	699	811	
					Total	744	842	1586	
					Sensitivity: 0.85 [0.82, 0.87] Specificity: 0.83 [0.80, 0.85]				
					Area-under-the-curve (AUC): 0.91 (0.9 - 0.93)				

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Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Maisel 2010[98]: BACH trial	Natriuretic peptide/s: MRproANP (BRAHMS) BNP Triage Biosite	N =1641 Inclusion criteria: attending ED with shortness of breath as the primary	Mean age: NR Male/Female (n):	Index test: Serum MRproANP Serum BNP Reference standard:		Ref std +	Ref std -	Total	Source of funding: Several authors directors and employees of manufacturing
					BNP 100 +	543	409	952	
					BNP 100-	25	664	689	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
	Threshold/s: Study type: Prospective cohort Setting: 15 ED centres with 8 USA; 1UK; 1 Germany; 1 Poland; 1 Italy; 1 Switzerland; 1 Greece; 1 New Zealand	complaint Exclusion criteria: Aged <18 years old, unable to provide consent, STEMI, receiving haemodialysis, had renal failure	859/782	Retrospective review by two cardiologists blinded to NP results. Access to medical records and investigation results including echo Time between index test and reference standard: NR Target condition: Heart failure	Total	568	1073	1641	companies Limitations: Patient Selection: Low Index test: Low Reference Standard: Low Flow and timing: Low Additional data: Prognostic utility
					Sensitivity: 0.96 [0.94, 0.97] Specificity: 0.62 [0.59, 0.65]				
					AUC:0.91 (0.9-0.93)				
					NTproBNP ROC curve shown with AUC: 0.9 (0.88-0.91) figure too small to extract data.				
						Ref std +	Ref std -	Total	
					MRpro ANP 120 +	551	430	981	
					MRpro ANP 120-	17	643	660	
					Total	568	1073	1641	
					Sensitivity: 0.97 [0.95, 0.98] Specificity: 0.60 [0.57, 0.63]				
					AUC:0.9 (0.88-0.91)				

1

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
Moe 2007[107] data from IMPROVE-	Natriuretic peptide/s: NTproBNP Roche	N = 500 Inclusion criteria: > 18 years of age,	Mean age: UC group: 71 (14) NTproBNP	Index test: Serum NTproBNP Reference standard:	AUC: 0.86 (0.84-0.89)		Source of funding: Supported by Roche

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
CHF study	Threshold/s: ROC curve analysis only Study type: Cohort data from RCT Setting: Multicentre trial from 7 EDs in Canada	presenting to the ED with dyspnoea of suspected cardiac origin Exclusion criteria: Advanced renal disease , AMI, malignancy, dyspnoea from clinically overt origins e.g. pneumothorax or chest trauma	group: 70 (15) Male/Female (n): 258/242	Retrospective review by two cardiologists with access to medical records and investigations including echocardiography Time between index test and reference standard: NR Target condition: AHF			diagnostics Limitations: Patient Selection: Low Index test: Low Reference Standard: Low Flow and timing: Low Overall: Low Additional data: Prognostic data and cost analysis

Table 45: Clinical evidence tables for Mueller 2005: BASEL study[111] (+Gegenhuber 2006[61]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Mueller 2005: BASEL study[111] (+Gegenh	Natriuretic peptide/s: BNP Abbot NTproBNP Roche MRproANP	N = 251 Inclusion criteria: Dyspnoea as the chief complaint sat the initial	Mean age: 72.8 years Male/Female (n):	Index test: Serum BNP Serum NTproBNP (+ Serum MRproANP)		Ref std +	Ref std -	Total	Source of funding: Grant from Upper Austrian Government. Reagents
					BNP 100 +	132	44	176	
					BNP 100 -	5	70	75	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
uber 2006[61] retrospective samples MRproANP results measured 1 year after collection)	BRAHMS Threshold/s: 100pg/mL BNP 292pg/mL NTproBNP Study type: Prospective Cohort Setting: Single ED in Austria	examination in the emergency department Exclusion criteria: ST-elevation myocardial infarction (STEMI), Non-ST-elevation myocardial infarction (NSTEMI), Troponin positive ACS and trauma patients were excluded	234/17	Reference standard: One study investigator retrospectively reviewed records after three days including echocardiographic results, thereafter the final classification was based upon Framingham criteria and evidence of systolic or diastolic dysfunction on echocardiography Time between index test and reference standard: Serum taken within 4 hours of admission: Clinical evaluation was complete within three days after initial patient classification Target condition: Heart failure causing dyspnoea requiring presentation to ED	Total	137	114	251	supplied free from Pharmaceutical companies Limitations: Patient Selection: Low Index test: Low Reference Standard: Low Flow and timing: Low Overall: Low Male/female imbalance Additional data: Thresholds: BNP: 118,168,295 NTproBNP: 125/450, 476, 825
					Sensitivity: 0.96 (0.92-0.99) Specificity: 0.61 (0.52-0.7)				
						Ref std +	Ref std -	Total	
					BNP 295 +	110	16	126	
					BNP 295 -	27	98	125	
					Total	137	114	251	
					Sensitivity: 0.80 [0.73, 0.87] Specificity: 0.86 [0.78, 0.92]				
					AUC: 0.916 (0.847-0.947)				
						Ref std +	Red std -	Total	
					NTpro BNP 292 +	130	54	184	
					NTpro BNP 2921 -	7	60	67	
					Total	137	114	251	
					Sensitivity: 0.95 (0.9-0.98) Specificity: 0.53 (0.43-0.62)				
						Ref std +	Ref std -	Total	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
					NTpro BNP 825 +	119	22	141	
					NTpro BNP 825 -	18	92	110	
					Total	137	114	251	
					Sensitivity: 0.87 [0.80, 0.92] Specificity: 0.81 [0.72, 0.87]				
					AUC: 0.903 (0.859-0.939)				
						Ref std+	Ref std -	Total	
					MRproANP 109 +	130	50	180	
					MRproANP 109-	7	64	71	
					Total	137	114	251	
					Sensitivity: 0.95 [0.90, 0.98] Specificity: 0.56 [0.47, 0.65]				
						Ref std+	Ref std -	Total	
					MRproANP 169 +	122	27	149	
					MRproANP 169 -	15	87	102	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
					Total	137	114	251	
					Sensitivity: 0.89 [0.83, 0.94] Specificity: 0.76 [0.67, 0.84]				
					AUC: 0.876 (0.829-0.914)				

1

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Nazarian 2009[120]	Natriuretic peptide/s: NTproBNP Roche Threshold/s: 300,2200 pg/mL Study type: Prospective cohort Setting: Single ED in Italy	N = 145 Inclusion criteria: Adult patients presenting to the ED with dyspnoea whilst an investigator was present (14 hours per day) Exclusion criteria: Trauma, STEMI, dyspnoea clearly caused by something other than heart failure, e.g. pneumothorax; received IV therapy in ED before echo/NTproBNP was performed	Mean age: Male/Female (n):	Index test: Serum NTproBNP Reference standard: Two cardiologists and one respiratory physician retrospective review with access to medical records and investigations Time between index test and reference standard: NR Target condition: Acute left ventricular heart failure		Ref std +	Ref std -	Total	Source of funding: NR Limitations: Patient Selection: Low Index test: High Reference Standard: High Flow and timing: Low Overall: Very High Additional data: Nil
					NTproBNP 300 +	63	63	126	
					NTproBNP 300 -	1	18	19	
					Total	64	81	145	
					Sensitivity: 0.98 [0.92, 1.00] Specificity: 0.22 [0.14, 0.33]				
						Ref std +	Ref std -	Total	
					NTpro BNP 2200 +	53	24	77	
					NTpro BNP 2200 -	11	57	68	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
					Total	64	81	145	
					Sensitivity: 0.83 [0.71, 0.91] Specificity: 0.70 [0.59, 0.80]				
					AUC: 0.81 (0.74-0.89)				

1

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Parab 2005[132]	Natriuretic peptide/s: BNP Biosite (Triage) Threshold/s: 100, 300 and 500 pg/mL Study type: Retrospective cohort Setting: Single ED in USA	N = 70 Inclusion criteria: patients who had presented to the ED and had a BNP level drawn Exclusion criteria: NR	Mean age: 76.5 (34-102) Male/Female (n): 24/46	Index test: Serum BNP Reference standard: Framingham criteria and retrospective chart review including investigation results and echo managing physicians were not blinded to BNP result but chart reviewers were blinded. Time between index test and reference standard: NR Target condition: Congestive heart failure presenting to the ED		Ref std +	Ref std -	Total	Source of funding: NR Limitations: Patient Selection: High Index test: Low Reference Standard: Low Flow and timing: Low Overall: High Additional data: Additional thresholds
					BNP 100+	45	17	62	
					BNP 100 -	2	6	8	
					Total	47	23	70	
					Sensitivity: 0.96 [0.85, 0.99] Specificity: 0.26 [0.10, 0.48]				
						Ref std +	Ref std -	Total	
					BNP 300 +	42	9	51	
					BNP 300 -	5	14	19	
					Total	47	23	70	
					Sensitivity: 0.89 [0.77, 0.96] Specificity: 0.61 [0.39, 0.80]				
						Ref std +	Ref std -	Total	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
					BNP 500 +	39	5	44	
					BNP 500 -	8	18	26	
					Total	47	23	70	
					Sensitivity: 0.83 [0.69, 0.92] Specificity: 0.78 [0.56, 0.93]				
					AUC:NR				

1

2

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures				Effect sizes		Comments
Potocki 2010[138]	Natriuretic peptide/s: NTproBNP (Roche) MRproANP (BRAHMS) Threshold/s: 1560pg/mL NTproBNP 206pmol/L MRproANP Study type: Prospective cohort	N = 287 Inclusion criteria: Patients with dyspnoea presenting to the ED Exclusion criteria: Patients under 18, on haemodialysis or with trauma were excluded.	Mean age: 77 (68-83) Male/Female (n): 149/138	Index test: Serum NTproBNP Serum MRproANP Reference standard: Two cardiologists retrospective review all medical records and investigations including echocardiography and BNP level Time between index test and reference standard: NR Target condition: Heart failure		Ref std +	Ref std -	Total			Source of funding: Swiss national science foundation, authors are shareholders and directors of companies making MRproANP Limitations: Patient Selection: Low Index test: Low Reference
					NTproBNP 1560 +	131	20	151			
					NTproBNP 1560 -	23	113	136			
					Total	154	133	287			
					Sensitivity: 0.85 [0.78, 0.90] Specificity: 0.85 [0.78, 0.91]						
					AUC:0.92						
						Ref std +	Ref std -	Total			

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
	Setting: Single ED in Switzerland				NTproBNP 206 +	129	21	150	Standard: Low Flow and timing: Low Overall: Low Additional data: Nil
					MRproANP 206 -	25	112	137	
					Total	154	133	287	
					Sensitivity: 0.84 [0.77, 0.89] Specificity: 0.84 [0.77, 0.90]				
					AUC:0.92				

1

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Prosen 2011[140]	Natriuretic peptide/s: NTproBNP Roche Threshold/s: 1000pg/mL Study type: Prospective cohort Setting: Single centre pre hospital emergency setting in	N = 218 Inclusion criteria: Shortness of breath as primary complaint Exclusion criteria: Age <18 years old, history of renal insufficiency, trauma, severe coronary ischemia (unless predominant complaint was dyspnoea), other causes of dyspnoea	Mean age: NR Male/Female (n): NR	Index test: Serum NTproBNP Reference standard: Final hospital diagnosis confirmed by cardiologists and or intensivists by using medical records and investigation results Time between index test and reference standard: NR Target condition: Heart failure related dyspnoea		Ref std +	Ref std -	Total	Source of funding: No industry involvement Limitations: Patient Selection: Low Index test: Low Reference Standard: Low Flow and timing: Low Overall Low
					NTproBNP 1000 +	119	10	129	
					BNP NTproBNP 1000 -	10	79	89	
					Total	129	89	218	
					Sensitivity: 0.92 [0.86, 0.96] Specificity: 0.89 [0.80, 0.94]				
					AUC: 0.9 (0.84-0.94)				

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
	Slovenia	comprising pneumonia, PE, carcinoma, pneumothorax, pleural effusion, intoxication (drugs), anaphylactic reactions, upper airway obstruction, bronchial stenosis and GORD according to the history and tests available in pre hospital setting.					Additional data: Nil

Table 46: Clinical evidence tables for Ray2004[142]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Ray2004[142]	Natriuretic peptide/s: BNP Biosite (Traige) Threshold/s: 100 pg/mL and 250	N = 150 Inclusion criteria: Presentation at the ED; age >65 years; acute dyspnoea of less than 2 weeks duration as the	Mean age: 80 years Male/Female (n): 154/154	Index test: Serum BNP Reference standard: Retrospective review by two independent experts blinded to BNP but had access to medical records and tests results including		Ref std +	Ref std -	Total	Source of funding: Departmental resources. Tests kits provided by industry Limitations:
					BNP 100 +	127	68	195	
					BNP 100 -	14	99	113	
					Total	141	167	308	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures				Effect sizes	Comments
	pg/mL reported Study type: Cross-sectional Setting: Single ED in France	prominent complaint. In addition one of the following had to be fulfilled: 1) a respiratory rate >25/min; 2) PaO_2 <70 mmHg; 3) $PaCO_2$ > 45 mmHg with pH < 7.35 or 4) peripheral O_2 <92% Exclusion criteria: Nil		pulmonary function tests (PFTs), echocardiography and high resolution computed tomography (HRCT). Time between index test and reference standard: NR Target condition: Heart failure presenting to ED	Sensitivity: 0.90 [0.84, 0.94] Specificity: 0.59 [0.51, 0.67]					Patient Selection: Low Index test: Low Reference Standard: Low Flow and timing: Low Overall: Low Additional data: Additional thresholds
						Ref std +	Ref std -	Total		
					BNP 250 +	110	17	127		
					BNP 250 -	31	150	181		
					Total	141	167	308		
					Sensitivity: 0.78 [0.70, 0.85] Specificity: 0.90 [0.84, 0.94]					
					AUC: 0.874 (0.793-0.955)					

Table 47: Clinical evidence tables for Ray2005[143]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures				Effect sizes	Comments
Ray2005[143] *Overlap with Ray 2004[142] Only NTproBNP	Natriuretic peptide/s: NTproBNP Roche Threshold/s: 1500 pg/mL	N = 202 Inclusion criteria: Presentation at the ED; age >65 years; acute dyspnoea of less than 2 weeks duration as the	Mean age: 80 years Male/Female (n): 100/102	Index test: Serum NTproBNP Reference standard: Retrospective review by two independent experts blinded to BNP but had access to medical records and tests results including		Ref std +	Ref std -	Total		Source of funding: Departmental resources. Tests kits provided by industry Limitations:
					NTproBNP 1500 +	66	27	93		
					NTproBNP 1500 -	22	87	109		

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
results extracted	Study type: Cross-sectional Setting: Single ED in France	prominent complaint. In addition one of the following had to be fulfilled: 1) a respiratory rate >25/min; 2) PaO_2 <70 mmHg; 3) $PaCO_2$ > 45 mmHg with pH < 7.35 or 4) peripheral O_2 <92% Exclusion criteria: Nil		PFTs, Echo and HRCT Time between index test and reference standard: NR Target condition: Heart failure presenting to ED	Total	88	114	202	Patient Selection: Low Index test: Low Reference Standard: Low Flow and timing: Low Overall: Low Additional data: Nil
					Sensitivity: 0.75 [0.65, 0.84] Specificity: 0.76 [0.67, 0.84]				
					AUC: NR				

1

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Rogers 2009[84]	Natriuretic peptide/s: BNP (5 sites Triage Biosite; 2 site Abbott) Threshold/s: 100pg/mL Study type: Prospective cohort	N = 740 Inclusion criteria: Over 40 years old; presenting to the Ed with a chief complaint of dyspnoea; having had a BNP assay on admission Exclusion criteria: Patients requiring	Mean age: Cardiac dyspnoea: 67.2 (13.9) Non Cardiac Dyspnoea: 64.4 (12.6) Male/Female (n): 399/341	Index test: Serum BNP Reference standard: Retrospective review by two cardiologists with access to medical records and investigation results including echocardiography, not blinded to BNP results Time between index test and reference standard: NR		Ref std +	Ref std -	Total	Source of funding: Inovise medical inc. Authors received funding from Aboott and Biosite and had shares in company Limitations: Patient
					BNP 100 +	353	115	468	
					BNP 100 -	15	257	272	
					Total	368	372	740	
					Sensitivity: 0.96 [0.93, 0.98] Specificity: 0.69 [0.64, 0.74]				
					AUC: 0.937 90.920-0.954)				

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
	Setting: Multicentre trial: 7 EDs in the USA; 1 ED in Switzerland; 1 ED Taiwan	haemodialysis; obvious non cardiac cause of dyspnoea; elevated troponin		Target condition: Cardiac dyspnoea			Selection: HIgh Index test: High Reference Standard: High Flow and timing: High Overall: Very High Additional data: Covariate model to improve accuracy

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Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Sanz 2006[153]	Natriuretic peptide/s: BNP (Access) Beckman NTproBNP (Roche) Threshold/s: BNP 100, 116pg/mL and	N = 75 Inclusion criteria: Patients admitted to the ED with dyspnoea as their primary symptom Exclusion criteria: NR	Mean age: 75 +/- 14.77 Male/Female (n): NR	Index test: Serum BNP Serum NTproBNP Reference standard: Diagnosed according to symptoms and signs and ECG, CXR and in some cases echocardiography Time between index test and		Ref std +	Ref std -	Total	Source of funding: NR Limitations: Patient Selection: High Index test: Low Reference Standard: High
					BNP 100 +	43	3	46	
					BNP 100 -	2	27	29	
					Total	45	30	75	
					Sensitivity: 0.96 [0.85, 0.99] Specificity: 0.90 [0.73, 0.98]				

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
	NTproBNP 300, 817 pg/mL <u>Study type:</u> Prospective cohort <u>Setting:</u> Single ED in Spain			reference standard: NR <u>Target condition:</u> NR		Ref std +	Ref std -	Total	Flow and timing: Low Overall: High <u>Additional data:</u> Advia BNP assay
					BNP 116 +	42	1	43	
					BNP 116 -	3	29	32	
					Total	45	30	75	
					Sensitivity: 0.93 [0.82, 0.99] Specificity: 0.97 [0.83, 1.00]				
					AUC:0.975				
						Ref std +	Ref std -	Total	
					NTproBNP 300 +	45	15	60	
					NTproBNP 300 -	0	15	15	
					Total	45	30	75	
					Sensitivity: 1.00 [0.92, 1.00] Specificity: 0.50 [0.31, 0.69]				
						Ref std +	Ref std -	Total	
					NTproBNP 817 +	44	2	46	
					NTproBNP 817 -	1	28	29	
					Total	45	30	75	
					Sensitivity: 0.98 [0.88, 1.00]				

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
					Specificity: 0.93 [0.78, 0.99]		
					AUC: 0.979		

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Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
Seronde 2013[155]	Natriuretic peptide/s: BNP, proBNP, NT-proBNP, MRproANP (Roche) Threshold/s: Not specified Study type: Prospective Cohort Setting: ED Country: France and Tunisia	N =1586 Inclusion criteria: SOB as the most prominent symptom; Aged 18 or over Exclusion criteria: Not explicitly reported.	Mean age: 64 Male/Female (n): 194/142	Index test Serum BNP Reference standard Diagnosis was independently performed after patient discharge by a senior cardiologist and an intensivist based on patient files and BNP with another cardiologist acting as an adjudicator for divergent diagnoses Time between index test and reference standard: Serum taken at initial presentation. Reference after hospital trajectory known. Target condition: Acute heart failure	BNP: AUC 0.973 (0.950 - 0.988) ProBNP: AUC 0.953 (0.925 - 0.973) NT-proBNP: AUC 0.922 (0.888 - 0.948) MRproANP: AUC 0.901 (0.864 - 0.931)		Source of funding: Not stated Limitations: Patient Selection: Index test: Reference Standard: Flow and timing:

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Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Shah 2012[159] (from PRIDE study data Januzzi 2005[79])	Natriuretic peptide/s: MRproANP (BRAHMS) Threshold/s: Study type: Prospective cohort Setting: Single centre ED in the USA	N = 560 Inclusion criteria: consenting patients ≥ 21 years old presenting to Ed with a complaint of dyspnoea Exclusion criteria: severe renal insufficiency, chest trauma, STEMI, >2 hour delay after IV loop diuretic administration, unblended NP level measurement	Mean age: NR Male/Female (n): NR	Index test: Serum MRproANP Reference standard: Retrospective cardiologist review access to medical records and investigations including echocardiography Time between index test and reference standard: NR Target condition: Acute decompensated heart failure		Ref std +	Ref std -	Total	Source of funding: Grant from manufacturers Limitations: Patient Selection: Low Index test: Low Reference Standard: Low Flow and timing: Low Overall: Low Additional data: Nil
					Mrpro ANP +	Unable to calculate			
					MRpro ANP -				
					Total	180	380	560	
					"using an age-adjusted cut point strategy to diagnose acute decompensated heart failure (ADHF) (age<65 years ≥104pmol/L; age ≥ 65 years ≥214pmol/L sensitivity of 82%, specificity 86%"				
					AUC:0.9(0.87-0.93)				

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Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Shaikh 2011[160]	Natriuretic peptide/s:	N = 100	Mean age:	Index test:		Ref std +	Ref std -	Total	Source of funding:

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
	NTproBNP Roche Threshold/s: 300, 900 pg/mL Study type: Cross sectional Setting: Single ED in Pakistan	Inclusion criteria: Patients presenting to the ED with a primary complaint of dyspnoea Exclusion criteria: Severe renal insufficiency, dyspnoea after chest trauma, dyspnoea secondary to severe coronary ischemia by ECG criteria	61 (+/-14) Male/Female (n): 48/52	Serum NTproBNP Reference standard: Cardiology discharge diagnosis aided by Framingham score and investigation results including echo Time between index test and reference standard: NR Target condition: Congestive heart failure	NTproBNP 300 +	79	12	91	NR Limitations: Patient Selection: Low Index test: High Reference Standard: High Flow and timing: Low Overall: Very High Additional data: Nil
				NTproBNP 300 -	0	9	9	
				Total	79	21	100	
				Sensitivity: 1.00 [0.95, 1.00] Specificity: 0.43 [0.22, 0.66]				
					Ref std +	Ref std -	Total	
				NTproBNP 900 +	76	4	80	
				NTproBNP 900 -	3	17	20	
				Total	79	21	100	
				Sensitivity: Specificity:				
				AUC:0.99				

Table 48: Clinical evidence tables for Villacorta 2002[178]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Villacorta 2002[178]	Natriuretic peptide/s: BNP Biosite (Triage) Threshold/s: 200pg/mL Study type: Cross-sectional Setting: Single ED in Brazil	N = 70 Inclusion criteria: Presenting to ED with acute dyspnoea Exclusion criteria: Patients with a clear diagnosis such as trachea stenosis or cardiac tamponade; ACS whose prominent complaint was not dyspnoea	Mean age: 72 years Male/Female (n): 33/37	Index test: Serum BNP Reference standard: One cardiologist reviewing all patients data using Boston criteria, hospital course, response to treatment, haemodynamic measures and test results were taken into account Time between index test and reference standard: NR Target condition: Acute heart failure		Ref std +	Ref std -	Total	Source of funding: NR Limitations: Patient Selection: Low Index test: Low Reference Standard: Low Flow and timing: Low Overall: Low Additional data: NR
					BNP 200 +	36	1	37	
					BNP 200 -	0	33	33	
					Total	36	34	70	
					Sensitivity: 1.0 (0.9-1.0) Specificity: 0.97 (0.85-1.0)				
					AUC: 0.99 (CI NR)				

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Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Wang 2010[179]	Natriuretic peptide/s: BNP Abbott Threshold/s: 100, 500pg/mL	N = 84 Inclusion criteria: Acute onset or worsening of chronic dyspnoea Exclusion criteria:	Mean age: 73.5 Male/Female (n): 40/44	Index test: Serum BNP Reference standard: Retrospective review by 2 independent cardiologists blinded to BNP and echo findings		Ref std +	Ref std -	Total	Source of funding: NR Limitations: Patient Selection: Low Index test: Low
					BNP 100 +	46	23	69	
					BNP 100 -	3	12	15	
					Total	49	35	84	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures				Effect sizes		Comments
	Study type: Prospective cohort Setting: Single ED in Taiwan	<18 years old, acute myocardial infarction, trauma, dyspnoea clearly caused by something other than heart failure e.g. pneumothorax		Time between index test and reference standard: NR Target condition: Acute heart failure	Sensitivity: 0.94 [0.83, 0.99] Specificity: 0.34 [0.19, 0.52]						Reference Standard: Low Flow and timing: Low Overall: Low Additional data: Nil
						Ref std +	Ref std -	Total			
					BNP 500 +	32	9	41			
					BNP 500 -	17	26	43			
					Total	49	35	84			
					Sensitivity: 0.65 [0.50, 0.78] Specificity: 0.74 [0.57, 0.88]						
					AUC:NR						

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Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures				Effect sizes		Comments
Zaninotto 2005[183]	Natriuretic peptide/s: NTproBNP (Roche) Threshold/s: 1760 pg/mL Study type:	N = 122 Inclusion criteria: Acute-severe dyspnoea as the most prominent symptom Exclusion criteria: Traumatic cause of	Mean age: 78 (27-93) Male/Female (n): 58/64	Index test: Serum NTproBNP Reference standard: Discharge diagnosis basis of clinical and instrumental investigations according to clinical guidelines Time between index test and reference standard: NR		Ref std +	Ref std -	Total			Source of funding: NR Limitations: Patient Selection: Low Index test: High Reference Standard: High
					NTproBNP 1760+	45	16	61			
					NtproBNP 1760 -	11	50	61			
					Total	56	66	122			

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
	Prospective cohort Setting: Single ED in Italy	dyspnoea; renal failure		Target condition: Cardiac related dyspnoea	Sensitivity: 0.80 [0.68, 0.90] Specificity: 0.76 [0.64, 0.85]		Flow and timing: Low Overall: Very High Additional data: Nil
					AUC:0.815 (+/- 0.041)		

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2 ### G.1.2 Invasive monitoring

3

Study (subsidiary papers)	ATTEND registry: Sotomi 2012[164] (Sato 2010[154])
Study type	Registry
Number of studies (number of participants)	Multicentre (n=4796)
Countries and setting	Conducted in Japan; Setting: Hospital
Duration of study	5 year recruitment into the registry
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Subgroup analysis within study	Not stratified but pre-specified
Inclusion criteria	Patients with acute heart failure as assessed by the modified Framingham criteria.
Exclusion criteria	Patients who are not considered suitable by the attending physician and patients with acute coronary syndrome
Age, gender and ethnicity	Age: Study presented as abstract only - at an interim analysis mean (sd) age was 73 (14). Gender (M:F): Unclear. Ethnicity: not reported
Interventions	(n=80) Intervention 1: Invasive monitoring - Pulmonary artery catheter. Not described. Duration Unknown. Concurrent medication/care: Standard medical treatment

	(n=80) Intervention 2: Standard medical care - Medical care including non-invasive monitoring. Medical assessment. Duration Unknown. Concurrent medication/care: Standard medical treatment
Funding	Academic or government funding (Japan Heart Foundation)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PULMONARY ARTERY CATHETER versus MEDICAL CARE INCLUDING NON-INVASIVE MONITORING Protocol outcome 1: Mortality - Actual outcome: In hospital mortality -OR 0.64 (95%CI 0.37 to 1.13); Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome: In hospital mortality - NYHA class IV - OR 0.43 (95%CI 0.2 to 0.92); Risk of bias: Unclear; Indirectness of outcome: No indirectness	

Study (subsidiary papers)	**ESCAPE trial: Binanay 2005[47] (Shah 2001[158])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	Multicentre (n=433)
Countries and setting	Conducted in USA
Duration of study	Follow up (post intervention): 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Inclusion criteria	1. Age >= 16 years; 2. Current admission under the care of the heart failure service at the site; 3. Current admission for NYHA class IV heart failure symptoms; 4. At least one prior admission for exacerbation of CHF within 12 months before randomisation; 5. left ventricular ejection fraction < 30% by contrast ventriculography, radionuclide ventriculography, or quantitative echocardiography within 1 year before randomisation. The most recent measure of left ventricular function should be used. 6. Documented history of heart failure for >= 3 months. 7. Attempted therapy with angiotensin converting enzyme inhibitors and diuretics for >= 3 months. 8. Systolic blood pressure <=125 mmHg. 9. Elevated filling pressures, indicated by one symptom and one physical sign: Symptoms - dyspnea at rest, in the supine position or immediately on routine activity within one room; abdominal discomfort, severe anorexia, or nausea without apparent cause other than hepatosplanchnic congestion. Signs - Jugular venous pressure elevation > 10 cm above the right atrium; square-wave Valsalva response; hepatomegaly, ascites, or edema in the absence of other obvious causes; rales greater than one third lung fields.

Exclusion criteria	1. Acute decompensation that, according to the attending heart failure physician, will likely require PAC insertion during the next 24 hrs. 2. Inability to undergo PAC placement within the next 12 hrs. 3. Active listing for cardiac transplantation. 4. Present or anticipated mechanical ventilation. 5. Present or anticipated mechanical circulatory assist device insertion, including intra-aortic balloon pumps and left ventricular assist devices. 6. Any administration of intravenous milrinone within the previous 48 hrs. 7. Current administration of intravenous dopamine of dobutamine at >3ug/kg/min or dopamine or dobutamine administration for 24 hrs before randomisation. 8. Acute MI or cardiac surgery within the the last 6 wks. 9. Current admission for an acute coronary syndrome, including acute MI or unstable angina. 10. Documented moderate to severe mitral or aortic stenosis. 11. Anticipated revascularization procedure during the admission. 12. Other planned surgical procedure during the admission. 13. Documented primary pulmonary hypertension. 14. Pulmonary infarction within the past month. 15. Current pneumothorax 16. Current serum creatinine >3.5 mg/dL 17. Temperature >37.8C 18. White blood cell count 13,000/mm3 19. Exacerbation of CHF because of primary factor requiring specific therapy, such as severe anaemia, clinical hypothyroidism or active systemic infection. 20. Presence of any noncardiac disease such as cancer likely to shorten life expectancy to <1 year. 21. Inability to return to the site's CHF program at 14+/-7 days, 30+/-14 days, 60+/-14 days, and 180+/-14 days after randomisation. Additional exclusion criteria (for which patients may be screened during same admission): 23. Estimated large volume reservoir (major ascites or anasarca) thought to require extensive diuresis (>48 hrs) before major adjustment of other medications such as vasodilators. 24. Temporary inability to place and monitor PAC, because of whether patient factors such as excessive anticoagulation or to logistic factors such as temporary lack of bedside monitoring equipment.
Age, gender	Age - Mean (SD): PAC - 56 (14) Clinical Assessment - 56 (14). Gender (M:F): 320:113.
Interventions	(n=215) Intervention 1: Invasive monitoring - Pulmonary artery catheter. The Pulmonary Artery Catheter Education Project, a computer based program created by the NHLBI, the Food and Drug Administration, and the American College of Physicians was used to train investigators and coordinators (http://www.pacep.org/asahq). Catheters were selected according to individual institutional practices. Duration Until the following specific goals have been achieved: absence of physical signs indicating elevated intracardiac filling pressures, evidence of adequate peripheral perfusion, and serum creatinine <=3.0 mg/dL.. Concurrent medication/care: Medication recommended in published guidelines for the advanced heart failure population. Patients may receive any of the standard therapies for heart failure, regardless of their treatment group. (n=218) Intervention 2: Standard medical care - Medical care including non-invasive monitoring. Medication recommended in published guidelines for the advanced heart failure population. Patients may receive any of the standard therapies for heart failure, regardless of their treatment group.. Duration until the following specific goals have been achieved: absence of physical signs indicating elevated intracardiac filling pressures, evidence of adequate peripheral perfusion, and serum creatinine <=3.0 mg/dL.. Concurrent medication/care: Standard medical care.

Funding	Academic or government funding (National Heart, Lung and Blood Institute to Duke Medical Center)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PULMONARY ARTERY CATHETER versus MEDICAL CARE INCLUDING NON-INVASIVE MONITORING

Protocol outcome 1: Mortality
- Actual outcome: Mortality at 180 days; Group 1: 43/209, Group 2: 38/212; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome: Early mortality at In hospital plus 30 days; Group 1: 10/209, Group 2: 11/212; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome: PAC-related death at 180 days; Group 1: 0/209, Group 2: 0/212; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome: Days alive and out of hospital at 180 days; HR 1 (95%CI 0.82 to 1.21) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: SAE - Major cardiovascular events
- Actual outcome: Cardiogenic shock at 180 days; Group 1: 6/209, Group 2: 2/212; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome: Ischemia/angina at 180 days; Group 1: 9/209, Group 2: 4/212; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome: Myocardial infarction at 180 days; Group 1: 0/209, Group 2: 1/212; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome: Stroke or transient ischemic attack at 180 days; Group 1: 1/212, Group 2: 0/212; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome: Patients with at least 1 adverse event at 180 days; Group 1: 47/209, Group 2: 25/212; Risk of bias: ; Indirectness of outcome: No indirectness

Protocol outcome 3: Quality of life
- Actual outcome: Minnesota Living with Heart Failure questionnaire at 1 month; Other: Only available as a Figure ; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome: Minnesota Living with Heart Failure questionnaire at 6 months; Other: Only presented in a figure - with similar group means; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: SAE - other
- Actual outcome: Cardiac arrest at 180 days; Group 1: 9/209, Group 2: 5/212; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome: Infection at 180 days; Group 1: 27/209, Group 2: 20/212; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 5: Length of stay
- Actual outcome: Total days initial hospitalisation at Until discharge; HR 1.04 (95%CI 0.86 to 1.27) Reported; Risk of bias: --; Indirectness of outcome: No indirectness

Study	**PAC-Man trial: Harvey 2005[72]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	Multicentre (n=1014)
Countries and setting	Conducted in United Kingdom
Duration of study	90 days
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Subgroup analysis within study	Stratified then randomised
Inclusion criteria	Patients admitted to adult intensive care and identified by the treating clinician as someone who should be managed with a PAC
Exclusion criteria	Elective admission for a preoperative optimisation; presence of a PAC on admission to intensive care; previous enrolment to the study; or haemodynamic optimisation before organ donation; and age younger than 16 years.
Recruitment/selection of patients	Participating units opted, a priori, to be in either stratum A, with no option to use alternative cardiac-output monitoring devices, or in stratum B, to have the option of using alternative cardiac-output monitoring devices in controls.
Age, gender	Age - Mean (SD): PAC 64.7 (14.3) Control 65.3 (13.1). Gender (M:F): 591:423.
Interventions	(n=55) Intervention 1: Invasive monitoring - Pulmonary artery catheter. Patients allocated to PAC had the catheter placed as soon as possible after randomisation according to local practice. Duration as long as the treating clinician thought necessary. Concurrent medication/care: Standard medical care (n=56) Intervention 2: Standard medical care - Medical care including non-invasive monitoring. Clinical management without PAC. Duration Not applicable. Concurrent medication/care: Standard medical care at the discretion of the treating clinician.
Funding	Other (It was stated that the sponsor of the study had no role in study design, data collection, data analysis, data interpretation or writing of the report.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PULMONARY ARTERY CATHETER versus MEDICAL CARE INCLUDING NON-INVASIVE MONITORING Protocol outcome 1: Mortality - Actual outcome: In hospital mortality; Group 1: 39/55, Group 2: 35/56; Risk of bias: ; Indirectness of outcome: No indirectness	

Study	**SPRINT Registry trial: Zion 1990[185]**
Study type	Registry
Number of studies (number of participants)	Multicentre (n=5841 patients with Acute MI of which 581 were patients with cardiogenic shock)
Countries and setting	Conducted in Israel
Duration of study	Follow up (post intervention): 1 year
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Inclusion criteria	Patients with acute myocardial infarction and cardiogenic shock
Exclusion criteria	No explicitly stated
Age, gender and ethnicity	Age - Other: <=40 N=159; 41-60 N=2250; 61-75 N=2955; >75 N=848. Gender (M:F): Unclear. Ethnicity:
Extra comments	2276 of the patients were randomized to receive nifedipine or placebo from 7 to 21 days after the onset of the AMI and comprised the patients from the SPRINT trial.
Indirectness of population	No indirectness
Interventions	(n=154) Intervention 1: Invasive monitoring - Pulmonary artery catheter. Pulmonary artery catheter. Duration Unclear. Concurrent medication/care: Standard medical care (n=427) Intervention 2: Standard medical care - Medical care including non-invasive monitoring. Non-invasive monitoring. Duration Unclear. Concurrent medication/care: standard medical care
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PULMONARY ARTERY CATHETER versus MEDICAL CARE INCLUDING NON-INVASIVE MONITORING Protocol outcome 1: Mortality - Actual outcome: In-hospital mortality Group 1: 139/154, Group 2: 388/427; Risk of bias: High; Indirectness of outcome: No indirectness	

1

G.2 Initial non-pharmacological treatment

G.2.1 Non-invasive ventilation

Table 15: Evidence tables

Study	**Agmy 2009[5]**
Study type	RCT (randomised; parallel)
Funding	Funding not stated
Number of studies (number of participants)	Single centre (N=129)
Countries and setting	Conducted in Egypt; Setting: ICU and CCU
Duration of study	Unclear
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis
Inclusion criteria	Cardiogenic pulmonary oedema confirmed radiologically and / or clinically; severe acute respiratory failure (PaO2/FIO2 less than 250); dyspnoea of sudden onset; systolic blood pressure < 18 mm Hg
Exclusion criteria	Immediate need for endotracheal intubation; severe chronic renal failure; pneumothorax; contraindication of non-invasive ventilation.
Recruitment/selection of patients	
Age, gender and ethnicity	Age - Mean (SD): CPAP 66 (7) PiPAP 68 (4) UC 69 (6). Gender (M:F): Male 93 Female 36. Ethnicity:

Intervention 1	Continuous positive airway pressure (CPAP) CPAP. No details provided. Duration Until no longer clinically required (no details provided). Concurrent medication/care: Standard medical treatment - no details provided (N=44)
Intervention 2	Bilevel ventilation (BiPAP) BiPAP. No details provided. Duration Until no longer clinically required (no details provided). Concurrent medication/care: Standard medical treatment - no details provided (N=44)
Intervention 3	Standard Medical Care any form of standard medical care provided for the management of cardiogenic pulmonary oedema excluding NIPPV or alternative methods of ventilatory support, - standard medical care e.g. oxygen by face mask, diuretics, nitrates etc. Standard medical care + oxygen mask. Duration Until no longer clinically required (no details provided). Concurrent medication/care: Standard medical treatment - no details provided (N=41)

Study	Bersten 1991[20]
Study type	RCT (Patient randomised; Parallel)
Funding	Funding not stated
Number of studies (number of participants)	Single centre (N=39)
Countries and setting	Conducted in Australia; Setting: ED and ICU
Duration of study	Until discharge from hospital
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Inclusion criteria	Respiratory distress was defined as either an arterial oxygen tension below 70 mm Hg or a CO tension above 45 mm Hg. Cardiogenic pulmonary oedema was diagnosed when the patient had dyspnoea of sudden onset, typical findings on chest film and widespread rales without a history suggesting pulmonary aspiration or infection.
Exclusion criteria	A diagnosis of myocardial infarction with shock; a systolic blood pressure below 90 mm Hg; severe stenotic valvular disease; or chronic airflow obstruction with known carbon dioxide retention before the current illness.
Recruitment/selection of patients	
Age, gender and ethnicity	Age - Mean (range): CPAP 76 (6) UC 75 (6). Gender (M:F): Male 13 Female 26. Ethnicity:
Extra comments	In most patients the jugular venous pressure was elevated and a third heart sound was heard.

Intervention 1	Continuous positive airway pressure (CPAP) CPAP. Described as 'pressure was applied by connecting a 10-cm water valve to the mask and by weighting the reservoir bag to minimize changes in airway pressure'.. Duration Mean (SD) hrs 9.3 (4.9). Concurrent medication/care: Could include: sublingual nitroglycerin, topical nitroglycerin, furosemide, morphine (N=19)
Intervention 2	Standard Medical Care any form of standard medical care provided for the management of cardiogenic pulmonary oedema excluding NIPPV or alternative methods of ventilatory support, - standard medical care e.g. oxygen by face mask, diuretics, nitrates etc. standard medical care + oxygen mask. Duration Until breathing stabilised. Concurrent medication/care: Could include: sublingual nitroglycerin, topical nitroglycerin, furosemide, morphine (N=20)

Study	Crane 2004[36]
Study type	RCT (Patient randomised; Parallel)
Funding	Equipment / drugs provided by industry (ResMed, Abingdon provided ventilators but had no role in study design or data analysis)

Number of studies (number of participants)	Two hospitals participated (N=60)
Countries and setting	Conducted in the UK
Duration of study	7 day follow-up
Method of assessment of guideline condition	Adequate method of assessment
Inclusion criteria	Adults who attended emergency department resuscitation rooms with acute dyspnoea and who had clinical evidence of cardiogenic pulmonary oedema: respiratory rate > 23 breaths per minute, chest radiological appearance consistent with pulmonary oedema and arterial blood pH<7.35 (H^+ ion concentration > 46.7 nmol/l)
Exclusion criteria	Hypotension (systolic blood pressure <90 mm Hg), temperatue > 38C, patients requiring immediate thrombolysis for myocardial infarction, patients requiring dialysis for renal impairment, patients with impaired consciousness (only responding to pain or not responding at all), and patients with dementia.
Age, gender and ethnicity	Age - Mean (SD): UC 75 (11) CPAP 75 (12) BiPAP 76 (8). Gender (M:F): Males 23 Females 37. Ethnicity:

Study	**Delclaux 2000[41]**
Study type	RCT (randomised; Parallel)
Funding	Equipment / drugs provided by industry (Supported by a grant from Vital Signs, Inc (Totowa, NJ) which provided some computer equipment and the equipment for continuous positive airway pressure treatment)
Number of studies (number of participants)	Multicentre study (N=123)
Countries and setting	Conducted in France; Setting: Coronary Care Unit
Duration of study	Until hospital discharge
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis. Chronic cardiac disease with Class, II, III or IV of the New York Heart Association functional classification or acute de novo cardiac disease.
Inclusion criteria	(1) Acute respiratory insufficiency defined as the PaO2/FiO2 ratio of 300 mg Hg or les after breathing oxygen at 10 L/min or more for 15 minutes, with inspired fraction of oxygen determined by a portable oxygen analyser; (2) the presence of bilateral lung infiltrates on a posterior-anterior chest radiograph; and (3) randomisation within 3 hours after the criteria were first fulfilled.
Exclusion criteria	Patients where intubation was refused or contraindicated; history of COPD; acute respiratory acidosis (defined as a pH < 7.30 and PaCO2 > 50 mm Hg); systolic blood pressure less than 90 mm Hg under optimal therapy (fluid repletion); ventricular arrhythmias; coma or seizures; life threatening hypoxemia (defined as an SaO2 < 80% with an oxygen mask);

	use of epinephrine or norepinephrine; and the inability to clear copious airway secretions.
Recruitment/selection of patients	Stratified by whether or not respiratory failure was due to cardiac causes. Chronic cardiac disease with Class, II, III or IV of the New York Heart Association functional classification or acute de novo cardiac disease.
Age, gender and ethnicity	Age - Median (range): (range 5 to 95 percentile) CPAP 56 (19-85) UC 60 (18 - 88). Gender (M:F): Male 78 Female 45. Ethnicity: Not reported

Intervention 1	Continuous positive airway pressure (CPAP) CPAP. CPAP was started at 7.5 cm H2O. Could be decreased or increased by 2.5 cm H2O based on the clinical response and tolerance.. Duration Minimum of 6 hrs and continued until: PaO2/FiO2 ratio > 300 mm Hg, or SaO2 between 95% and 100% and FiO2 of 40% or less without CPAP. Concurrent medication/care: Diuretics, antibiotics (according to clinical need) (N=22)
Intervention 2	Standard Medical Care any form of standard medical care provided for the management of cardiogenic pulmonary oedema excluding NIPPV or alternative methods of ventilatory support, - standard medical care e.g. oxygen by face mask, diuretics, nitrates etc. Standard medical care + oxygen mask. Duration Until fulfilment of oxygen delivery cessation criteria (SaO2 >=92% without oxygen and respiratory rate < 30 b/min). Concurrent medication/care: Diuretics, antibiotics (N=20)

Study	**Ducros 2011[44]**
Study type	RCT (Patient randomised; Parallel)
Funding	Academic or government funding (The PNP assay and CPAP mask were gifts from Biosite company and Respironics Philips through an agreement between the French Health Ministry and the companies. Laurent Ducros conducted NIV training sessions funded by Respironics Philips France.)
Number of studies (number of participants)	Multicentre (N=207)
Countries and setting	Conducted in France; Setting: Pre-hospital and in-hospital settings
Duration of study	Follow up (post intervention): Primary endpoints assessed in the first 48 hrs; secondary outcomes assessed until hospital discharge
Method of assessment of guideline condition	Adequate method of assessment/diagnosis According to a set of clinically defined symptoms
Inclusion criteria	Clinical symptoms of acute pulmonary oedema: orthopoea, diffuse cackles (Killip score at least III), respiratory rate greater than 25 b/m and pulse oxygen saturation (SpO2) less than 90% in room air.

Exclusion criteria	Patients were excluded if they had a history of chronic obstructive pulmonary disease, asthma, severe stenotic valve disease, immediate indication for intubation (severe impairment of consciousness, bradypnoea), cardiovascular collapse or suspicion of ST segment elevation acute coronary syndrome.
Recruitment/selection of patients	Participants were enrolled in mobile emergency medical services. In France these services are capable of providing advanced life support care (including advanced airway support) and are always manned by a physician and a nurse.
Age, gender and ethnicity	Age - Mean (SD): CPAP: 80 (11) UC: 81(9). Gender (M:F): Males 85 Females 122. Ethnicity: Not reported
Intervention 1	Continuous positive airway pressure (CPAP) CPAP. CPAP was generated by an oxygen-driven Venturi device (Whisperflow). Using mainly the 7.5 cm H2O pressure valve which shift to the 10 cm H2O valve 15 min later if well tolerated. Inspiratory oxygen fraction was set to reach 95% SpO2.. Duration Median (IQR) CPAP treatment was 60 min (40, 65) in the hospital setting and 120 min (60, 242) in the cardiac ICU. Concurrent medication/care: Pharmacological treatment had to include at least 40 mg furosemide or 1 mg bumetanide but not more than 120 and 3 mg respectively, unless systolic arterial blood pressure (SBP) was below 90mmHg. (N=107)
Comments	The median (IQR) FiO2 to reach 95% SpO2 with CPAP did not exceed 60%: 35% (31, 45) 30 minutes after inclusion, 36% (30, 60) at hospital arrival and 40% (31, 60) after 2 hours. Half of the patients had a CPAP set at 7.5 cmH2O and the other half at 10 cmH2O.
Intervention 2	Standard Medical Care any form of standard medical care provided for the management of cardiogenic pulmonary oedema excluding NIPPV or alternative methods of ventilatory support, - standard medical care e.g. oxygen by face mask, diuretics, nitrates etc. Oxygen at 15 L/min. Duration Until breathing stabilised. Concurrent medication/care: Pharmacological treatment had to include at least 40 mg furosemide or 1 mg bumetanide but not more than 120 and 3 mg respectively, unless systolic arterial blood pressure (SBP) was below 90 mmHg. (N=100)

Study	**Ferrer 2003[53]**
Study type	RCT (Patient randomised; Parallel)
Funding	Academic or government funding (Red GIRA, Red Respira and Carburos Metalicos)
Number of studies (number of participants)	Multi centre (N=Overall N= 105 but N=30 (subgroup of patients with cardiogenic pulmonary oedema))
Countries and setting	Conducted in Spain; Setting: ICU
Duration of study	Until discharge from hospital
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Inclusion criteria	Patients with severe acute hypoxemic respiratory failure defined as PaCO2 persistently (more than 6 to 8 hours) less

	than 60 mm Hg or arterial oxygen saturation by pulse oximetry (SpO2) persistently less than 90% while breathing conventional Venturi oxygen at a maximal concentration (50%). Cardiogenic pulmonary oedema was diagnosed if patients had dyspnoea of sudden onset with physical findings consistent with pulmonary oedema, such as widespread rales with or without third heart sound, and typical findings of congestion on a chest x-ray.
Exclusion criteria	(1) Hypercapnia (PaCO2 of more than 45 mmHg) on admission; (2) need for emergency intubation; (3) recent oesophageal, facial, or cranial trauma or surgery; (4) severely decreased consciousness (Glasgow coma scale of 11 or less); (5) severe hemodynamic instability despite fluid repletion and use of vasoactive agents; (6) a lack of cooperation; (7) tracheotomy or other upper airway disorders; (8) severe ventricular arrhythmia or myocardial ischemia; (9) active upper gastrointestinal bleeding; (10) an inability to clear respiratory secretions; and (11) more than one severe organ dysfunction in addition to respiratory failure.
Recruitment/selection of patients	All patients were randomised within 24 hours of fulfilling inclusion criteria.
Age, gender and ethnicity	Age - Mean (SD): BiPAP 71 (13) UC 76 (9). Gender (M:F): Males 10 Females 20. Ethnicity:
Intervention 1	Bilevel ventilation (BiPAP) BiPAP. The level of inspiratory and expiratory positive airway pressure were - mean (sd) - 16 (3) cm H2O (range 10-24) and 7 (2) H2O (range 4-12), during the first day.. Duration NIV was delivered for a period of - mean (sd) - 3.5 (2.6) hrs. Concurrent medication/care: Standard medical treatment (N=15)
Intervention 2	Standard Medical Care any form of standard medical care provided for the management of cardiogenic pulmonary oedema excluding NIPPV or alternative methods of ventilatory support, - standard medical care e.g. oxygen by face mask, diuretics, nitrates etc. Oxygen mask - FiO2 was set to achieve SpO2>92% or PaO2 >65 mm Hg. Initially, oxygen therapy was set at the maximal FiO2 available. Duration Until a pre-specified end of the protocol - when patients could persistently achieve PaO2 > 65 mm Hg or SpO2> 92% while breathing Venturi oxygen at FiO2 <=0.50. Concurrent medication/care: Presumable standard medical care (N=15)

Study	**Frontin 2011[58]**
Study type	RCT (Patient randomised; Parallel)
Funding	Support was provided by institutional sources sponsored by the University Hospital of Toulouse.
Number of studies (number of participants)	Single centre (N=124)
Countries and setting	Conducted in France; Setting: Pre-hospital (mobile intensive care units) and hospital setting
Duration of study	30 days
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis Pre-hospital setting
Inclusion criteria	Clinical symptoms of acute cardiogenic pulmonary oedema such as othopnoea, diffuse cackles without evidence of

	pulmonary aspiration or infection, pulse oximetry (SpO2 less than 90% and a respiratory rate greater than 25 b/min.
Exclusion criteria	Patients with cardiovascular collapse or an impaired level of consciousness acute myocardial infarction or if they had an immediate need for intubation. Also excluded were patients with a history of gastric surgery (< 8 days) and patients vomiting.
Recruitment/selection of patients	
Age, gender and ethnicity	Age - Mean (SD): CPAP 79.4 (10.7) UC 79.3 (10.5). Gender (M:F): Male 52 Female 70. Ethnicity: White European
Extra comments	3 patients in the CPAP and 5 in the UC group did not meet inclusion criteria (determined after hospital admission), but were analysed in the ITT analysis.

Intervention 1	Continuous positive airway pressure (CPAP) CPAP. 10 cm H2O CPAP through a facemask with a CPAP valve and controlled with a portable flow generator.. Duration Until arrival at hospital - but with a minimum time of 1 hr. Concurrent medication/care: Included furosemide, 1mg/kg; continuous infusion of isosorbide dinitrate at an initial rate of 2 mg/h. If systolic blood pressure was above 180 mm Hg, 2 mg of intravenous isosorbide dinitrate was administered. Further doses of nitrate were unrestricted according to clinical response. Intravenous morphine use was not forbidden in the protocol of the study, but no patient received morphine during the pre-hospital phase of the treatment. (N=60)
Intervention 2	Standard Medical Care any form of standard medical care provided for the management of cardiogenic pulmonary oedema excluding NIPPV or alternative methods of ventilatory support, - standard medical care e.g. oxygen by face mask, diuretics, nitrates etc. Standard medical care + oxygen mask (15 L/min). Duration Until arrival at hospital or a minimum of 1 hr. Concurrent medication/care: Included furosemide, 1mg/kg; continuous infusion of isosorbide dinitrate at an initial rate of 2 mg/h. If systolic blood pressure was above 180 mm Hg, 2 mg of intravenous isosorbide dinitrate was administered. Further doses of nitrate were unrestricted according to clinical response. Intravenous morphine use was not forbidden in the protocol of the study, but no patient received morphine during the pre-hospital phase of the treatment. (N=62)

Study	**Gray 2009**[67] (Gray 2008[65], Goodacre 2011[63])
Study type	RCT (Patient randomised; Parallel)
Funding	Academic or government funding (National Institute for Health Research)
Number of studies (number of participants)	Multicentre (N=1069)
Countries and setting	Conducted in United Kingdom; Setting: Emergency department
Duration of study	

Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Inclusion criteria	Adults or young persons over age 16 years with signs and symptoms consistent with acute cardiogenic pulmonary oedema as the principal complaint: acute dyspnoea and bilateral crackles on chest auscultation; chest radiograph confirming the diagnosis of acute cardiogenic pulmonary oedema: typical features of interstitial oedema present; arterial blood gas analysis with a pH of < 7.35 (hydrogen ion concentration > 45nmol/l); respiratory rate of > 20 b/min.
Exclusion criteria	Severely altered consciousness (unconscious or responding to pain only); any patient requiring an immediate lifesaving intervention, such as cardiopulmonary resuscitation, airway control, cardioversion or inotropic support; any patient requiring thrombolysis or percutaneous coronary intervention for acute ST-segment elevation myocardial infarction; a clear alternative primary diagnosis, such as lobar pneumonia; an inability to provide informed consent at any time within the trial period such as dementia or other form of incapacity; previous inclusion in the 3CPO study.
Recruitment/selection of patients	
Age, gender and ethnicity	Age - Mean (SD): UC 79 (9) CPAP 78 (10) BiPAP 77 (10). Gender (M:F): Males 460 Females 609. Ethnicity:

Intervention 1	Continuous positive airway pressure (CPAP) CPAP. CPAP was started with a pressure of 5 cmH2O. Oxygen was entrained into the system at 15 l/min and subsequently adjusted to maintain oxygen saturation above 92%. CPAP pressure was titrated in 2-cm H2O steps at 2-3-minute intervals over the first 10-15 minutes to a maximum pressure of 15 cmH2O. The average ventilation pressure was 10 with a standard deviation of 4.. Duration The average durations of CPAP therapy was - mean (sd) 2.2 (1.5) hrs. Concurrent medication/care: All groups received standard therapy at the discretion of the attending physician. This would usually include nitrates but loop diuretic and opioid therapy could also be administered. This was done according to a trial treatment guideline which was available in all recruiting emergency departments. (N=346)
Intervention 2	Bilevel ventilation (BiPAP) BiPAP. The starting inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP) were pre-set to 8 cmH2O and 4 cmH2O respectively. Oxygen was entrained into the system at 15 l/min and subsequently adjusted to maintain oxygen saturation above 92%. IPAP and EPAP were titrated at 2- to 3-minute intervals over the first 15-18 minutes to maximum pressure of 20 cmH2O and 10 cmH2O respectively. IPAP was increased by 2-cmH2O and EPAP by 1-cmH2O increments. Average ventilation pressures (SD) were 14(5) and 7(3) respectively.. Duration The average duration of treatment was - mean (SD) 2 (1.3) hrs. Concurrent medication/care: All groups received standard therapy at the discretion of the attending physician. This would usually include nitrates but loop diuretic and opioid therapy could also be administered. This was done according to a trial treatment guideline which was available in all recruiting emergency departments. (N=356)
Intervention 3	Standard Medical Care any form of standard medical care provided for the management of cardiogenic pulmonary oedema excluding NIPPV or alternative methods of ventilatory support, - standard medical care e.g. oxygen by face mask, diuretics, nitrates etc. Standard therapy at the discretion of the attending physician + supplemental oxygen via a variable delivery oxygen mask.. Duration Until no longer clinically required. Concurrent medication/care: This would usually include nitrates but loop diuretic and opioid therapy could also be administered. This would usually include nitrates but loop diuretic and opioid therapy could also be administered. This was done according to a trial treatment guideline which was available in all recruiting emergency departments (N=367)

Study	**Kelly 2002[83]**
Study type	RCT (Patient randomised; Parallel)
Funding	Funded by a grant from the San Diego Foundation
Number of studies (number of participants)	Single centre (N=58; UC=31; CPAP=27)
Countries and setting	Conducted in United Kingdom; Setting: Emergency department
Duration of study	Until hospital discharge

Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Inclusion criteria	Acute onset of breathlessness (within 6 hrs); respiratory rate < 20/min; and typical chest X-ray appearance of pulmonary oedema
Exclusion criteria	If patients had a chest X-ray consistent with pneumonia or pneumothorax, or if they had received pre-hospital treatment with interventions other than oxygen, diuretics or opiates.
Recruitment/selection of patients	
Age, gender and ethnicity	Age - Mean (SD): UC 78 (2) CPAP 77 (2). Gender (M:F): Male 26 female 32. Ethnicity:
Intervention 1	Continuous positive airway pressure (CPAP) CPAP. Delivered through a full face mask with a pressure of 7.5 cmH2O (with an inspired oxygen concentration of 60% confirmed by an integral oxygen analyser). Duration Minimum of 6 hrs. Concurrent medication/care: 50-100mg intravenous furosemide, 5 mg buccal nitrate (if systolic blood pressure >90 mmHg) and 2.5-10 mg intravenous morphine sulphate. (N=27)
Intervention 2	Standard Medical Care any form of standard medical care provided for the management of cardiogenic pulmonary oedema excluding NIPPV or alternative methods of ventilatory support, - standard medical care e.g. oxygen by face mask, diuretics, nitrates etc. standard medical care + 60% oxygen delivered through a Venturi masks. Duration Until no longer clinically indicated. Concurrent medication/care: 50-100mg intravenous furosemide, 5 mg buccal nitrate (if systolic blood pressure >90 mmHg) and 2.5-10 mg intravenous morphine sulphate. (N=31)
Study	**Levitt 2001[92]**
Study type	RCT (Patient randomised; Parallel)
Funding	Funding not stated
Number of studies (number of participants)	Single centre (N=38)
Countries and setting	Conducted in USA; Setting: ED
Duration of study	Until hospital discharge
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Inclusion criteria	Patients presenting with severe respiratory distress (tachypnoea - generally 30 b/min, diaphoresis or accessory muscle use) and suspected congestive heart failure. Congestive heart failure was suspected by clinical finding of pulmonary rales, distended neck veins, peripheral oedema or a history of congestive heart failure.
Exclusion criteria	If they met inclusion criteria but required immediate intubation
Recruitment/selection of patients	Study period commenced in December 1995 and finished June 1997.

Age, gender and ethnicity	Age - Mean (SD): BiPAP 67 (15) UC 69 (15). Gender (M:F): Male 13 Female 25. Ethnicity:
Extra comments	Study terminated early due to findings of another trial reporting increased AMI rates associated with BiPAP.

Intervention 1	bilevel ventilation (BiPAP) BiPAP. It was strated on an initial inspiratory positive airway pressure of 8 cm H2O and an initial expiratory positive airway pressure of 3 cm H2O. These initial pressures could be adjusted in 2 cm H2O increments maintaining a pressure support of 5 cm H2O (IPAP-expiratory positive airway pressure).. Duration 2 hrs. Concurrent medication/care: Furosemide, morphine and nitroglycerine. (N=21)
Intervention 2	Standard Medical Care any form of standard medical care provided for the management of cardiogenic pulmonary oedema excluding NIPPV or alternative methods of ventilatory support, - standard medical care e.g. oxygen by face mask, diuretics, nitrates etc. Standard medical care + oxygen mask.. Duration 2hrs. Concurrent medication/care: Furosemide, morphine and nitroglycerine. (N=17)
Comments	The number randomised was probably 21 since 4 patients were removed who did not meet criteria for congestive heart failure (however, it is unclear whether they originated from this group only).

Study	**L'her 2004[87]**
Study type	RCT (Patient randomised; Parallel)
Funding	-- (Technical support (material and ventilatory circuits) was provided by Allegiance SA (Paris, France))
Number of studies (number of participants)	Multicentre (N=89)
Countries and setting	Conducted in France; Setting: ED
Duration of study	Until discharge from hospital
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Inclusion criteria	(a) Age >= 75 (b) acute hypoxemic respiratory failure, i.e. PaO2 / FiO2<=300 mm Hg despite oxygen >=8 l/min for 15 min, respiratory rate >=25 b/min, contraction of the accessory muscles of respiration (c) clinical examination (systolic and/or diastolic hypertension; widespread crackles or wheezing), medical record (previous cardiomyopathy, and / or acute dyspnoea with progressive orthopnoea), electrocardiographic tracing (Q waves and / or abnormalities in the T wave and ST segment; left ventricular hypertrophy; bundle branch block; atrial fibrillation); and (d) chest radiography (cardiac enlargement with a cardiothoracic ratio > 50% and / or pulmonary congestion with Kerley B lines, alveolar filling, pleural effusions).
Exclusion criteria	(a) Coma (Glasgow coma scale <=7) (b) life-threatening hypoxemia (systolic blood pressure <= 90 mm Hg despite

	optimal therapy); and (d) chronic respiratory insufficiency.
Recruitment/selection of patients	
Age, gender and ethnicity	Age - Mean (SD): CPAP 84 (6) UC 84 (6). Gender (M:F): Males 37 Females 51. Ethnicity:
Intervention 1	Continuous positive airway pressure (CPAP) CPAP. A CPAP device delivering a high gas flow (90-140 l/min), with adjustable FiO2 within the 35-100% range a 7.5-cm water-positive end-expiratory pressure valve, a face mask and a MR640 heated-humidifier.. Duration At least 1 hr but overall it was use on average 8 (6) or until SpO2>=92% without oxygen, respiratory rate <25 b/min. Concurrent medication/care: At least an initial 80 mg intravenous furosemide and a continuous infusion of glyceryl-trinitrate (1 mg/h increase each 5 min, if systolic blood pressure >= 100 mm Hg). If the arterial carbon dioxide tension was <=50 mm Hg, morphine could be given intravenously in 2-mg increments, up to 10 mg. If any patient complaint of subsequent chest pain, sublingual nitroglycerin and orally isosorbide dinitrate were administered. (N=43)
Intervention 2	Standard Medical Care any form of standard medical care provided for the management of cardiogenic pulmonary oedema excluding NIPPV or alternative methods of ventilatory support, - standard medical care e.g. oxygen by face mask, diuretics, nitrates etc. Standard medical care + oxygen mask. Duration Until SpO2>=92% without oxygen, respiratory rate <25 b/min. Concurrent medication/care: At least an initial 80 mg intravenous furosemide and a continuous infusion of glyceryl-trinitrate (1 mg/h increase each 5 min, if systolic blood pressure >= 100 mm Hg). If the arterial carbon dioxide tension was <=50 mm Hg, morphine could be given intravenously in 2-mg increments, up to 10 mg. If any patient complaint of subsequent chest pain, sublingual nitroglycerin and orally isosorbide dinitrate were administered. (N=46)

Study	**Lin 1995[94]**
Study type	RCT (Patient randomised; Parallel)
Funding	Funding not stated
Number of studies (number of participants)	Single centre study (N=100)
Countries and setting	Conducted in Taiwan; Setting: ED or coronary care unit
Duration of study	Until hospital discharge and monthly follow-up up to 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Inclusion criteria	Dyspnoea and tachypnoea, signs of impending respiratory failure, such as the use of accessory muscles, and a respiratory rate of more than 22 b/min with an initial ratio of arterial blood oxygen partial pressure (PaO2) to a fraction of inspired oxygen (FiO2) content in the range of 200 to 400 mmHg. Cardiogenic pulmonary oedema was diagnosed

	when the patient had dyspnoea of sudden onset, typical findings on chest radiograph such as bilateral diffuse interstitial or alveolar oedema, and bilateral basal or diffuse moist rales on physical examination without a history suggesting pulmonary aspiration or infection.
Exclusion criteria	Patients unresponsive to speech; unable to maintain a patent airway and who had cardiogenic shock, ventricular septal rupture, and severe stenotic valvular disease or chronic lung disease with carbon dioxide retention at rest
Recruitment/selection of patients	
Age, gender and ethnicity	Age - Mean (SD): CPAP 72 (8) UC 73 (9). Gender (M:F): Male 90 Female 10. Ethnicity:
Intervention 1	Continuous positive airway pressure (CPAP) CPAP. Pressure wash applied by connecting a serial CPAP valve (2.5 cm, 5 cm, 7.5 cm and 12.5 cm) to the face mask at each 30-min interval. During the first 3 hr investigation period the inspired oxygen concentration was not changed. Within the second 3 hr observation period, FIO2 and CPAP levels in each patient were adjusted to keep PaO2 > 80 mmHg. Duration 6 hrs. Concurrent medication/care: According to pre-specified protocol this could include: isosorbide dinitrate, furosemide, morphine, dopamine, nitroglycerin and nitroprusside. (N=50)
Intervention 2	Medical care any form of standard medical care provided for the management of cardiogenic pulmonary oedema excluding NIPPV or alternative methods of ventilatory support, Medical care e.g. oxygen by face mask, diuretics, nitrates, etc. Medical care + oxygen face mask. Duration 6 hrs or unless no longer clinically indicated. Concurrent medication/care: According to pre-specified protocol this could include: furosemide, morphine, dopamine, nitroglycerin and nitroprusside. (N=50)

Study	**Masip 2000[102]**
Study type	RCT (Patient randomised; Parallel)
Funding	Academic or government funding (financed by the Fondo de Investigación Sanitaria (FIS Grant 1996) Ministerio de Sanidad y Consumo)
Number of studies (number of participants)	Single centre (N=40)
Countries and setting	Conducted in Spain
Duration of study	Until hospital discharge
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Inclusion criteria	Dyspnoea of sudden onset with physical findings consistent with pulmonary oedema (widespread rales with or without third heart sound) and typical findings of congestion on a chest radiograph
Exclusion criteria	Patients with mild acute cardiogenic pulmonary oedema (acute heart failure not presenting evident shortness of

	breath). Patients with cardiogenic shock (systolic blood pressure <90 mm Hg); severe acute or chronic airflow obstruction without evidence of cardiogenic pulmonary oedema; severe chronic renal failure (serum creatinine concentration > 265umol/L); any neurological impairment that would prevent adherence to the protocol; acute myocardial infarction necessitating thrombolysis; evidence of pneumonia; immediate need for intubation; and absence of pulmonary oedema on a first chest radiograph.
Recruitment/selection of patients	To allow treatment to commence promptly chest x-ray was not always carried out before randomisation.
Age, gender and ethnicity	Age - Mean (SD): BiPAP 75.3 (11) UC 78.5 (5). Gender (M:F): Males 19 Females 18. Ethnicity:
Intervention 1	Bilevel ventilation (BiPAP) BiPAP. PEEP of 5 cm H2O was administered to all patients. Sensitivity of the ventilatory was decreased to a minimum (0.5 cm water) to allow easier triggering of the machine. Means setting pressure support was 15.2 cm water (2.4; range 10-20). Tidal volumes obtained with NIPSV ranged from a mean of 531 mL (134) at study entry to 627 mL (137) at 4 hrs.. Duration Minimum duration was 4 hours but if a patient responded very rapidly the treatment could be stopped earlier. The average time was 254 min (SD 90). Concurrent medication/care: Furosemide, morphine, glyceryl trinitrate and digoxin (N=20)
Intervention 2	Standard Medical Care any form of standard medical care provided for the management of cardiogenic pulmonary oedema excluding NIPPV or alternative methods of ventilatory support, - standard medical care e.g. oxygen by face mask, diuretics, nitrates etc. Standard medical care + oxygen mask. Duration Until evident clinical improvement with a respiratory of less than 30 b/min and oxygen saturation of 96% or more.. Concurrent medication/care: Furosemide, morphine, glyceryl trinitrate and digoxin (N=20)
Study	**Nava 2003[119]**
Study type	RCT (Patient randomised; Parallel)
Funding	Funding not stated (A conflict of interest section is provided: None of the authors declared any conflicts of interest)
Number of studies (number of participants)	Multicentre (N=130)
Countries and setting	Conducted in Italy; Setting: ED
Duration of study	Other: Study was performed over a 21-month period.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Inclusion criteria	Severe acute respiratory failure (PaO2/FiO2<250) breathing oxygen at >10L/m for at least 15 min (FiO2 determined by a portable oxygen analyser, dyspnoea of sudden onset with respiratory rate > 30 breaths/min, typical physical signs of pulmonary oedema (widespread rales), congestion on chest X-ray, without a history of pulmonary aspiration or infection.
Exclusion criteria	Immediate need for endotracheal intubation, severe sensorial impairment (Kelly score > 3), shock, ventricular

	arrhythmia, life-threatening hypoxia (SpO_2 < 80% with oxygen), acute myocardial infarction necessitating thrombolysis, severe chronic renal failure, and pneumothorax.
Recruitment/selection of patients	The patients were enrolled in the protocol fifteen minutes after the arrival in the hospital, this waiting period included the time necessary to stabilise the patients (the large majority coming directly from home) and especially to make a diagnosis (clinical examination, and anamnesis).
Age, gender and ethnicity	Age - Mean (SD): Bilevel: 73.1 (8.3) Medical care: 72.1 (9.1). Gender (M:F): 110 males / 29 females. Ethnicity: not reported
Intervention 1	Bilevel ventilation (BiPAP) BiPAP. The positive end-expiratory pressure was initially set at 5 cm H2O and could be increased by 1 cm H2O until a brisk increase in SpO2 was observed, whereas the inspiratory pressure support was initially set at 10 cm H2O and then increased in increments of 2 cm H2O to the maximum tolerated. After the initial adjustments, the ventilatory settings were set at 14.5 (21.1) cm H2O for the inspiratory support and at 6.1 (3.2) for positive end-expiratory pressure. Duration: At least 4 hours of NPSV were given continuously and then intermittently, as appropriate based on the patient's tolerance and the achievement of SpO_2>92% without oxygen with a respiratory rate < 30 b/m. Mean duration 11.4 (3.6) hours. Concurrent medication/care: morphine sulphate, furosemide, glyceryl trinitrate (N=65)
Intervention 2	Standard Medical Care any form of standard medical care provided for the management of cardiogenic pulmonary oedema excluding NIPPV or alternative methods of ventilatory support, - standard medical care e.g. oxygen by face mask, diuretics, nitrates etc. Standard medical care + O2 mask (to maintain an SpO2>90%). Duration Oxygen therapy was continued until intubation, death or fulfilment of oxygen delivery cessation criteria (SpO2>92% without oxygen and a respiratory rate < 30 b/m). Concurrent medication/care: Morphine sulphate, furosemide, glyceryl trinitrate (N=65)
Study	**Park 2001[133]**
Study type	RCT (Patient randomised; Parallel)
Funding	Funding not stated
Number of studies (number of participants)	Single centre (N=26)
Countries and setting	Conducted in
Duration of study	Until hospital discharge
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Inclusion criteria	Dyspnoea of acute onset or worsening, respiration rate >=25 inspirations per minute, and pulmonary findings comparative with pulmonary congestion which was radiographically confirmed at a later stage.

Exclusion criteria	Systolic blood pressure < 90 mmHg, cardiac arrhythmias requiring electric cardioversion, decrease of the consciousness level, bradypnoea, lack of cooperation or agitation, repetitive vomiting despite the use of antiemetics, upper digestive haemorrhage, facial deformities or any other decompensated respiratory disease.
Recruitment/selection of patients	
Age, gender and ethnicity	Age - Mean (SD): Overall 69 (7). Gender (M:F): Males 10 Females 16. Ethnicity:
Extra comments	The study was terminated because the BiPAP group had a significantly greater number of patients with acute myocardial infarction.
Intervention 1	Continuous positive airway pressure (CPAP) CPAP. PEEP = 7.5 cmH2O. Duration Mean (SD) minutes 170 (90) - when patients were able to maintain O2 saturation above 90% and a comfortable respiratory pattern with a respiration rate below 30 breaths per minute ventilatory support was gradually withdrawn.. Concurrent medication/care: Isosorbide dinitrate 5 mg sublingually if the patient had systolic blood pressure >= 100 mmHg (N=9)
Intervention 2	Bilevel ventilation (BiPAP) BiPAP. Expiratory positive pressure of 4cm H2O and mean inspiratory pressure of 12cm H2O. Duration Mean (SD) minutes 155 (38) - when patients were able to maintain O2 saturation above 90% and a comfortable respiratory pattern with a respiration rate below 30 breaths per minute ventilatory support was gradually withdrawn.. Concurrent medication/care: Isosorbide dinitrate 5 mg sublingually if the patient had systolic blood pressure ≥100 mmHg (N=7)
Intervention 3	Standard Medical Care any form of standard medical care provided for the management of cardiogenic pulmonary oedema excluding NIPPV or alternative methods of ventilatory support, - standard medical care e.g. oxygen by face mask, diuretics, nitrates etc. Standard medical treatment + oxygen mask. Duration Until patients were able to maintain O2 saturation above 90% and a comfortable respiratory pattern with a respiration rate below 30 breaths per minute ventilatory support was gradually withdrawn.. Concurrent medication/care: Isosorbide dinitrate 5 mg sublingually if the patient had systolic blood pressure ≥100 mmHg (N=10)
Study	**Park 2004[134]**
Study type	RCT (Patient randomised; Parallel)
Funding	Funding not stated
Number of studies (number of participants)	Single centre (N=83)
Countries and setting	Conducted in Brazil; Setting: Tertiary hospital emergency room
Duration of study	60-day follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis

Inclusion criteria	Acute onset of severe respiratory distress (breathing rate ≥25 b/min) associated tachycardia and diaphoresis, and findings of pulmonary congestion on physical examination. Chest x-ray taken within 2 hrs after randomisation to confirm diagnosis.
Exclusion criteria	Impaired level of consciousness at presentation; intractable vomiting; acute myocardial infarction with persistent ST segment elevation; systolic pressure < 90 mmHg at presentation; or another decompensated pulmonary disease such as pulmonary embolism, COPD, pneumonia and pneumothorax.
Recruitment/selection of patients	
Age, gender and ethnicity	Age - Mean (SD): BiPAP 66 (14) CPAP 61 (17) UC 65 (15). Gender (M:F): Male 34 Female 46. Ethnicity:
Extra comments	The study was stopped during the second interim analysis after 80 patients had been studies because of a significant difference in endotracheal intubation rates among the groups.

Intervention 1	Continuous positive airway pressure (CPAP) CPAP. Mean (SD) PEEP=11 (2) cm H2O. Duration Mean (SD) duration 102 (41) until the patient had (a) absence of respiratory distress; (b) SpO_2 >= 95%; and (c) respiratory rate <25 b/min. Concurrent medication/care: Standard medical treatment which could include: Isosorbide dinitrate, morphine, furosemide, nitroprusside, nitroglycerin (N=27)
Intervention 2	Bilevel ventilation (BiPAP) BiPAP. Mean (SD) EPAP=11 (2) cm H_2O. Duration Mean (SD) duration 124(62) until the patient had (a) absence of respiratory distress; (b) SpO_2 >= 95%; and (c) respiratory rate <25 b/min. Concurrent medication/care: Standard medical treatment which could include: Isosorbide dinitrate, morphine, furosemide, nitroprusside, nitroglycerin (N=29)
Intervention 3	Standard Medical Care any form of standard medical care provided for the management of cardiogenic pulmonary oedema excluding NIPPV or alternative methods of ventilatory support, - standard medical care e.g. oxygen by face mask, diuretics, nitrates etc. Standard medical treatment + oxygen mask. Duration Until the patient had (a) absence of respiratory distress; (b) SpO_2 >= 95%; and (c) respiratory rate <25 b/min. Concurrent medication/care: Standard medical treatment which could include: Isosorbide dinitrate, morphine, furosemide, nitroprusside, nitroglycerin (N=27)

Study	**Plaisance 2007[137]**
Study type	RCT (Patient randomised; Parallel)
Funding	Funding not stated
Number of studies (number of participants)	Single centre (N=124)
Countries and setting	Conducted in
Duration of study	Until discharge

Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis Pre-hospital setting
Inclusion criteria	Define
Exclusion criteria	Define
Recruitment/selection of patients	
Age, gender and ethnicity	Age - Mean (SD): CPAP . Gender (M:F): Male 61 Female 63. Ethnicity:

Study	**Rasanen 1985[141]**
Study type	RCT (Patient randomised; Parallel)
Funding	Funding not stated
Number of studies (number of participants)	Single centre (CPAP n= 20; UC n=20)
Countries and setting	Conducted in Finland; Setting: ICU
Duration of study	Until hospital discharge
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Inclusion criteria	Patients with respiratory failure and clinical and radiologic evidence of acute, alveolar pulmonary oedema of cardiac origin. Dyspnoea, signs of increased respiratory work such as intercostal and suprasternal retractions or use of accessory respiratory muscles during inspiration, a respiratory rate of more than 25 b/min or arterial blood oxygen partial pressure to inspired oxygen concentration ratio of less than 200.
Exclusion criteria	Patients unresponsive to speech, those unable to maintain patent airway, and those who had sings of lung infection, evidence of pulmonary embolism or chronic lung disease with carbon dioxide retention at rest.
Recruitment/selection of patients	
Age, gender and ethnicity	Age - Mean (SD): CPAP 74 (9) UC 73 (9). Gender (M:F): Males 13 Females 27. Ethnicity:

Intervention 1	Continuous positive airway pressure (CPAP) CPAP. 10 cm H_2O. Duration 3 hrs. Concurrent medication/care: Included: furosemide, morphine, diazepam, chlorpromazine, nitroglycerin, nitroprusside, digitalis, dopamine, dobutamine (N=20)
Intervention 2	Standard Medical Care any form of standard medical care provided for the management of cardiogenic pulmonary oedema excluding NIPPV or alternative methods of ventilatory support, - standard medical care e.g. oxygen by face mask, diuretics, nitrates etc. dose/quantity, brand name, extra details. Duration 3 hrs. Concurrent medication/care: Standard medical care + oxygen mask (with inspired oxygen concentration of 28 to 30%, depending on the entrainment ratio of the particular venturi in use. (N=20)

Study	**Sharon 2000[161]**
Study type	RCT (Patient randomised; Parallel)
Funding	Funding not stated
Number of studies (number of participants)	Single centre (N=40)
Countries and setting	Conducted in Israel
Duration of study	6 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Inclusion criteria	Patients with severe pulmonary oedema which was defined as symptoms and signs of pulmonary oedema accompanied by oxygen saturation of < 90% measured by pulse oximetry upon hospital admission, prior to oxygen administration
Exclusion criteria	(1) previous treatment with nitrates above 40 mg/d, or mono-nitrates or long-actingtri-nitrates administered more than three times a day; (2) previosu treatment with furosemide > 80 mg/d; (3) hypotension (blood pressure <110/70 mmHg); (4) previous adverse effect of nitrates; (5) ST elevations consistent with acute MI on baseline ECG; and (6) absence of pulmonary oedema on chest radiograph obtained on arrival to the emergency department.
Age, gender and ethnicity	Age - Mean (SD): High dose IV ISDN 73 (7) BiPAP 72 (6). Gender (M:F): Males 19 Females 21. Ethnicity:

Study	**Takeda 1997[168]**
Study type	RCT (Patient randomised; Parallel)
Funding	Funding not stated
Number of studies (number of participants)	Single centre (N=30)

Countries and setting	Conducted in Japan; Setting: ICU
Duration of study	Unclear - presumably until discharge from ICU
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Inclusion criteria	Cardiogenic pulmonary oedema was diagnosed if a patient had dyspnoea of sudden onset, typical findings on chest radiographs and widespread rales
Exclusion criteria	A history suggesting pulmonary aspiration or infection.
Recruitment/selection of patients	All patients were enrolled within 2 hrs of admission to ICU
Age, gender and ethnicity	Age - Mean (SD): CPAP 69 (10) UC 64 (9). Gender (M:F): Male 22 female 8. Ethnicity: Not reported

Intervention 1	Continuous positive airway pressure (CPAP) CPAP. Each patient in the CPAP group received from 4 to 10 cm H2O of CPAP. The inspired oxygen concentration could be increased to 70%.. Duration Mean hrs (SD): 11.9 (8.4). Concurrent medication/care: Could include: furosemide, morphine, nitroglycerin, digitalis, dopamine, dobutamine, norepinephrine (N=15)
Intervention 2	Standard Medical Care any form of standard medical care provided for the management of cardiogenic pulmonary oedema excluding NIPPV or alternative methods of ventilatory support, - standard medical care e.g. oxygen by face mask, diuretics, nitrates etc. Standard medical care + oxygen mask. Duration Until breathing stabilised. Concurrent medication/care: Could include: furosemide, morphine, nitroglycerin, digitalis, dopamine, dobutamine, norepinephrine (N=15)

Study	**Takeda 1998[167]**
Study type	RCT (Patient randomised; Parallel)
Funding	Funding not stated
Number of studies (number of participants)	Single centre (N=22)
Countries and setting	Conducted in Japan; Setting: Coronary care unit
Duration of study	Until hospital discharge
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Inclusion criteria	All patients with cardiogenic pulmonary oedema as diagnosed by the following criteria: dyspnoea of sudden onset, typical findings on chest radiograph and widespread rales. Furthermore the diagnosis of acute myocardial infarction was based on the presence of the following 3 criteria: (a) typical chest pain lasting at least 30 min; (b) serum creatinine

	kinase levels that were at least twice the normal value and (c) electrocardiographic changes consistent with acute myocardial infarction. Cardiogenic shock was defined according to standard criteria.
Exclusion criteria	A history suggesting pulmonary aspiration or infection
Recruitment/selection of patients	
Age, gender and ethnicity	Age - Mean (SD): CPAP 74 (11) UC 75 (10). Gender (M:F): Male 17 Female 5. Ethnicity:
Intervention 1	Continuous positive airway pressure (CPAP) CPAP. PEEP= 7 (3) cm H2O. Duration 48 hrs. Concurrent medication/care: Could include: dopamine, dobutamine, epinephrine, norepinephrine, nitroglycerin, furosemide, morphine (N=11)
Intervention 2	Standard Medical Care any form of standard medical care provided for the management of cardiogenic pulmonary oedema excluding NIPPV or alternative methods of ventilatory support, - standard medical care e.g. oxygen by face mask, diuretics, nitrates etc. Standard medical care + oxygen mask. Duration 48 hrs. Concurrent medication/care: Could include: dopamine, dobutamine, epinephrine, norepinephrine, nitroglycerin, furosemide, morphine (N=11)

Study	**Weitz 2007[181]**
Study type	RCT (Patient randomised; Parallel)
Funding	Funding not stated
Number of studies (number of participants)	Single centre (N=23)
Countries and setting	Conducted in Germany; Setting: Pre-hospital (home and transfer to hospital)
Duration of study	Until discharge from hospital
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis Assessed in pre-hospital setting
Inclusion criteria	Severe dyspnoea and showing additional signs of acute cardiogenic pulmonary oedema (SpO_2 <90% and basal rales).
Exclusion criteria	Severe uncontrolled agitation, angina, obvious ST elevation in the ECG, emesis and aspiration, cardiogenic shock, life threating arrhythmias, coma or any obvious need for intubation.
Recruitment/selection of patients	
Age, gender and ethnicity	Age - Range: BiPAP 54-85 UC 72-92. Gender (M:F): Male 12 Female 11. Ethnicity:

Intervention 1	Bilevel ventilation (BiPAP) BiPAP. Patients were ventilated with an end-expiratory pressure of 5cm H_2O according to the protocol and a pressure support of 12.5 (SD 1.2) cm H_2O.. Duration Until discharge from hospital. Concurrent medication/care: Could include furosemide, nitroglycerin and morphine (N=10)
Intervention 2	Standard Medical Care any form of standard medical care provided for the management of cardiogenic pulmonary oedema excluding NIPPV or alternative methods of ventilatory support, - standard medical care e.g. oxygen by face mask, diuretics, nitrates etc. Standard medical care + oxygen mask. Duration Until hospital discharge. Concurrent medication/care: Could include furosemide, nitroglycerin and morphine (N=13)

G.2.2 Mechanical ventilation

Table 49:

Reference	Study type and analysis	No. of patients	Patient characteristics	Confounders included in multivariate analysis	Length of follow-up	Outcome	Source of funding
Fedullo 1991[51]	Retrospective cohort at a single ICU in the USA Stepwise logistic regression analysis Model 1: Using only hospital admission variables Age + all variables which by the univariate analysis were statistically associated (p<0.05) with mortality at the time of intubation	Derivation Cohort: N=88 episodes of cardiogenic pulmonary oedema N=79 individual patients Validation Cohort: N=46 patients	Derivation and validation cohorts: Respiratory failure was attributed to pulmonary oedema by clinical criteria. For each episode both the attending physician and cardiologist agreed on the diagnosis. Inclusion: Pulmonary oedema on CXR plus at least two of; rales; elevated JVP; peripheral oedema; S3 gallop; dyspnoea with exertion; acute MI or acute ischaemic chest pain. Derivation cohort: In hospital survivors: 56	Model 1: Using only hospital admission variables Age (10 year OR) Previous history of hospitalisation for pulmonary oedema Congestive heart failure Diabetes Cardiovascular disease Taking a Ca2+ channel blocker	Until discharge	In hospital mortality	NR

Reference	Study type and analysis	No. of patients	Patient characteristics	Confounders included in multivariate analysis	Length of follow-up	Outcome	Source of funding
	Model 2: Using hospital admission variables and variables available at 24 hours Age + all variables which by the univariate analysis were statistically associated (p<0.05) with mortality at the time of intubation and those recorded 24 hours later		In hospital non survivors: 26 Mean age (years): Survivors: 72.9 +/- 9.3 Non-survivors: 73.8 +/- 10.1 Male/female (n): Survivors: 27/29 Non-survivors: 20/12	Taking a diuretic MI at onset Anterior MI Peripheral oedema Respiratory rate Systolic blood pressure Arterial pH Arterial pCO2 HCO3 Model 2: Using hospital admission variables and variables available at 24 hours Those above plus Use of vasopressors Use of lidocaine Improvement in CXR Awake and responsive On ventilator Peak CPK > 1000U/ml High HR (during 24-48 hours after			

Reference	Study type and analysis	No. of patients	Patient characteristics	Confounders included in multivariate analysis	Length of follow-up	Outcome	Source of funding
				intubation) Low Systolic BP High Systolic BP Arterial pCO2 a/A for O2 HCO3			

Table 50:

Reference	Study type and analysis	No. of patients	Patient characteristics	Confounders included in multivariate analysis	Length of follow-up	Outcome	Source of funding
Papaioannou 2010[131]	Prospective cohort at a single ICU in Greece 1) Multiple linear regression analysis conducted to obtain associations with length of mechanical ventilation 2) Multivariate logistic regression conducted for independent predictors of prolonged weaning >7 days: not	N=32	Primary diagnosis of severe acute respiratory failure due to acute pulmonary oedema. Diagnosis confirmed by echocardiography in the ICU. All patients were mechanically ventilated. Exclusions: Patients with inappropriate acoustic windows, significant valvular pathologies and ventricular arrhythmia or atrial fibrillation were excluded from the study. Duration of weaning < 7 days: 20 Duration of weaning >7 days: 12 Mean age (years): 63.31 +/- 5.23 Male/female (n): 26/6	Lack of clear reporting on confounders Linear regression analysis revealed significant associations between duration of ventilation and: TAPSE: Beta slope = -0.89, SE = 0.14, p<0.001 Sm: Beta slope = -0.57. SE = 0.09, p<0.001 Em/Am: Beta slope	Until discharge	Duration of mechanical ventilation Prolonged weaning >7 days	NR

Reference	Study type and analysis	No. of patients	Patient characteristics	Confounders included in multivariate analysis	Length of follow-up	Outcome	Source of funding
	extracted)			= -0.27. SE = 0.05, p<0.001 Logistic regression analysis revealed that the following can predict length of weaning > 7 days: TAPSE: beta = 0.76, SE = 0.043, p<0.001 LVEF: beta = 0.87, SE= 0.03, p<0.001 Sm: beta = 0.75, SE = 0.03, p< 0.001 Em/Am: beta = 0.32, SE = 0.05, p<0.001 RVFAC: beta = 0.74, SE = 0.03, p<0.001 Multivariate analysis after adjustment of predictors found in univariate models for age, SBP, HR, BSA and duration of intravenous therapy concluded that they were independently associated with the outcome of interest (p<0.05)			

Table 51:

Reference	Study type and analysis	No. of patients	Patient characteristics	Confounders included in multivariate analysis	Length of follow-up	Outcome	Source of funding
Brezins 1993[24]	Prospective cohort at a single CCU in Israel Stepwise logistic regression analysis	N=69	Patients with acute myocardial infarction admitted to the coronary care units who were treated with mechanical ventilation because of pulmonary oedema that was not responding to classic treatment. Exclusions: Patients requiring mechanical ventilation due to brain anoxia. One patient with severe idiopathic hypertrophic subaortic stenosis and a small MI was also excluded. In hospital deaths: 46 Deaths within 1 year: 12 Survivors at 1 year: 11 Mean age (years): 68.4 +/- 7.2 Male/female (n): 41/28	22 variables included Age(yr) Gender Shock Anterior MI Transmural MI Previous MI Past angina Past hypertension Diabetes Past smoking Thrombolytic therapy CPR before ventilation Not severe LV dysfunction Severe LV dysfunction VT/VF Atrial fibrillation Pacing Severe VSD, Mitral regurgitation or	1 year	In hospital mortality 1 year mortality	NR

Reference	Study type and analysis	No. of patients	Patient characteristics	Confounders included in multivariate analysis	Length of follow-up	Outcome	Source of funding
				tamponade LV score CK (LN units) BP (mm Hg) HR (beats/min)			

1

2 ### G.2.3 Ultrafiltration

Study	Badawy 2012[13]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	Single center (n=40)
Countries and setting	Conducted in Egypt; Setting: ICU
Duration of study	Intervention + follow up: 30 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Congestive Heart Failure with NYHA class III or IV. All had oedema of the lower extremities and at least 1 of the following: elevated jugular venous pressure more than 10 cm H2O; pulmonary oedema or pleural effusion on chest x-ray; pulmonary rales; pulmonary wedge or left ventricular end-diastolic pressure more than 20 mmHg, ascites or presacral

	oedema.
Exclusion criteria	SBP 85 mmHg or less at the time of consent, hematocrit 40% or more. end-stage renal disease requiring dialysis, mechanical ventilation and participation in another research study or previously in this trial.
Age, gender and ethnicity	Age - Mean (SD): Diuretics 62 (14) Ultrafiltration 64 (11). Gender (M:F): 26/14. Ethnicity:
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Diuretic - Furosemide. The dose of administration was determined by the attending physician according to the ICU protocol (A loading bolus dose of 1 mg/kg then a continuous infusion starting with 20 mg/h. The rate of the continuous infusion could be increased to maintain the urine output > 1 mL/kg per hour.). Duration of the trial. Concurrent medication/care: All baseline cardiac medications were continued during the study period according to the ICU protocol. (n=20) Intervention 2: Ultrafiltration - Any type of ultrafiltration device. Continuous veno-venous hemodiafiltration was done with either a Multifiltrate machine (Fresenious Medical Care, Bad Homburg Germany) or Prismaflex machine (Gambro Lundia AB, Sweden). The rate of ultrafiltration was determined by the attending physician but never exceeded 200 mL/h. A loading bolus of 5000 IU of heparin and then a continuous heparin infusion rate of 500 to 100 IU/h was given to maintain the activated clotting time between 180 to 220 seconds.. Duration 72 hours. Concurrent medication/care: All baseline cardiac mediactions except for diuretics
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ANY TYPE OF ULTRAFILTRATION DEVICE versus FUROSEMIDE Protocol outcome 1: Length of stay - Actual outcome: Length of ICU stay at Until ICU discharge; Group 1: mean 12 days (SD 6); n=20, Group 2: mean 19 days (SD 7); n=20; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: All cause mortality - Actual outcome: Mortality at 30 days; Group 1: 3/20, Group 2: 5/20; Risk of bias: High; Indirectness of outcome: No indirectness	

Protocol outcome 3: Weight loss
- Actual outcome: Weight loss in kg at 72 hrs; Group 1: mean -6.3 (SD 3.5); n=20, Group 2: mean -3.7 (SD 3.2); n=20; Risk of bias: ; Indirectness of outcome: No indirectness

Protocol outcome 4: Change in renal function
- Actual outcome: Dialysis dependence at At discharge from hospital; Group 1: 1/15, Group 2: 1/17; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 5: Change in serum creatinine
- Actual outcome: Serum creatinine mg/dL at At 72 hours; Risk of bias: High; Indirectness of outcome: No indirectness

Study	**Bart 2005[15]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	Multicentre (n=40)
Countries and setting	Conducted in USA; Setting: Hospitalised patients
Line of therapy	1st line
Duration of study	24 hours; 30 days follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Required to have at least 2+ oedema of the lower extremeties and at least one of the following: elevated JVP >10cm H20; pulmonary oedema or pleural effusion on chest xray; pulmonary crackles; pulmonary wedge or left ventricular end diastolic pressure ?20 mmHg; ascites or pre-sacral oedema
Exclusion criteria	severe stenotic valvular disease; ACS; SBP <90mm Hg at time of consent; haematocrit >40%; poor peripheral venous access; haemodynamic instability; use of isolated radiocontrast within 72 hours of consent or anticipated use during hospitalisation; severe concomitant disease
Recruitment/selection of patients	NR
Age, gender and ethnicity	Age - Other: Median UF: 67.5 Median Usual Care: 69.5. Gender (M:F): Define. Ethnicity: NR
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Ultrafiltration - Any type of ultrafiltration device. Single 8 hour session fluid removal rates

	determined by the attending physician (to a maximum of 500cc/h)Median time from consent to UF initiation was 3.69 hours System 100, CHF Solutions Inc., Brooklyn Park, Minnesota. Duration 8 hours of UF; Measured at 24 hours. Concurrent medication/care: Diuretics were held during the 8hr of UF thereafter they were administered at the discretion of the treating physician. No further courses of UF were permitted until after 24 hours. Percentage of patients receiving following medications: IV Diuretics: 65%; Nesiritide: 20%; IV inotropes 0% (n=20) Intervention 2: Diuretic - Furosemide. Usual Care. Duration 24 hours. Concurrent medication/care: Percentage of patients receiving following medications: IV Diuretics: 95%; Nesiritide: 50%; IV inotropes 10%
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ANY TYPE OF ULTRAFILTRATION DEVICE versus USUAL CARE

Protocol outcome 1: Length of stay
- Actual outcome: length of hospital stay at days; Mean Median UF: 6 days; Usual care; 5 days; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Dyspnea
- Actual outcome: Number of patients with marked, moderate or mild improvement in dyspnoea at 24 hours; Group 1: 0/0, Group 2: 0/0; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome: Number of patients with marked, moderate or mild improvement in global well being at 24 hours; Group 1: 0/0, Group 2: 0/0; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 3: Weight loss
- Actual outcome: Weight loss (kg) at 24 hours; Other: Weight loss in the UF group was greater in the UF group but failed to reach statistical significance (p=0.24); Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 4: Change in renal function
- Actual outcome: Difference in change in creatinine from baseline (micromol/l) at 24 hours ; Mean +0.1. NS difference between groups at 24 hours; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 5: All cause mortality
- Actual outcome: All cause mortality at 30 days; Group 1: 1/20, Group 2: 0/20; Risk of bias: Very high; Indirectness of outcome: No indirectness

Study	**Bart 2012**[16]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	Multicentre study (n=188)
Countries and setting	Conducted in Canada, Multiple countries, USA; Setting: Hospitalised patients
Duration of study	Follow up (post intervention): 60 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Worsened renal function (defined as an increase of at least 26.5µmol/l) within 12 weeks before or 10 days after the index admission with heart failure. All patients were required to have two of the following: at least 2+ peripheral oedema, JVP > 10cm of water or pulmonary oedema or pleural effusion on chest radiography
Exclusion criteria	Patients receiving intravenous vasodilators or inotropic agents; patients with a serum creatinine of >309.4µmol/l
Age, gender and ethnicity	Age - Median (range): Diuretics 66 (57-78) Ultrafiltration 69 (61-78). Gender (M:F): 141/47. Ethnicity: NR
Extra comments	ADHF with persistent congestion and worsened renal function. Trial recruitment stopped early by drug and safety monitoring board due to lack of evidence of benefit and excess of adverse events with ultrafiltration
Indirectness of population	No indirectness
Interventions	(n=94) Intervention 1: Ultrafiltration - Any type of ultrafiltration device. Ultrafiltration (Aquadex system 100 (CHF solutions)) at fluid removal rate of 200ml/hour started a median of 8 hours post randomisation. . Duration The median duration of treatment was 40 hours (IQR: 28 to 67) . Concurrent medication/care: 30% received loop IV diuretics before 96 hours 3% received IV vasodilators and 3% received inotropic agents

	(n=94) Intervention 2: Diuretic - Furosemide. Diuretic-based stepped pharmacological therapy aimed at maintaining urine output at 3-5litres/day. Duration The median duration of treatment was 92 hours (IQR: 56 to 138). Concurrent medication/care: In addition to loop diuretics 46% received metolazone, 5% received IV vasodilators, 12% with an inotropic agent
Funding	Academic or government funding (National Heart, Lung, and Blood Institute)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ULTRAFILTRATION versus PHARMACOLOGICAL THERAPY

Protocol outcome 1: Number of patients readmitted due to any cause
- Actual outcome: Number of patients readmitted for any cause at 60 days; Group 1: 46/90, Group 2: 37/93; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: All cause mortality
- Actual outcome: All-cause mortality at 60 days; HR 1.32 (95%CI 0.26 to 2.38) Reported; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Dyspnea
- Actual outcome: Change in score on dyspnoea assessment scale (100mm VAS) *improvement with higher scores* at 96 hours; Group 1: mean 16.5 100mm VAS (SD 29.2); n=94, Group 2: mean 20.5 100mm VAS (SD 27.8); n=94; 100mm VAS 0-100mm Top=High is good outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 4: Weight loss
- Actual outcome: Mean change from baseline in body weight (kg) at 96 hours; Group 1: mean -5.7 kg (SD 3.9); n=94, Group 2: mean -5.5 kg (SD 5.1); n=94; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome: Mean change from baseline in body weight (kg) at 60 days; Group 1: mean -16 kg (SD 7.9566); n=94, Group 2: mean -17 kg (SD 7.9566); n=94; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 5: Change in renal function
- Actual outcome: Mean change from baseline in serum creatinine (µmol/l) at 96 hours; Group 1: mean 20.3 µmol/l (SD 61.9); n=94, Group 2: mean -3.5 µmol/l (SD 46.9); n=94; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome: Mean change from baseline in serum creatinine (µmol/l) at 60 days; Group 1: mean -10.608 µmol/l (SD 77.3698); n=94, Group 2: mean -35.36 µmol/l (SD 77.3698); n=94; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 6: Number of patients readmitted due to heart failure
- Actual outcome: Number of patients readmitted for due to heart failure at 60 days; Group 1: 23/90, Group 2: 24/93; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 7: Number of patients achieving clinical decongestion
- Actual outcome: Number of patients achieving clinical decongestion at 96 hours; Group 1: 8/82, Group 2: 7/80; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 8: Global well being
- Actual outcome: Change in score on global well-being scale from baseline (100mm VAS) *improvement with higher scores* at 96 hours; Group 1: mean 13.7 100mm VAS (SD 27.9); n=94, Group 2: mean 22.8 100mm VAS (SD 25.8); n=94; 100mm VAS 0-100mm VAS Top=High is good outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 9: Total number of patients with any SAE
- Actual outcome: Total number of patients with any SAE at 60 days; Group 1: 68/94, Group 2: 54/94; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 10: Total number of patients with any heart failure SAE
- Actual outcome: Total number of patients with heart failure SAE at 60 days; Group 1: 31/94, Group 2: 28/94; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 11: Total number of patients with any cardiovascular SAE
- Actual outcome: Total number of patients with other cardiovascular SAEs at 60 days; Group 1: 6/94, Group 2: 5/94; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 12: Total number of patients with any renal failure SAE
- Actual outcome: Total number of patients with renal failure SAE at 60 days; Group 1: 17/94, Group 2: 14/94; Risk of bias: High; Indirectness of outcome: No indirectness

Study	**Costanzo 2007[34]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=200)
Countries and setting	Conducted in USA; Setting: Hospitalised patients
Duration of study	48 hours; 90 days follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	At least 18 years of age; hospitalised for heart failure; hypervolaemic by at least 2 of the following: 1) peripheral oedema ≥ 2+ 2) jugular venous distension 3)radiographic pulmonary oedema or pleural effusion 4) enlarged liver or ascites or 5) pulmonary crackles, PND or orthopnoea.
Exclusion criteria	Acute coronary syndrome; serum creatinine ≥ 265 µmol/litre; SBP ≤ 90 mmHg; haematocrit > 45%; unattainable venous access; requirement for intravenous vasopressors; vasoactive drug use during the index hospitalistaion before trial entry; use of iodinated radiocontrast material; comorbidities expected to prolong hospitalisation; contraindications to anticoagulation; systemic infection; heart transplant
Age, gender and ethnicity	Age - Mean (SD): Ultrafiltration: 62 (15) Standard Care: 63 (14). Gender (M:F): 138/62. Ethnicity: NR
Extra comments	No ejection fraction criteria
Indirectness of population	No indirectness
Interventions	(n=100) Intervention 1: Ultrafiltration - Any type of ultrafiltration device. Aquadex System 100 (CHF solutions) Fluid removed at an average rate of 241ml/h . Duration 12.3 +/- 12 hours. Concurrent medication/care: Treated with heparin

	according to standard protocols to mainatin apTT between 180 and 220s. Treatment with intravenous diuretics prohibited. (n=100) Intervention 2: Diuretic - Furosemide. Average IV diuretic dose was 181 +/- 121mg. 68 patients recieved diuretics as bolus, 32 as a continuous infusion. . Duration 48 hours. Concurrent medication/care: Standard care
Funding	Study funded by industry (CHF solutions funded)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ANY TYPE OF ULTRAFILTRATION DEVICE versus STANDARD CARE WITH DIURETICS

Protocol outcome 1: Quality of life
- Actual outcome: Minnesota Living with heart failure score at 90 days; Mean N/A; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Length of stay
- Actual outcome: Length of index hospitalisation at until discharge; Group 1: mean 6.3 days (SD 4.9); n=100, Group 2: mean 5.8 days (SD 3.8); n=100; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Dyspnea
- Actual outcome: Dyspnoea score at 48 hours; Group 1: mean 6.4 Dyspnoea score (SD 0.502); n=80, Group 2: mean 6.1 Dyspnoea score (SD 0.697); n=83; 7 point Likert scale 1-7 Top=High is good outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 4: Weight loss
- Actual outcome: Mean change in weight (kg) at 48 hours; Group 1: mean -5 kg (SD 3.1); n=83, Group 2: mean -3.1 kg (SD 3.5); n=84; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 5: Change in renal function
- Actual outcome: Change in serum creatinine (µmol/l) at 48 hours -90 days; Other: N/A; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 6: Number of patients readmitted due to heart failure
- Actual outcome: number of patients rehospitalised due to heart failure at 90 days; Group 1: 16/89, Group 2: 28/87; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 7: All cause mortality

- Actual outcome: All cause mortality at 90 days; Group 1: 9/94, Group 2: 11/95; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 8: Number of patients with a rise in serum creatinine >26.5micromoles/l at 24 hours
- Actual outcome: Number of patients with a rise in serum creatinine > 26.5micromoles/l at 24 hours; Group 1: 13/90, Group 2: 7/91; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 9: Number of patients with a rise in serum creatinine >26.5micromoles/l at 48 hours
- Actual outcome: Number of patients with a rise in serum creatinine > 26.5micromoles/l at 48 hours; Group 1: 18/68, Group 2: 15/74; Risk of bias: High; Indirectness of outcome: No indirectness

Study	**CUORE trial: Marenzi 2014[101]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=56)
Countries and setting	Conducted in Italy; Setting: Hospital
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Age > 18 yrs; NYHA class III or IV; LVEF<=40%; estimated weight gain due to peripheral fluid overload >=4 kg in the preceding 2 months (estimation of reference body weight was based on body weight referred by the patient as his or her normal weight).
Exclusion criteria	Contraindications to anticoagulation; severe renal insufficiency (serum creatinie > 3.0 mg/dL); acute pulmonary edema; cardiogenic shock; expected impossibility of completing follow-up for reasons other than patients' health; presence of acute or chronic clinical conditions considered by clinicians to be potential contraindications to ultrafiltration; patients with planned heart transplantation, left ventricular assist device, or other major cardiac surgery procedures.
Age, gender and ethnicity	Age - Mean (SD): Control 73 (9) Ultrafiltration 75 (8). Gender (M:F): 46/10. Ethnicity:
Indirectness of population	No indirectness
Interventions	(n=27) Intervention 1: Ultrafiltration - Any type of ultrafiltration device. Treatment with a single or double session of ultrafiltration performed with the use of a simplified device (Dedyca; Bellco, Mirandola, Italy) specific for patients with heart failure, consisting of a peristaltic pump, a polysuphone filter with a 50,000-Da membrane cut-off, a blood flow adjustable from 40 to 100 mL/min and a total extracorporeal blood volume of 100 mL. Anticoagulation was part of this

	treatment (loading bolus 3,000-5,000 IU heparin and then continuous heparin infusion rate of 500IU/h was maintained during the ultrafiltration session.. Duration Up to a cumulative fluid removal of > 2 liters. Concurrent medication/care: Additional medical therapy was left to the discretion of the cardiologist responsible for the patient. Pharmacological therapy withdrawal, including diuretics, was not required and actually not advised during ultrafiltration sessions. (n=29) Intervention 2: Diuretic - Furosemide. It only states that the control group was treated with intravenous loop diuretics by experienced HF cardiologists according to guideline recommendations. The average dose of furosemide during hospitalisation was 253 mg/d (sd 137). Duration Up to 12 months follow-up. Concurrent medication/care: Additional medical therapy was left to the discretion of the cardiologist responsible for the patient.
Funding	Equipment / drugs provided by industry (Bellco)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ANY TYPE OF ULTRAFILTRATION DEVICE versus FUROSEMIDE

Protocol outcome 1: All cause mortality
- Actual outcome: Mortality at 12 months; Group 1: 7/26, Group 2: 11/28; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Number of patients readmitted due to heart failure
- Actual outcome: Freedom from rehospitalisations at 12 months; HR 0.14 (95%CI 0.04 to 0.48) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Combined mortality and rehospitalisations
- Actual outcome: Rehospitalisations for congestive heart failure and death at 12 months; HR 0.35 (95%CI 0.15 to 0.69) Reported; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: Change in serum creatinine
- Actual outcome: Serum creatinine level (mg/dL) at 12 months; Group 1: mean 1.8 (SD 0.6); n=19, Group 2: mean 1.8 (SD 0.5); n=17; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome: Serum creatinine level (mg/dL) at Hospital discharge; Group 1: mean 1.8 (SD 0.7); n=27, Group 2: mean 1.9 (SD 0.7); n=29; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome: Serum creatinine level (mg/dL) at 6 months; Group 1: mean 1.8 (SD 0.6); n=24, Group 2: mean 2.3 (SD 1.1); n=27; Risk of bias: Low; Indirectness of outcome: No indirectness

Study	**Giglioli 2011[62]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	Single centre (n=30)
Countries and setting	Conducted in Italy; Setting: Hospitalised patients
Duration of study	36 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	At least 18 years old; peripheral oedema >=2+ and at least one of the following 1)pulmonary crackles, 2) dyspnoea, PND, orthopnoea or tachypnoea, 3)third heart sound, 4) jugular venous distension, 5) positive hepato jugular reflux, 6) maximal pulmonary pressure values >50mmHg or 7) Radiographic pleural effusions
Exclusion criteria	Severe valvular stenosis; ACS; serum creatinine >265.2micromol/litre; SBP <=80mmHg; Haematocrit >45%; poor venous access; vasoactive drug and/or > 60mg IV diuretic use before trial entry; severe comorbidities; contraindication to unfractionated heparin administration
Age, gender and ethnicity	Age - Mean (SD): Ultrafiltration: 72.4 (14.1) Diuretics: 65.8 (18.4). Gender (M:F): Define. Ethnicity: NR
Extra comments	ADHF with over hydration
Indirectness of population	No indirectness
Interventions	(n=15) Intervention 1: Ultrafiltration - Any type of ultrafiltration device. PRISMA System (HOSPAL-GAMBRO DASCO, Medolla, Italy) using a M 100 PRESET PRISMA filter and a blood flow rate of 150mL/hFluid removal rate from 100 to 300mL/h adjusted for the SBP (mmHg):<100: 100mL/h>100 ≤110: 200mL/h>110: 300mL/hIn 13 patients fluid removal

	rate was 100mL/hIn 2 patients fluid removal rate was 200mL/h. Duration Differed according to clinical condition of patient. Discontinued when clinical score had decreased by a third or when a reduction in SBP or HR by 15% was observed Median length of treatment 46(IQR 39-71) hours . Concurrent medication/care: Unfractionated heparin was used as an anticoagulant to maintain an apTT between 65 and 85s.No concurrent IV diuretic administration, nil progressed to inotrope therapy (n=15) Intervention 2: Diuretic - Furosemide. Continuous infusion of furosemide at initial dose of 250mg/24 hours. Dose lowered or if plasma creatinine > 44µmol/l when clinical score had decreased by a third or when a reduction in SBP or HR by 15% was observed. Initial dose increased to 500mg/25 hours if achievement of negative fluid balance was not sufficient to reach >2000mL/day. Duration Median length of treatment was 57 (IQR48-85) hours. Concurrent medication/care: Nil progressed to inotrope therapy
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ULTRAFILTRATION versus DIURETIC THERAPY

Protocol outcome 1: Dyspnea
- Actual outcome: End NYHA class at 36 hours; Group 1: mean 2 (SD 0.5); n=15, Group 2: mean 2.4 (SD 0.52); n=15; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Weight loss
- Actual outcome: % of baseline (kg) at 36 hours; Group 1: mean 90.9 % baseline (Kg) (SD 1.7); n=15, Group 2: mean 93.1 % baseline (Kg) (SD 1.8); n=15; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Change in renal function
- Actual outcome: End creatinine score (µmol/l) at 36 hours; Group 1: mean 147.628 µmol/l (SD 65.416); n=15, Group 2: mean 170.612 µmol/l (SD 54.808); n=15; Risk of bias: Very high; Indirectness of outcome: No indirectness

Study	**Hanna 2012[71]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	Single centre (n=36)
Countries and setting	Conducted in USA; Setting: Hospitalised Patients
Line of therapy	1st line
Duration of study	Time until discharge; 90 day follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: Stratified by eGFP above and below 50mL/min/1.73m2
Subgroup analysis within study	Stratified then randomised
Inclusion criteria	NYHA III/IV symptoms with a pulmonary artery catheter in situ; LVEF <40%; PCWP >= 20 mmHg; age 18 years or older; ability to give informed consent
Exclusion criteria	renal replacement therapy or determined to need renal replacement therapy at the time of enrollment; eGFR <15mL/min/1.73m2; SBP <80mmHg; ACS; Haematocrit >50%; malignancy other than prostate or skin cancer; chronic oedematous states other than HF (including nephrotic syndrome and cirrhosis); a chronic inflammatory or infectious condition; pregnancy; pulmonary failure requiring intubation and mechanical ventilation; known or suspected hypersensitivity to dialysis membranes; severe aortic stenosis or regurgitation; severe mitral stenosis and expectation of the need for cardiac transplant or a cardiac assist device within 1 week
Age, gender and ethnicity	Age - Mean (SD): Ultrafiltration: 60 (9.1); Diuretics: 59 (15.5). Gender (M:F): Define. Ethnicity: NR
Further population details	1. Cardiogenic shock: Not stated
Extra comments	ADHF

Indirectness of population	No indirectness
Interventions	(n=19) Intervention 1: Ultrafiltration - Any type of ultrafiltration device. (NXstage System One; NXStage System inc. Lawrence MA) inital therapy prescribed a blood flow rate of 200-300mL/min via an 11.5 fresh haemodialysis catheter inserted into the femoral veinUF rate of 400mL/h for 6 hours and then decreased to 200Ml/hour (changes permited as clinically directed) . Duration Mean time to achieve primary end point (PCWP <18mmHg for at least 4 hours) 22 hours (4.2). Concurrent medication/care: Heparin at 500U/h was administered if there were no contraindications Diuretics stopped except for spirnolactone (<=25mg/day)Recieved IV vasoactive medication (including dopamine, dobutamine, nitroprusside or milrinone)19 (n=17) Intervention 2: Diuretic - Furosemide. IV diuretics at doses and frequencies designated byb the treating physician. Duration Mean time to achieve primary end point (PCWP <18mmHg for at least 4 hours) 34.8 hours (6.7). Concurrent medication/care: Received IV vasoactive medication (including dopamine, dobutamine, nitroprusside or milrinone)
Funding	Study funded by industry (NxStage Medical, Inc, Lawrence MA sponsored the study)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ANY TYPE OF ULTRAFILTRATION DEVICE versus DIURETIC THERAPY

Protocol outcome 1: Quality of life
- Actual outcome: Quality of life at 90 days; Mean Ninety day follow up for quality of life was not statistically different; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Length of stay
- Actual outcome: median time to discharge at days; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Total number of patient reporting any adverse events
- Actual outcome: Adverse events at 90 days; Mean There were no significant differences in the adverse events between both groups ; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: Weight loss
- Actual outcome: Weight loss at Within 48 hours; Group 1: mean 4.7 Kg (SD 3.5); n=19, Group 2: mean 1 Kg (SD 2.5); n=17; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 5: Change in renal function
- Actual outcome: Readmission rate at 90 days; Group 1: 8/19, Group 2: 6/17; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome: End creatinine micromol/l at 96 hours; Group 1: mean 194.48 micromol/lire (SD 106.08); n=19, Group 2: mean 167.96 micromol/lire (SD 79.56); n=17; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 6: All cause mortality
- Actual outcome: All cause mortality at 90 days; Group 1: 4/19, Group 2: 4/17; Risk of bias: ; Indirectness of outcome: No indirectness

Protocol outcome 7: Number of patients with a rise in serum creatinine >26.5micromoles/l at 48 hours
- Actual outcome: Number of patients with atrise in serum creatinine >26.5micromoles/litre at 48 hours; Group 1: 6/19, Group 2: 4/17; Risk of bias: High; Indirectness of outcome: No indirectness

1 G.3 Treatment after stabilisation

2 G.3.1 Beta blockers

3 G.3.1.1 Clinical evidence tables – continuing vs. reducing or discontinuing beta-blockers

Study (subsidiary papers)	Fonarow 2008[57]

Study type	Other non-randomised study
Funding	Study funded by industry (GlaxoSmithKline)
Number of studies (number of participants)	1 (N=2,720)
Countries and setting	Conducted in USA; Setting: Secondary care
Line of therapy	Unclear
Duration of study	Not clear: 60-90 days
Method of assessment of guideline condition	Unclear method of assessment/diagnosis ~ Not stated
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Hospitalised for new or worsening HF as primary cause of admission or developed HF during admission with HF as primary discharge diagnosis; pre-specified subgroup with consent for 60-90 day follow up; eligible for beta-blockers; LVEF <40% or moderate to severe systolic dysfunction
Exclusion criteria	Contra-indications or intolerance of beta-blockers at discharge
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Mean (SD): 69.5 (14.5). Gender (M:F): 1714:1006. Ethnicity: Hispanic 3%; African American 21%; Native American <1%
Further population details	1. Acute decompensated heart failure: 2. Acute heart failure with pulmonary oedema: 3. Acute right-sided heart failure: 4. Cardiogenic shock:
Interventions	Intervention 1: Continuation of beta-blockers Any beta-blocker. Continued beta-blocker - no further details. Duration Not stated. Concurrent medication/care: Not stated (N=1,350) Further details: Intervention 2: reduction or discontinuation, and reinstatement of beta-blockers ~ Any beta-blocker. Beta-blocker withdrawn. Duration Not stated. Concurrent medication/care: Not stated (N=79) Further details:
Study (subsidiary papers)	**Jondeau 2009[80]**
Study type	RCT (Patient randomised; Parallel)

Funding	Academic or government funding (French Ministry of Health)
Number of studies (number of participants)	1 (N=169)
Countries and setting	Conducted in France; Setting: Secondary care
Line of therapy	Adjunctive to current care
Duration of study	Not clear: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis ~ Acute heart failure with pulmonary oedema, including dyspnoea and pulmonary rales or radiological evidence of oedema
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients on beta-blocker at stable dosage >1 month, hospitalised for acute HF with pulmonary oedema, including dyspnoea and pulmonary rales or radiological evidence of oedema, respiratory rate >24/min during the acute HF episode prior to or at the time of inclusion, LVEF < 40% within the preceding 12 months
Exclusion criteria	Acute ST elevation myocardial infarction, clinical indications for dobutamine according to the practicing physician at entry, second or third degree AV block, heart rate lower than 50/min, patients in the uptitration phase of beta-blocker therapy, participation in another research protocol, pregnancy.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 72.3 (11.9). Gender (M:F): 96:51. Ethnicity: Not reported
Further population details	1. Acute decompensated heart failure: 2. Acute heart failure with pulmonary oedema: 3. Acute right-sided heart failure: 4. Cardiogenic shock:
Interventions	Intervention 1: Continuation of beta-blockers ~ Any beta-blocker. Duration of hospitalisation and at 3 months. Concurrent medication/care: Diuretics 69/69, Nitrates 35/69(N=69) Further details: Intervention 2: reduction or discontinuation, and reinstatement of beta-blockers ~ Any beta-blocker. Discontinuation of beta-blockers. Duration Duration of hospitalisation and at 3 months. Concurrent medication/care: Diuretics 77/78, Nitrates 28/78(N=78) Further details:

G.3.1.2 Clinical evidence tables – commencing beta-blockers

Review question	For people with confirmed acute heart failure not already on beta-blocker therapy should beta-blocker treatment commence in hospital after stabilisation or following discharge?
Study	**Ahmed 2011[6]**
Study type	Other non-randomised study
Funding	Funding not stated
Number of studies (number of participants)	1 (N=6,764)
Countries and setting	Conducted in USA; Setting: Secondary care
Line of therapy	Unclear
Duration of study	Not clear: 6 years
Method of assessment of guideline condition	Unclear method of assessment/diagnosis Not stated
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients hospitalised with acute heart failure linked with Medicare outcomes data
Exclusion criteria	LVEF <45%
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 78 (11). Gender (M:F): 2367:4397. Ethnicity: Not stated
Further population details	1. Acute decompensated heart failure: 2. Acute heart failure with pulmonary oedema: 3. Acute right-sided heart failure: 4. Cardiogenic shock:
Interventions	Intervention 1: Commencing Beta-blockers early in hospital. On beta-blockers at discharge, no further details. Duration Not stated. Concurrent medication/care: Not stated(N=3382) Further details: Intervention 2: Commencing Beta-blockers after discharge Any beta-blockers after discharge. Patients not receiving beta-blockers at discharge. Duration Not stated. Concurrent medication/care: Not stated (N=3,382) Further details:

1

Study	**Ezekowitz 2008[48]**
Study type	Other non-randomised study (randomised; Parallel)
Funding	Academic or government funding
Number of studies (number of participants)	1 (N=2,924)
Countries and setting	Conducted in Canada; Setting: Secondary care
Line of therapy	Unclear
Duration of study	Not clear: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis - ICD codes on hospital discharge abstracts
Stratum	Overall
Subgroup analysis within study	Not stratified but pre-specified: Analysed by ejection fraction >50% or <50%
Inclusion criteria	Newly admitted patients with primary discharge diagnosis of HF for the first time; met Framingham Study HF criteria
Exclusion criteria	Transferred from another acute care facility; non-residents on Province of Ontario; invalid health care number; HF as complication/secondary diagnosis; died during admission; no LV assessment; medication at discharge not recorded; transferred to another hospital; date inconsistency
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): EF>50%: 75.61 (11.48); EF <50%: 72.4 (11.86). Gender (M:F): 1523:1401. Ethnicity: Not stated
Further population details	1. Acute decompensated heart failure: 2. Acute heart failure with pulmonary oedema: 3. Acute right-sided heart failure: 4. Cardiogenic shock:
Interventions	Intervention 1: Commencing Beta-blockers early Commencing any beta-blockers in hospital. Beta-blockers at discharge no further details. Duration Not stated. Concurrent medication/care: Patients could also be on one or more of: ACE inhibitors, ARB, statins, spironolactone, warfarin, aspirin, digoxin, calcium channel blocker(N=691) Further details: Comments: 212 with EF >50% and 479 with EF <50% Intervention 2: Commencing Beta-blockers after discharge Any beta-blockers after discharge. No beta-blockers at discharge, no further details. Duration Not stated. Concurrent medication/care: Patients could also be on one or more of:

	ACE inhibitors, ARB, statins, spironolactone, warfarin, aspirin, digoxin, calcium channel blocker(N=2233) Further details: Comments: 814 with EF >50% and 1,419 with EF <50%

1

Study	**Fonarow 2007[56]**
Study type	Other non-randomised study (randomised; Parallel)
Funding	Study funded by industry (GlaxoSmithKline)
Number of studies (number of participants)	1 (N=2,720)
Countries and setting	Conducted in USA; Setting: Secondary care
Line of therapy	Unclear
Duration of study	Not clear: 90 days
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients hospitalised with heart failure (worsening HF as primary cause of admission or significant HF symptoms developed during hospitalisation for another primary reason and HF primary discharge diagnosis); documented LVSD; eligible for beta-blockers at discharge; pre-specified cohort with consent for 60-90 day follow up
Exclusion criteria	Patients who left against medical advice; transferred out; died in hospital; <18 years old; missing discharge status; beta-blockers contraindicated/not tolerated
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 69.5 (14.5). Gender (M:F): 1714:1006. Ethnicity: 3% Hispanic; 21% African American; <1% Native American
Further population details	1. Acute decompensated heart failure: 2. Acute heart failure with pulmonary oedema: 3. Acute right-sided heart failure: 4. Cardiogenic shock:
Interventions	Intervention 1: Commencing Beta-blockers early Commencing any beta-blockers in hospital. Beta-blocker at discharge, no

	further details. Duration Not stated. Concurrent medication/care: Patients could additionally be treated with ACE inhibitors/ARBs(N=1959) Further details: Intervention 2: Commencing Beta-blockers after discharge. Any beta-blockers after discharge. No beta-blockers at discharge, no further details. Duration Not stated. Concurrent medication/care: Patients could additionally be treated with ACE inhibitors/ARBs (N=374) Further details:

1

Study	**Fonarow 2007[55]**
Study type	Other non-randomised study (randomised; Parallel)
Funding	Study funded by industry (GlaxoSmithKline)
Number of studies (number of participants)	1 (N=2,720)
Countries and setting	Conducted in USA; Setting: Secondary care
Line of therapy	Unclear
Duration of study	Not clear: 60 to 90 days
Method of assessment of guideline condition	Unclear method of assessment/diagnosis Not stated
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with new-onset or worsening HF as primary cause of admission or developed HF during hospitalisation and HF primary discharge diagnosis; LVEF <40% or moderate to severe left systolic dysfunction
Exclusion criteria	Contra-indications to beta-blockers
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 69.7 (14.0). Gender (M:F): 982:562. Ethnicity: Hispanic 3%; African American 21%; Native American <1%; Asian/Pacific Islander <1%

Further population details	1. Acute decompensated heart failure: 2. Acute heart failure with pulmonary oedema: 3. Acute right-sided heart failure: 4. Cardiogenic shock:
Interventions	Intervention 1: Commencing Beta-blockers early /Commencing any beta-blockers in hospital. Carvedilol at discharge mean daily dose 17.8 (17.5)mg at discharge. Duration Not stated. Concurrent medication/care: Patients could also be on ACE inhibitor, aldosterone antagonist, ARB, digoxin, diuretic, lipid-lowering agent(N=1162) Further details: Intervention 2: Commencing Beta-blockers after discharge Any beta-blockers after discharge. dose/quantity, brand name, extra details. Duration Not stated. Concurrent medication/care: Patients could also be on ACE inhibitor, aldosterone antagonist, ARB, digoxin, diuretic, lipid-lowering agent(N=382) Further details:

1

Study	**Gattis 2004[60]**
Study type	RCT (Patient randomised; Parallel)
Funding	Equipment / drugs provided by industry (GlaxoSmithKline)
Number of studies (number of participants)	1 (N=363)
Countries and setting	Conducted in USA; Setting: 45 centres across the US
Line of therapy	Adjunctive to current care
Duration of study	Intervention time:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Primary diagnosis of heart failure and LVEF<40% within the previous 12 months, inform consent
Exclusion criteria	treatment with any beta-blocker within 30 days prior to randomisation, decompensated NYHA class IV requiring intravenous inotropics at randomisation, second or third degree AV block or sick sinus syndrome unless functional pacemaker present, symptomatic bradycardia unless functional pacemaker present, bronchial asthma or related

	bronchospastic conditions, symptomatic hypotension defined by the investigator, cardiogenic shock, expected survival <60 days, hypersensitivity to carvedilol, clinically manifest hepatic impairment, pregnancy or lactating women
Recruitment/selection of patients	Screening of hospitalised patients
Age, gender and ethnicity	Gender (M:F): 193:170. Ethnicity: Not reported
Further population details	1. Acute decompensated heart failure: 2. Acute heart failure with pulmonary oedema: 3. Acute right-sided heart failure: 4. Cardiogenic shock:
Interventions	Intervention 1: Commencing Beta-blockers after discharge. Any beta-blockers after discharge. Physician discretion post-discharged for initiation of b-blocker based on HFSA HF guidelines (standard practice). Duration May or may not receive prescribed b-blockers after discharge. Concurrent medication/care: Any standard medical care (N=178) Further details: Intervention 2: Commencing Beta-blockers early. Commencing any beta-blockers in hospital. Physician discretion post-discharge for initiation of b-blocker based on HFSA HF guidelines (standard practice). Duration May or may not receive prescribed b-blockers at discharge. Concurrent medication/care: Standard medical care(N=185) Further details:

G.3.2 ACE inhibitors

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Cleland et al, 2012[30]	Audit report of 142 out of 155 NHS Trusts	N=32,906 index admissions and N=4,170 readmissions	Acute patients discharged from hospital with a primary diagnosis of heart failure	Receiving ACE inhibitor prescription at discharge	Not receiving ACE inhibitor prescription at discharge	3 years for mortality (multivariate analysis)	1 year mortality: (adjusted for age, NYHA class III/IV and previous AMI)	HR 0.59 (0.56-0.63)	Healthcare quality improvement Partnership	Multivariate adjustment a bit limited.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
	in England and Health Boards in Wales		Inclusion criteria: A primary diagnosis of heart failure on discharge designated by any of the following ICD-10 descriptions – hypertensive heart disease with (congestive) heart failure; ischaemic cardiomyopathy; cardiomyopathy unspecified; congestive heart failure; left ventricular failure; heart failure unspecified Exclusions: It states that '….patients admitted for elective procedures ought not to be included.'				3 year mortality: (adjusted for age, NYHA class III/IV and previous AMI;)	HR 0.63 (0.61-0.66)		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
			54.1% of men were treated on cardiology wards, compared with 39.5% of women. Women were more likely to be treated on general medical wards (47.9% vs. 36.0%) and other wards (12.4% vs. 9.5%). The likelihood of being treated on a cardiology ward decreased with age: 76.3% of patients who were 16-44 were treated on cardiology wards, compared with 47.1 of patients in the 74-84 age group, and 32.1% of patients over 84 years of age.							

1

Study	Ezekowitz 2008[48]

Study type	Other non-randomised study (randomised; Parallel)
Funding	Academic or government funding
Number of studies (number of participants)	1 (N=2,924)
Countries and setting	Conducted in Canada; Setting: Secondary care
Line of therapy	Unclear
Duration of study	Not clear: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis - ICD codes on hospital discharge abstracts
Stratum	Overall
Subgroup analysis within study	Not stratified but pre-specified: Analysed by ejection fraction >50% or <50%
Inclusion criteria	Newly admitted patients with primary discharge diagnosis of HF for the first time; met Framingham Study HF criteria
Exclusion criteria	Transferred from another acute care facility; non-residents on Province of Ontario; invalid health care number; HF as complication/secondary diagnosis; died during admission; no LV assessment; medication at discharge not recorded; transferred to another hospital; date inconsistency
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): EF>50%: 75.61 (11.48); EF <50%: 72.4 (11.86). Gender (M:F): 1523:1401. Ethnicity: Not stated
Further population details	1. Acute decompensated heart failure: 2. Acute heart failure with pulmonary oedema: 3. Acute right-sided heart failure: 4. Cardiogenic shock:
Interventions	Intervention 1: Commencing Beta blockers early. Commencing any ACE inhibitors in hospital. ACE inhibitors at discharge no further details. Duration Not stated. Concurrent medication/care: Patients could also be on one or more of: ACE inhibitors, ARB, statins, spironolactone, warfarin, aspirin, digoxin, calcium channel blocker (N=691) Further details: Comments: 212 with EF >50% and 479 with EF <50% Intervention 2: Commencing Beta blockers after discharge Any beta blockers after discharge. No beta-blockers at discharge, no further details. Duration Not stated. Concurrent medication/care: Patients could also be on one or more of: ACE inhibitors, ARB, statins, spironolactone, warfarin, aspirin, digoxin, calcium channel blocker(N=2233) Further details: Comments: 814 with EF >50% and 1419 with EF <50%

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Study (subsidiary papers)	**Mujib 2013[112] (O'connor 2008[123])**
Study type	Other non-randomised study (Patient randomised; Parallel)
Funding	Academic or government funding (Supported by a grant from the Heart, Lung and Blood Institute/National Institutes of Health.)
Number of studies (number of participants)	(N=1,706 (patients who received ACE inhibitors) This study also evaluated patients who did not receive ACE inhibitors.
Countries and setting	Conducted in USA; Setting: Organized Program to Initiate Lifesaving Treatment in Hospitalizes Patients with Heart Failure (OPTIMIZE-HF)
Line of therapy	1st line
Duration of study	Follow up (post intervention): mean 2.4 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis ~ ICD-9
Stratum	Overall: Older adults with heart failure and preserved ejection fraction (=>40%)
Subgroup analysis within study	Not stratified but pre-specified: Subgroup analyses were conducted by age, sex, ethnic background, heart failure history, hypertension, diabetes mellitus, coronary artery disease, GFR, and left ventricular EF
Inclusion criteria	Adults with heart failure and preserved ejection fraction (=>40%) who received a new discharge prescription for ACE inhibitors.
Exclusion criteria	Not reported for patient characteristics.
Recruitment/selection of patients	Charts from 48,612 hospitalisations due to heart failure occurring in 259 hospitals from 48 states between March 2003 and December 2004 were analysed.
Age, gender and ethnicity	Age - Mean (SD): 81(8) years. Gender (M:F): 36% men/64% women. Ethnicity: 10% African American
Further population details	1. Acute decompensated heart failure: Not applicable / Not stated / Unclear 2. Acute heart failure with pulmonary oedema: Not applicable / Not stated / Unclear 3. Acute right-sided heart failure: Not applicable / Not stated / Unclear 4. Cardiogenic shock: Not applicable / Not stated / Unclear
Interventions	Intervention 1: Commencing ACE inhibitors in hospital or at discharge ~ Any ACE inhibitors in hospital / at discharge. ACE inhibitors received at hospital discharge. Duration Median 2.4 years. Concurrent medication/care: A full list of

	admission medication, in-hospital treatment/procedure, and discharge medication was presented (N=1,706) Further details: Intervention 2: Commencing ACE inhibitors after discharge ~ Any ACE inhibitors after hospital discharge. ACE inhibitor after discharge. Duration Median 2.4 years. Concurrent medication/care: A full list of admission medication, in-hospital treatment/procedure, and discharge medication was presented (N=1,706) Further details:

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G.3.3 MRA

Study (subsidiary papers)	**Adamopoulos 2009[3]**
Study type	RCT (Patient randomised; Parallel)
Funding	Study funded by industry (Pfizer, Inc.)
Number of studies (number of participants)	(N=6,632 (3,319 taking eplerenone))
Countries and setting	Conducted in France, Greece, USA; Setting: EPHESUS trial
Line of therapy	1st line
Duration of study	Follow-up (post-intervention): mean 16 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis ~ see below
Stratum	Overall: Patients with acute myocardial infarction (AMI) complicated by left ventricular systolic dysfunction and heart failure
Subgroup analysis within study	Post-hoc subgroup analysis: Eplerenone >7 days vs. ≤ 7 days after AMI
Inclusion criteria	Acute Myocardial infarction complicated by clinical heart failure and left ventricular ejection fraction ≤40%.
Exclusion criteria	(1) patients with HF of primary valvular or congenital etiology; (2) patients who have current evidence of clinical instability (arrhythmias other than atrial fibrillation, cardiogenic shock etc.); (3) patients who have PTCR during screening must be clinically stable for ra minimum of 24 hrs following the procedure and before randomisation; (4) patients who have CABG during the screening period must be clinically stable for a minimum of 72 hours following the procedure and

	before randomisation; (5) patients who have an implanted cardiac defibrillator (ICD); (6) patients who have uncontrolled hypotension (SBP < 90 mmHg); (7) patients requiring the use of potassium-sparing diuretics or spirolactone; (8) patients who have a serum creatinine level > 2.5 mg/dL during the screening period; (9) patients who have a serum potassium level > 5.0 mEq/L during the screening period; (10) patients who have a planned cardiac transplantation; (11); patients who have current evidence of alcohol or drug abuse problems which in the opinion of the investigator precludes study participation; (12) patients who hav any condition which in the opinion of the investigator makes participation in this study not in the best interest of the patient; (13) patients who have known hypersensitivity to eplerenone or spironolactone; (14) patient who have a severe organic disorder or have had surgery or disease of the gastrointestinal tract which in the opinion of the investigator may interfere with the absorption, pharmacokinetics, or elimination of the study medication; (15) patients who have chronic psychoses or behavioural conditons which in the opinion of the investigator would limit the ability of the patient to comply with the requirements fo the study; (16) patients who have a comorbid condition that would be expected to result in death during the next three years (e.g. terminal cancer, AIDS, etc) including patients receiving immunosuppressive or antieoplsatic therapy; (17) patients who have received any investigational medication or investigational device within 30 days prior to the first dose of the study medication, or is actively participating in any investigational drug or device study, or is schedulted to receive an investigational drug other than eplerenone or be treated with an investigational device during the course of this study; (18) patients who have been previously admitted to the study.
Recruitment/selection of patients	Patients were randomised during a 12-day period (3-14) days after AMI
Age, gender and ethnicity	Age - Mean (SD): 64 (11) years. Gender (M:F): Define. Ethnicity: 90% Caucasian; 1% 'Black'; 9% 'other'
Extra comments	Subgroup analysis of RCT
Interventions	Intervention 1: Commencing MRAs (aldosterone antagonists) in hospital or at discharge ~ Any MRAs (aldosterone antagonists) in hospital / at discharge. Eplerenone <7 days after AMI; eplerenone 25 mg/day (titrated to 50 mg/day after 4 weeks). Duration mean 16 months. Concurrent medication/care: Patients were receiving background therapy with ACE inhibitors/ARBs (86%), beta-blockers (75%), diuretics (60%), and coronary reperfusion therapy. (N=1,369) Further details: Intervention 2: Commencing MRAs (aldosterone antagonists) after discharge ~ Any MRAs (aldosterone antagonists) after hospital discharge. Eplerenone =>7 days after the AMI; eplerenone 25 mg/day (titrated to 50 mg/day after 4 weeks). Duration mean 16 months. Concurrent medication/care: Patients were receiving background therapy with ACE inhibitors/ARBs (86%), beta-blockers (75%), diuretics (60%), and coronary reperfusion therapy. (N=1,950) Further details:

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Study	Ezekowitz 2008[48]
Study type	Other non-randomised study (randomised; Parallel)
Funding	Academic or government funding
Number of studies (number of participants)	1 (N=2,924)
Countries and setting	Conducted in Canada; Setting: Secondary care
Line of therapy	Unclear
Duration of study	Not clear: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis ICD codes on hospital discharge abstracts
Stratum	Overall
Subgroup analysis within study	Not stratified but pre-specified: Analysed by ejection fraction >50% or <50%
Inclusion criteria	Newly admitted patients with primary discharge diagnosis of HF for the first time; met Framingham Study HF criteria
Exclusion criteria	Transferred from another acute care facility; non-residents on province of Ontario; invalid health care number; HF as complication/secondary diagnosis; died during admission; no LV assessment; medication at discharge not recorded; transferred to another hospital; date inconsistency
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): EF>50%: 75.61 (11.48); EF <50%: 72.4 (11.86). Gender (M:F): 1523:1401. Ethnicity: Not stated
Interventions	Intervention 1: Commencing MRAs at discharge no further details. Duration Not stated. Concurrent medication/care: Patients could also be on one or more of: ACE inhibitors, ARB, statins, spironolactone, warfarin, aspirin, digoxin, calcium channel blocker (N=691) Further details: Comments: 212 with EF >50% and 479 with EF <50% Intervention 2: No MRAs at discharge, no further details. Duration Not stated. Concurrent medication/care: Patients could also be on one or more of: ACE inhibitors, ARB, statins, spironolactone, warfarin, aspirin, digoxin, calcium channel blocker(N=2,233) Further details: Comments: 814 with EF >50% and 1419 with EF <50%

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Study	Ahmed 2011[7] as part of OPTIMIZE-HF (US national hospital based registry) conference abstract
Study type	Other non-randomised study
Funding	Funding not stated
Number of studies (number of participants)	1 (N=10,429)
Countries and setting	Conducted in USA; Setting: Secondary care
Line of therapy	Unclear
Duration of study	6 years
Method of assessment of guideline condition	Unclear method of assessment/diagnosis Not stated
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients hospitalised with acute heart failure linked with Medicare outcomes data
Exclusion criteria	Left ventricular ejection fraction <45%
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 78 (11). Gender (M:F): 2367:4397. Ethnicity: Not stated
Interventions	Intervention 1: Commencing MRAs early. On MRAs at discharge, no further details. Duration Not stated. Concurrent medication/care: Not stated (N=864) Further details: Intervention 2: Commencing MRAs after discharge. Patients not receiving MRAs at discharge. Duration Not stated. Concurrent medication/care: Not stated(N=864) Further details:

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G.4 Surgical and percutaneous interventions

G.4.1 Aortic stenosis

Study (subsidiary papers)	Leon 2010[91] (Hancock-howard 2013[70], Leon 2010[90], Makkar 2012[100], Reynolds 2011[146])
Study type	RCT (Patient randomised; Parallel)
Funding	Equipment / drugs provided by industry (Edwards Lifesciences)
Number of studies (number of participants)	multicentre (N=358)
Countries and setting	Conducted in Canada, Germany, USA; Setting: 22 centres in the United States, 2 centres in Canada and 1 centre in Germany (do not specify if secondary care centres or other level)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Inclusion criteria	1. Senile degenerative aortic valve stenosis with echocardiography derived criteria: mean gradient >4.0 m/s or an aortic valve area (AVA) of < 0.8 cm2 (or AVA index< 0.5 cm2/m2).2. Symptomatic due to aortic valve stenosis as demonstrated by NYHA Functional Class ≥ II. 3. The subject or the subject's legal representative was informed of the nature of the study, agreed to its provisions and provided written informed consent as approved by the Institutional Review Board of the respective clinical site. 4. The subject and the treating physician agreed that the subject would return for all required postprocedure follow-up visits. 5. The subject, after formal consults by a cardiologist and two cardiovascular surgeons agreed that medical factors precluding operation, based on a conclusion that the probability of death or serious, irreversible morbidity exceeded the probability of meaningful improvement. Specifically, the probability of death or serious, irreversible morbidity exceeded 50%. The surgeons' consult notes should specify medical or anatomic factors leading to that conclusion and included should be a printout of the STS score calculation to further identify the risks in these patients.
Exclusion criteria	1. Evidence of an acute myocardial infarction ≤ 1 month before the intended treatment (defined as Q wave MI, or non-Q wave MI with total CK elevation ≥ twice normal in the presence of CK-MB elevation and/or troponin level elevation (WHO definition) 2. Aortic valve was a congenital unicuspid or congenital bicuspid valve, or was non-calcified 3. Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation >3+) 4. Any therapeutic invasive cardiac procedure performed within 30 days of the index procedure, (or 6 months if the procedure was a drug eluting coronary stent implantation) 5. Pre-existing prosthetic heart valve in any position, prosthetic ring, severe mitral annular calcification, or severe (greater than 3+) mitral regurgitation 6. Blood dyscrasias as defined: leukopenia (WBC < 3000 mm3), acute anaemia (Hb < 9 mg%),thrombocytopenia (platelet count < 50,000 cells/mm^3), history of bleeding diathesis or coagulopathy 7. Untreated clinically significant coronary artery disease requiring revascularization 8. Hemodynamic instability requiring inotropic therapy or mechanical hemodynamic support devices 9. Need for emergency

Study (subsidiary papers)	Leon 2010[91] (Hancock-howard 2013[70], Leon 2010[90], Makkar 2012[100], Reynolds 2011[146])
	surgery for any reason 10. Hypertrophic cardiomyopathy with or without obstruction 11. Severe ventricular dysfunction with LVEF < 20%.12. Echocardiographic evidence of intracardiac mass, thrombus or vegetation 13. Active peptic ulcer or upper gastro-intestinal bleeding within the prior 3 months 14. A known hypersensitivity or contraindication to aspirin, heparin, ticlopidine (Ticlid), or clopidogrel(Plavix), or sensitivity to contrast media, which cannot be adequately pre-medicated 15. Native aortic annulus size < 18mm or > 25mm as measured by echocardiogram 16. Recent (within 6 months) cerebrovascular accident or transient ischemic attack 17. Renal insufficiency (creatinine > 3.0mg/dL) and/or end stage renal disease requiring chronic dialysis 18. Life expectancy < 12 months due to non-cardiac co-morbid conditions19. Significant abdominal or thoracic aorta disease, including aneurysm (defined as maximal luminal diameter 5cm or greater), marked tortuosity (hyperacute bend), aortic arch atheroma (especially if thick [> 5 mm], protruding or ulcerated), narrowing of the abdominal aorta (especially with calcification and surface irregularities), or severe "unfolding" and tortuosity of the thoracic aorta 20. Iliofemoral vessel characteristics that would preclude safe placement of 22F or 24F introducer sheath such as severe calcification, severe tortuosity or vessels size diameter < 7 mm for 22F sheath or < 8mm for 24F sheath 21. Currently participating in an investigational drug or another device study 22. Active bacterial endocarditis or other active infections 23. Bulky calcified aortic valve leaflets in close proximity to coronary ostia 24. Patient has been offered surgery but has refused surgery.
Age, gender and ethnicity	Age - Mean (SD): Percutaneous 83.1 (8.6) Standard medical 83.2 (8.3). Gender (M:F): 166:192. Ethnicity:
Interventions	Intervention 1: Percutaneous treatment Patients who were assigned to the transcatheter group underwent either transfemoral placement of the aortic valve on the basis of whether peripheral arteries could accomodate the large French sheats required (22 french for the 23-mm valve and 24 French for the 260mm valve).. Duration Not applicable. Concurrent medication/care: Not stated(N=179) Intervention 2: Standard medical care (N=179)

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Study (subsidiary papers)	Nielsen 2012[121]
Study type	RCT (Patient randomised; Parallel)
Funding	Other
Number of studies (number of participants)	1 (N=70)
Countries and setting	Conducted in Denmark; Setting: 2 hospitals (centres): Departments of cardiothoracic/thoracic surgery and cardiology at Aarhus University and Odense University Hospitals
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	Overall

Study (subsidiary papers)	Nielsen 2012[121]
Subgroup analysis within study	Not applicable
Inclusion criteria	Significant valvular aortic stenosis (defined as valve area < 1 cm2), age initially equal or >70, later equal or >75 years, condition accessible by surgical aortic valve replacement (SAVR) and transapical transcatheter aortic valve implantation (a-TAVI), expected survival >1 year following successful treatment, patient accceptance of participation in the study and in the scheduled follow-up investigations.
Exclusion criteria	Coronary artery disease requiring percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), previous myocardial infarction and PCI within 12 months, previous heart surgery, need of other heart surgery (i.e., mitral or tricuspid valve surgery), emergency surgery (within 24 hours of indication for surgery), unstable cardiac condition (requiring an assist device, inotropes or i.v. nitrates in operating room), ongoing infection requiring antibiotics, stroke within one month, reduced pulmonary function (FEV1 <11 or < 40% of expected), renal failure requiring haemodialysis, allergy to acetylsalicylic acid, clopidogrel, prasugrel or x-ray contrast material
Age, gender and ethnicity	Age - Mean (SD): . Gender (M:F): 21:49. Ethnicity: None reported
Further population details	1. Cardiogenic shock: Not stated
Interventions	Intervention 1: Surgical treatment ~ Any type of surgery for aortic stenosis. Surgical aortic valve replacement (SAVR). Duration --. Concurrent medication/care: --(N=36) Further details: Intervention 2: Percutaneous treatment ~ any type of percutaneous. Transapical transcatheter aortic valve implantation (a-TAVI). Duration --. Concurrent medication/care: --(N=34) Further details:

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Study (subsidiary papers)	Smith 2011[163] (Elmariah 2012[46], Kodali 2012[86], Miller 2012[106], Reynolds 2012[145], Reynolds 2012[147])
Study type	RCT (Patient randomised; Parallel)
Funding	Study funded by industry (Edwards Lifesciences (sponsor))
Number of studies (number of participants)	1 (N=699)
Countries and setting	Conducted in Canada, Germany, USA; Setting: 22 centres in the United States, 2 centres in Canada and 1 centre in Germany (do not specify if secondary care centres or other level)
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): median 1.4 ans maximum 3.3 years

Study (subsidiary papers)	Smith 2011[163] (Elmariah 2012[46], Kodali 2012[86], Miller 2012[106], Reynolds 2012[145], Reynolds 2012[147])
Method of assessment of guideline condition	Method of assessment /diagnosis not stated ~
Stratum	Overall:
Subgroup analysis within study	Stratified then randomised: Transfemoral-placement and transapical-placement
Inclusion criteria	1. Patients must have co-morbidities such that the surgeon and cardiologist Co-PIs concur that the predicted risk of operative mortality is ≥15% and/or a minimum STS score of 10. A candidate who does not meet the STS score criteria of ≥ 10 can be included in the study if a peer review by at least two surgeon investigators (not including the enrolling surgeon) concludes and documents that the patient's predicted risk of operative mortality is ≥15%. The surgeon's assessment of operative 2. Senile degenerative aortic valve stenosis with echocardiography derived criteria: mean gradient >4.0 m/s or an aortic valve area (AVA) of < 0.8 cm2 (or AVA index< 0.5 cm2/m2).3. Symptomatic due to aortic valve stenosis as demonstrated by NYHA Functional Class ≥ II. 4. The subject or the subject's legal representative was informed of the nature of the study, agreed to its provisions and provided written informed consent as approved by the Institutional Review Board of the respective clinical site. 5. The subject and the treating physician agreed that the subject would return for all required postprocedure follow-up visits.
Exclusion criteria	1. Evidence of an acute myocardial infarction ≤ 1 month before the intended treatment (defined as Q wave MI, or non-Q wave MI with total CK elevation ≥ twice normal in the presence of CK-MB elevation and/or troponin level elevation (WHO definition) 2. Aortic valve was a congenital unicuspid or congenital bicuspid valve, or was non-calcified 3. Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation >3+) 4. Any therapeutic invasive cardiac procedure performed within 30 days of the index procedure, (or 6 months if the procedure was a drug eluting coronary stent implantation) 5. Pre-existing prosthetic heart valve in any position, prosthetic ring, severe mitral annular calcification,or severe (greater than 3+) mitral regurgitation 6. Blood dyscrasias as defined: leukopenia (WBC < 3000 mm3), acute anemia (Hb < 9 mg%),thrombocytopenia (platelet count < 50,000 cells/mm^3), history of bleeding diathesis or coagulopathy 7. Untreated clinically significant coronary artery disease requiring revascularization 8. Hemodynamic instability requiring inotropic therapy or mechanical hemodynamic support devices 9. Need for emergency surgery for any reason 10. Hypertrophic cardiomyopathy with or without obstruction 11. Severe ventricular dysfunction with LVEF < 20%.12. Echocardiographic evidence of intracardiac mass, thrombus or vegetation 13. Active peptic ulcer or upper gastro-intestinal bleeding within the prior 3 months 14. A known hypersensitivity or contraindication to aspirin, heparin, ticlopidine (Ticlid), or clopidogrel(Plavix), or sensitivity to contrast media, which cannot be adequately pre-medicated 15. Native aortic annulus size < 18mm or > 25mm as measured by echocardiogram 16. Recent (within 6 months) cerebrovascular accident or transient ischemic attack 17. Renal insufficiency (creatinine > 3.0mg/dL) and/or end stage renal disease requiring chronic dialysis 18. Life expectancy < 12 months due to non-cardiac co-morbid conditions19. Significant abdominal or thoracic aorta disease, including aneurysm (defined as maximal luminal diameter 5cm or greater), marked tortuosity (hyperacute bend), aortic arch atheroma (especially if thick [> 5 mm], protruding or ulcerated), narrowing of the abdominal aorta (especially with calcification and surface irregularities), or severe

Study (subsidiary papers)	Smith 2011[163] (Elmariah 2012[46], Kodali 2012[86], Miller 2012[106], Reynolds 2012[145], Reynolds 2012[147])
	"unfolding" and tortuosity of the thoracic aorta 20. Iliofemoral vessel characteristics that would preclude safe placement of 22F or 24F introducer sheath such as severe calcification, severe tortuosity or vessels size diameter < 7 mm for 22F sheath or < 8mm for 24F sheath 21. Currently participating in an investigational drug or another device study 22. Active bacterial endocarditis or other active infections 23. Bulky calcified aortic valve leaflets in close proximity to coronary ostia 24. Patient has been offered surgery but has refused surgery.
Recruitment/selection of patients	Patients were enrolled from May, 11 2007 through August 28, 2009. All the patients were considered to be candidates for conventional surgical aortic-valve repair (no information stated on recruitment if consecutive patients or not)
Age, gender and ethnicity	Age - Mean (SD): Percutaneous 83.6 (6.8) Surgery 84.5 (6.4). Gender (M:F): 399/300. Ethnicity: None reported
Further population details	1. Cardiogenic shock: Not stated
Interventions	Intervention 1: Surgical treatment ~ Any type of surgery for aortic stenosis. Surgical aortic-valve replacement. Duration Not applicable. Concurrent medication/care: Patients in two cohorts (transfemoral-placement and transapical-placement) were randomised to either surgical aourtic-valve replacement or transcatheter aortic-valve replacement (N=351) Further details: Intervention 2: Percutaneous treatment ~ any type of percutaneous. Patients who were assigned to the transcatheter group underwent either transfemoral or transapical placement of the aortic valve on the basis of whether peripheral arteries could accommodate the large French sheats required (22 French for the 23-mm valve and 24 French for the 260mm valve).. Duration Not applicable. Concurrent medication/care: Not stated(N=348) Further details:

G.4.2 Mitral regurgitation

Table 7: Evidence extraction table

Study	Feldman et al., 2011[52]
Study type	RCT (Patient randomised; Parallel)
Funding	Equipment / drugs provided by industry (Abbott Vascular (MitraClip device)
Number of studies (number of participants)	Multicentre (N=279)

Countries and setting	USA
Line of therapy	Not applicable
Duration of study	Intervention + follow-up: 30 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis - Assessed via a detailed protocol
Inclusion criteria	Moderate to severe (3+) or severe (4+) chronic mitral valve regurgitation as defined by a minimum of 3 of the following criteria: (1) colour flow jet may be central and large (> 6 cm2 or > 30% of LA area) or smaller if eccentric, encircling the left atrium (2) pulmonary vein flow may show systolic blunting or systolic flow reversal (3) vena contracta width >= 0.5 cm measured in the prasternal long axis view (4) regurgitant volume of >= 45ml/beat (5) regurgitant fraction >= 40% (6) regurgitant orifice area >= 0.30 cm2- and: Symptomatic with > 25% LVEF and LVESD ≤ 55mm or, Asymptomatic with one or more of the following: i. LVEF 25% to 60%; ii. LVESD ≥ 40 mm; iii. New onset of atrial fibrillation; iv. Pulmonary hypertension defined as pulmonary artery systolic pressure (PASP) >50mmHg at rest or >60mmHg with exercise. Candidate for mitral valve repair or replacement surgery, including cardiopulmonary bypass. The primary regurgitant jet originates from malcoaptation of the A2 and P2 scallops of the mitral valve. If a secondary jet exists, it must be considered clinically insignificant. Trans-septal catheterisation is determined to be feasible by the treating physician.
Exclusion criteria	Any of: (1) Evidence of an acute myocardial infarction in the prior 12 weeks of the intended treatment (defined as: Q wave or non-Q wave infarction having CK enzymes >= "X the upper laboratory normal limit with the presence of a CK-MB elevated above the institution's upper limit of normal. (2) The need for any other cardiac surgery including surgery for coronary artery disease, atrial fibrillation, pulmonic, aortic or trcuspi9d valve disease. (3) any endovascular therapeutic interventional or surgical procedure performed within 30 days prior to the index procedure. (4) In the judgement of the investigator, the femoral vein cannot accommodate a 24 F catheter or the presence of an inferior vena cave (IVC) filter would interfere with advancement of the catheter or ipsilateral DVT is present. (5) Severe left ventricular dysfunction, defined as an ejection fraction <= 25% and/or end-systolic dimension > 55 mm as defined by (a) left ventricular ejection fraction (biplane theod of disks) and (b) left ventricular end systolic dimension (LVIDs) (m-mode or 2 dimensional derived) (6) Mitral valve orifice area <4.0 cm2 as defined by planimetered mitral valve orifice area (MVA) (prasternal short axis (PSAX) at tips of MV just above papillary muscles). (7) If leaflet flail is present - flail width: the width of the flail segment is greater than or equal to 15 mm, as defined by the width of the leaflet segment that moves in and out of plane during systole in the short axis (SAX) view or flail gap: the flail gap is greater than or equal to 10 mm, as defined by the greatest distance between the ventricular side of the flail segment to the atrial side of the opposing leaflet. This distance is measured perpendicular to the plane of the annulus in tow views and the largest measurement is used. The two views for measurement are the four-chamber long axis (LAX) view and the left ventricular outflow tract (LVOT) view. (8) If leaflet tethering is present - coaptation depth: the mitral valve coaptation depth is more than 11 mm, as defined as the distance from the plane of the mitral valve annulus to the first point of leaflet coaptation in the atrial-to-ventricular direction in the four-chamber view or, coaptation length: the vertical coaption length is less than 2 mm, as defined as

	the vertical length of leaflets that is in contact or is available for contact, during systole in the atrical-to-ventricular direction in the four-chamber view. (9) severe mitral annular calcification. (10) Leaflet anatomy which may preclude clip implantation, proper clip positioning on the leaflets or sufficient reduction in MR. This may include evidence of calcification in the grasping area of the A2 and/or P2 scallops; presence of a significant cleft of A2 or P2 scallops; more than one anatomic criteria dimensional near the exclusion limits; bileaflet flail or severe bileaflet prolapse; lack of both primary and secondary chordal support (11) Hemodynamic instability as defined as systolic pressure < 90 mmHg without afterload reduction or cardiogenic shock or the need for inotropic support or intra-aortic balloon pump (12) Need for emergency surgery for any reason (13) prior mitral valve surgery or valvuloplasty or any currently implanted mechanical prosthetic valve or currently implanted VAD. (14) systolic anterior motion of the mitral valve leaflet (15) hypertrophic cardiomyopathy (16) echocardiographic evidence of intracardiac mass, thrombus or vegetation (17) history of, or active endocarditis (18) history of, or active, rheumatic heart disease (19) history of ASD, whether repaired or not (20) history of PFO associated with clinical symptoms (e.g. cerebral ischemia) or previously repaired or when, in the judgment of the investigator, an atrial septal aneurysm is present that may interfere with transseptal crossing (21) history of a stroke or documented TIA within the prior 6 months. (22) upper GI bleeding within the prior 6 months (23) history of bleeding diathesis or coagulopathy or subject will refuse blood transfusions. (24) concurrent medical condition with a life expectancy of less than 12 months (defined in a separate section) (25) A platelet count <75,000 cells/mm3 (26) renal insufficiency (creatinine >2.5 mg/dL) (27) active infections requiring current antibiotic therapy (if temporary illness patients may enrol 2 weeks after discontinuation of antibiotics). Patients must be free from infection prior to treatment. Any required dental work should be completed a minimum of 3 wks prior to treatment. (28) Intravenous drug abuse or suspected inability to adhere to follow-up. (29) Patients in whom transoesophageal echocardiography (TEE) is contraindicated. (30) a known hypersensitivity or contraindication to study or procedure mediations which cannot be adequately managed medically (31) in the judgment of the investigator, patients in whom the presence of a permanent pacemaker or pacing leads would interfere with placement of the test device or the placement of the test device would disrupt the leads (32) Currently participating in an investigational drug or another device study that has not completed the primary endpoint or that clinically interferes with the current study endpoints [Note: trials requiring extended follow-up for products that were investigational but have since become commercially available are not considered investigational trials].
Age, gender and ethnicity	Age - Mean (SD): Percutaneous group 67 (13) Surgery 66 (13) Percentage of participants > 75 yrs n(%) Percutaneous 55 (30) surgery 26 (27). Gender (M:F): 178/101. Ethnicity:
Extra comments	Cause of mitral regurgitation: Functional - Percutaneous 49 (27) Surgery 26 (27); Degenerative (a) With anterior or bileaflet flail or prolapse - Percutaneous 58 (32) Surgery 25 (26) (b) With posterior flail or prolapse - Percutaneous 72 (39) Surgery 42 (44) (c) With no flail and no prolapse - Percutaneous 5 (3) Surgery 2 (2)
Interventions	Intervention 1: Surgical treatment ~ Any type of surgery for aortic stenosis. Mitral valve surgery. Duration n/a. Concurrent medication/care: Standard medical therapy (N=95)

	Further details: Intervention 2: Percutaneous treatment ~ any type of percutaneous. Performed under general anaesthesia with the use of fluoroscopic and transoesophageal echocardiographic guidance. Atrial transseptal puncture is performed. The device is steered until it is aligned over the origin of the regurgitant jet and advanced into the left ventricle. The mitral leaflets are grasped and the device is closed to approximate the leaflets. Adequate reduction of mitral regurgitation to a grade of 2+ or less is assessed with the use of echocardiography. If the reduction is inadequate with one device the device may be removed or a second device placed. Duration n/a. Concurrent medication/care: Patients were treated with heparin during the procedure with aspirin (at a dose of 325 mg daily) for 6 mths and with clopidogrel (at a dose of 75 mg daily) for 30 days after the procedure.(N=184) Further details:

G.5 Mechanical assist devices

Study	**Unverzagt 2011[175] (Ohman 2005[127], Thiele 2005[171], Seyfarth 2008[157], Burkhoff 2006[25], Prondzinsky 2010[139], Arias 2005[9]) – Cochrane systematic review**
Study type	Systematic review
Number of studies (number of participants)	6 studies (n=190)
Countries and setting	Conducted in Germany, USA; Setting: Not specified
Duration of study	Intervention + Follow-up: Various
Method of assessment of guideline condition	Systematic review: Adequately assessed but condition restricted to patients with myocardial infarction complicated by cardiogenic shock
Stratum	Overall
Subgroup analysis within study	Age < 75 or ≥ 75 years; sex
Inclusion criteria	Randomised controlled trials with adult patients with myocardial infarction complicated by cardiogenic shock
Exclusion criteria	Any publications irrelevant to the criteria specified in the study. Although cross-sectional studies were set to be included observational trials were set to be excluded.

Recruitment/selection of patients	Mixed
Age, gender and ethnicity	Age - --: N/A. Gender (M:F): N/A.
Further population details	1. Cardiogenic shock: Systematic review
Indirectness of population	No indirectness
Interventions	(n=131) Intervention 1: IABP - IABP any. Any IABP. Duration N/A. Concurrent medication/care: Standard medical care (n=58) Intervention 2: Best medical care - Optimal standard therapy. Guideline compliant therapies. Duration N/A. Concurrent medication/care: Best medical care (n=53) Intervention 3: LVADs - Any suitable device. Assist devices. Duration N/A. Concurrent medication/care: Standard medical care
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-AORTIC BALLOON PUMP COUNTERPULSATION versus OPTIMAL STANDARD THERAPY

Protocol outcome 1: All-cause mortality
- Actual outcome: All-cause mortality at 30 days; HR 1.09 (95%CI 0.46 to 2.58) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome: All-cause mortality at 6 months; HR 1.05 (95%CI 0.4 to 2.76) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: All-cause mortality
- Actual outcome: In-hospital mortality at Before discharge; Group 1: 24/64, Group 2: 18/46; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Serious adverse events - cardiovascular
- Actual outcome: Serious adverse events - cardiovascular at Up to discharge; Group 1: 4/93, Group 2: 1/93; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: Serious adverse events - other
- Actual outcome: Serious adverse events - other at Up to discharge; Group 1: 0/50, Group 2: 0/52; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 5: Length of hospital stay
- Actual outcome: Length of hospital stay at Up to discharge; Group 1: mean 18.3 Days (SD 14.5); n=19, Group 2: mean 29.4 Days (SD 28.6); n=21; Risk of bias: Low; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-AORTIC BALLOON PUMP COUNTERPULSATION versus LVADS

Protocol outcome 1: All-cause mortality
- Actual outcome: All-cause mortality at 30 days; HR 1.02 (95%CI 0.62 to 1.74) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome: All-cause mortality at 6 months; HR 0.93 (95%CI 1.49 to 1.77) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: All-cause mortality
- Actual outcome: In-hospital mortality at Before discharge; Group 1: 15/33, Group 2: 16/34; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Serious adverse events - cardiovascular
- Actual outcome: Serious adverse events - cardiovascular at Up to discharge; Group 1: 3/113, Group 2: 13/121; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: Serious adverse events - other
- Actual outcome: Serious adverse events - other at Up to discharge; Group 1: 22/94, Group 2: 44/106; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 5: Length of stay
- Actual outcome: Length of hospital stay at Up to discharge; Risk of bias: Low; Indirectness of outcome: No indirectness

Study	**O'Rourke 1981[124]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=30)
Countries and setting	Conducted in New Zealand; Setting: Two hospitals
Duration of study	Intervention + Follow-up (before and after discharge of up to 36 months)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Inclusion criteria	1) Acute transmural infarction with either evolving Q waves or S-T segment elevation > 2mm in at least two leads. 2) Onset of typical symptoms of infarction < 12 hours before randomisation. 3) Unequivocal evidence of cardiac failure by clinical and radiologic criteria. 4) Absence of pre-existing cardiac failure or other life-threatening disease. 5) Age < 70 years. 6) Absence of contraindications to counterpulsation.
Exclusion criteria	1) Failure to notify investigators within the appointed time. 2) Unavailability of surgeons or balloon pump within the

	appointed time. 3) Reluctance of the attending physician to have a patient enter the trial.
Recruitment/selection of patients	At one of the hospitals, all patients were considered for the trial. At the second hospital, patients with cardiogenic shock or florid pulmonary oedema underwent counterpulsation electively, thus, patients entering the trial there usually had less severe heart failure than in the first hospital.
Age, gender and ethnicity	Age - Mean (range): IABP 60 (52-67) vs. medical care 54 (42-69). Gender (M:F): 24:6.
Further population details	
Indirectness of population	No indirectness
Interventions	(n=14) Intervention 1: IABP - IABP any. The balloon catheter was inserted through a side graft into the femoral artery. Avco catheters and consoles were used throughout. No patient underwent diagnostic angiography or cardiac surgery within the first month after infarction. . Duration Counterpulsation was continued electively for 3 to 11 days. The balloon catheter was removed when the patient's condition had been stable without evidence of heart failure for 48 hours. Concurrent medication/care: All patients received standard therapy. (n=16) Intervention 2: Best medical care - Optimal standard therapy. Most patients had pulmonary arterial cannulation. All patients received oxygen (2 to 6 L/min) by mask or nasal catheter. All were given furosemide (40 to 160 mg intravenously) as required for relief of cardiac failure, and heparin 20,000 to 30,000 IU/day by continuous infusion or by intermittent intravenous injections every 4 hours. Duration N/A. Concurrent medication/care: Standard therapy.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IABP ANY versus OPTIMAL STANDARD THERAPY Protocol outcome 1: All-cause mortality - Actual outcome: In-hospital mortality at Before discharge; Group 1: 7/14, Group 2: 7/16; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome: Late mortality at Up to 36 months post-infarction; Group 1: 1/14, Group 2: 3/16; Risk of bias: Low; Indirectness of outcome: Serious indirectness Protocol outcome 2: Serious adverse events - other - Actual outcome: Other serious adverse events at Before discharge; Group 1: 3/14, Group 2: 0/16; Risk of bias: Low; Indirectness of outcome: No indirectness	

1

Study	**Thiele 2012[173] (Thiele 2012A[170], Thiele 2013[172]) - IABP-SHOCK II trial**

Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=600)
Countries and setting	Conducted in Germany; Setting: Hospitals
Duration of study	Not clear
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Subgroup analysis within study	Sex; age (<50 yrs / 50 – 75 yrs / >75 yrs); +/- diabetes; +/- arterial hypertension; MI +/- ST-segment elevation; anterior/non-anterior MI; previous/no previous MI
Inclusion criteria	Presentation of an acute myocardial infarction complicated by cardiogenic shock and if early revascularisation was planned.
Exclusion criteria	1) Had undergone resuscitation for > 30 mins. 2) Had no intrinsic heart action. 3) Were in a coma with fixed dilation of pupils that was not induced by drugs. 4) Had a mechanical cause of cardiogenic shock. 5) Had onset of shock > 12 hours before screening. 6) Had a massive pulmonary embolism, severe peripheral arterial disease precluding insertion of an intra-aortic balloon pump, or aortic regurgitation greater than grade II in severity. 7) Older than 90 years of age. 8) Were in shock as a result of a condition other than acute myocardial infarction. 9) Had a severe concomitant disease associated with a life expectancy of < 6 months.
Recruitment/selection of patients	Patients of ≥ 18 to ≤ 90 years with the stated inclusion criteria (as described in the inclusion criteria above) were recruited at a number of centres. Since most patients would not be able to provide full informed consent before randomisation, an individualised informed consent process covering 4 different scenarios have been validated and approved by the central ethical committee of the study and also all local ethical committees. If the patient were not able to provide informed consent, 2 independent physicians assessed the assumed patient's will (if possible by additional contact of relatives). In patients with limited ability to provide consent, a short version, and in patients with full capacity to consent, a long version of the informed consent was to be used. If an initially impaired patient recovers, it was required to obtain the long version of informed consent retrospectively.[170]
Age, gender and ethnicity	Age - Median (IQR): IABP = 60.7 (43.4 - 86.6) vs. Control = 69 (58 - 76). Gender (M:F): M = 413; F = 187. Ethnicity: Not reported
Further population details	1. Cardiogenic shock
Indirectness of population	No indirectness

Interventions	(n=301) Intervention 1: IABP - IABP any. The IABP was inserted either before the percutaneous coronary intervention (PCI) or immediately after the PCI, with the timing of the insertion at the discretion of the investigator. Duration Median duration of IABP = 3.0 (IQR 2.0 to 4.0). Concurrent medication/care: All the patients were expected to undergo early revascularization and to receive the best available medical treatment according to guidelines. (n=299) Intervention 2: Best medical care - Optimal standard therapy. All patients were expected to undergo early revascularization and to receive the best available medical treatment according to guidelines. Intensive care treatment was standardized according to the German-Austrian S3 Guideline. Duration Unknown. Concurrent medication/care: N/A
Funding	Academic or government funding (German Research Foundation, German Heart Research Foundation, German Cardiac Society, Arbeitsgemeinschaft Leitende Kardiologische Krankenhausarzte, the University of Leipzig-Heart Center, Maquet Cardiopulmonary and Teleflex Medical)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IABP ANY versus OPTIMAL STANDARD THERAPY

Protocol outcome 1: All-cause mortality at 30 days
- Actual outcome: All-cause mortality at 30 days; HR 0.99 (95%CI 0.77 to 1.28) Calculated – from Cox proportional Hazard Ratio P-value; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: All-cause mortality at 6 months and 12 months
- Actual outcome: All-cause mortality at 12 months; Group 1: 155/299, Group 2: 152/296; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome: All-cause mortality at 6 months; Group 1: 146/299, Group 2: 146/296; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Cardiac mortality at 12 months
- Actual outcome: Cardiac mortality at 12 months; Group 1: 150/299, Group 2: 148/296; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: Serious adverse events - cardiovascular
- Actual outcome: Cardiovascular events before discharge; Group 1: 28/300, Group 2: 22/298; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome: Cardiovascular events at 12 months amongst 1-year survivors; Group 1: 16/144, Group 2: 7/144; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 5: Serious adverse events - other
- Actual outcome: Other serious adverse events before discharge; Group 1: 57/300, Group 2: 74/298; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 6: Health-related quality of life at 12 months

- Actual outcome: Health-related quality of life (EuroQol EQ-5D-3L) at 12 months; Results from the quality of life assessments were presented in graphical formats and raw figures were not available. However, the authors report that there were no significant differences between IABP or medical care recipients (survivors at 12 months) in terms of QoL outcomes in any of the dimensions (i.e. mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Risk of bias: ; Indirectness of outcome: Serious indirectness

Study (subsidiary papers)	**REMATCH trial: Rose 2001[148] (Rose 1999[149])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	N/A (n=129)
Countries and setting	Conducted in USA
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Enrolment was stopped, as pre-specified, after the 92nd death and the study has recorded 95 deaths at its final analysis. Patients were followed up for at least 30 months based on the data given.
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: The enrolment criteria are stated clearly and in detail, however, they allow inclusion of chronic heart failure patients as well as those with acute symptoms.
Stratum	Overall: 1) by centre and 2) by age groups: 18 to 59; 60 to 69; 70 yrs and over
Subgroup analysis within study	Not applicable
Inclusion criteria	Over the age of 18 and ineligible for cardiac transplantation. Initial entry criteria: i) presence of symptoms of NYHA class IV HF for ≥ 90 days despite attempted therapy with angiotensin-converting enzyme inhibitors, diuretics and digoxin; ii) LVEF ≤ 25%; and iii) Peak O2 consumption of ≤ 12 ml/kg/min or a continued need for intravenous inotropic therapy owing to symptomatic hypotension, decreasing renal function or worsening pulmonary congestion. Entry criteria were broadened 18 months after enrolment to also include patients with: i) symptoms of NYHA class IV HF for ≥ 60 days and had peak O2 consumption of ≤ 14 ml/kg/min; and ii) Symptoms of NYHA class III or IV HF for ≥ 28 days and received ≥ 14 days of support with IABP or with dependence of intravenous inotropic agents, with 2 failed weaning attempts.
Exclusion criteria	1) Cause of heart failure due to or associated with uncorrected thyroid disease, obstructive cardiomyopathy, pericardial disease, amyloidosis or active myocarditis. 2) Technical obstacles that pose an inordinately high surgical risk in the judgement of the certified surgeon. 3) International normalised ratio > 1.3 or prothrombin time > 15 secs within 24 hrs before randomisation. 4) Body surface area < 1.5 m^2. 5) BMI > 40. 6) Severe chronic obstructive pulmonary

	disease as evidenced by forced expiratory volume of 1.5l/min or more. 7) Pre-menopausal or pregnant. 8) Fixed pulmonary hypertension with pulmonary vascular resistance of 8 Wood units or more that is unresponsive to pharmacologic intervention, documented within 90 days before randomisation. 9) Patient under consideration for conventional revascularisation procedure, therapeutic valvular repair, left ventricular reduction procedure or cardiomyoplasty. 10) History of cardiac transplantation, left ventricular reduction procedure or cardiomyoplasty. 11) Presence of implanted mechanical aortic valve that will not be converted to bioprosthesis at time of LVAD implantation. 12) Evidence of intrinsic hepatic disease defined as liver enzyme values > 5 times the upper limit of normal within 4 days before randomisation or biopsy-proved liver cirrhosis. 13) Occurrence of stroke within 90 days before randomisation or history of cerebrovascular disease with major (>80%) extracranial or carotid stenosis documented by Doppler study. 14) Confirmation by neurologist of impairment of cognitive function, presence of Alzheimer's disease or any other form of irreversible dementia, or both. 15) Evidence of untreated abdominal aortic aneurysm 5 cm or larger as measured by abdominal ultrasound within 30 days before randomisation.
Recruitment/selection of patients	The eligibility of patients was determined by investigators at each site and confirmed by a gatekeeper at the co-ordinating centre.
Age, gender and ethnicity	Age - Mean (SD): . Gender (M:F): M:F = 103:26. Ethnicity: Not reported
Further population details	1. Cardiogenic shock:
Indirectness of population	Serious indirectness: The study population consists of a mixture of chronic and acute heart failure patients. Based on the description given, it is likely that a considerable proportion of the participants have chronic end-stage heart failure. The baseline characteristics do not allow identification of the number of participants with acute decompensated heart failure.
Interventions	(n=68) Intervention 1: LVADs - Any suitable device. Implantable first generation LVAD (TCI HeartMate VE LVAD). Duration Not stated. Concurrent medication/care: Optimal medical care (n=61) Intervention 2: Best medical care - Optimal standard therapy. Optimal standard therapy followed guidelines developed by the medical committee, with the goals of optimising organ perfusion and minimising symptoms of congestive heart failure. . Duration Not stated. Concurrent medication/care: N/A
Funding	Academic or government funding (Also by industry: Thoratec Corporation)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LVAD versus OPTIMAL STANDARD THERAPY	

Protocol outcome 1: All-cause mortality - Actual outcome: Deaths from all causes at Study period; Group 1: 41/68, Group 2: 54/61; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome: Survival at 2 years at 2 years; HR 0.7 (95%CI 0.47 to 1.06) Calculated – from logrank P-value; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Cardiac mortality - Actual outcome: Deaths attributable to cardiovascular events at Study period; Group 1: 16/68, Group 2: 53/61; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Serious adverse events (all) - Actual outcome: Incidence of serious adverse events (all) at Study period; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Quality of life - Actual outcome: Minnesota Living with Heart Failure Questionnaire Score at 1 year; Group 1: mean 41 N/A (SD 22); n=23, Group 2: mean 58 N/A (SD 21); n=6; MLHFQ total score 0 - 105 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome: SF-36 physical function at 1 year; Group 1: mean 46 N/A (SD 19); n=23, Group 2: mean 21 N/A (SD 21); n=6; SF-36 0 - 100 Top=High is good outcome; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome: SF-36 emotional role at 1 year; Group 1: mean 64 N/A (SD 45); n=23, Group 2: mean 17 N/A (SD 28); n=6; SF-36 0 - 100 Top=High is good outcome; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 5: Length of hospital stay (median days) - Actual outcome: Number of days spent in the hospital at Study period; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Admission to critical care units; re-admission rates; number of patients requiring invasive ventilation

G.6 Organisation of care

G.6.1 Specialist management units

Table 52: Evidence extraction for Auerbach et al, 2000[12]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes (OR>1 indicate outcome more frequent occuring among patient of cardiologists)	Source of funding	Comments
Auerbach et al, 2000[12]	Post-hoc analysis of a prospective multicenter cohort study (the Study to Understand Prognoses and	N=1298 (Patients of cardiologists N=743; Patients of generalists N=555)	Age mean (sd): CARD 63 (14) – GEN 71 (21) Male/Female: CARD 524/219 – GEN 289/266 Patients enrolled in the SUPPORT study who had a primary diagnosis of acute exacerbation of congestive heart failure and whose attending physicians were	Cardiologist management 42.5% stated that they would be providing care to their patient after discharge	Generalist management 41.5% stated that they would be providing care to their patient after discharge	Maximum follow-up was a median of 4.6 years	Transfer to intensive care unit	Adjusted OR 2.8 (1.6-4.9)	Robert Wood Johnson foundation	All multivariable models included adjustment for patient baseline differences and included also a propensity score modelas an additional covariate (which included factors such
							Discharge medication: ACE inhibitors Diuretics Beta-blocker	Adjusted OR: 1.15 (0.82-1.6); 0.85 (0.6-1.3); 1.0 (0.49-2.1)		
							Mortality	Adjuste		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes (OR>1 indicate outcome more frequent occuring among patient of cardiologists)	Source of funding	Comments
	Preferences for Outcomes and Risk of Treatments - SUPPORT study Conducted between		cardiologists or general internists. Inclusion criteria: patients admitted to hospital or who were transferred to the intensive care unit (ICU) with a primary diagnosis of an acute exacerbation of congestive heart failure and one of the following: (1) history of severe congestive heart				30 days 180 days 1 year Maximum follow-up (median 4.6 years)	d HR: 0.78 (0.48-1.28); 0.72 (0.54-0.96); 0.82 (0.65-1.04); 0.80 (0.66-0.96)		as life-extending care and preferences regarding resuscitation)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes (OR>1 indicate outcome more frequent occuring among patient of cardiologists)	Source of funding	Comments
	1989 and 1994 Conducted in the USA		failure at baseline (NYHA class III or IV) and medications – before admission that included two or more representatives from the diuretic, vasodilator, or ACE inhibitor drug classes; (2) history of NYHA class IV congestive heart failure, manifested by baseline dyspnea at test; systolic blood pressure of							

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes (OR>1 indicate outcome more frequent occuring among patient of cardiologists)	Source of funding	Comments
			100 mm Hg or less; or a history of hypotension precluding use of the medications listed above; or (3) chart documentation of congestive heart failure and left ventricular ejection fraction of 20% or less. Patients of cardiologists were younger, more likely to be male,							

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes (OR>1 indicate outcome more frequent occuring among patient of cardiologists)	Source of funding	Comments
			more likely to have private insurance, had fewer comorbid conditions, more likely to want life-extending care and cardiopulmonary resuscitation, and had a lower mean number of dependencies in activities of daily living (most other characteristics were also different across the group, but are							

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes (OR>1 indicate outcome more frequent occuring among patient of cardiologists)	Source of funding	Comments
			not all described in detail here)							

1

2 **Table 53: Evidence extraction for Boom et al, 2012[23]**

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Boom et al, 2012[23]	Post hoc analysis of a randomised controlled	N=7634 patients newly hospitalised for heart failure	HF patients treated by: Cardiologists – age mean (Sd) 73 (12); female % 44.9; Cardiovascular comorbidities/risk	Patients who were treated by a cardiologist	Patients treated by generalist with cardiology consult Patients treated by	1 year	Outcome 1 30 day mortality 1 year mortality	Cardiologists 30 day: 91/1523 (6%) year:	Heart and stroke foundation of Ontario, Clinician scientist award	Statistical methods were used to account for differences between groups but it

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
	study odds ratios adjusted age, sex, respiratory rate, systolic blood pressure, urea nitrogen, haemoglobin, serum sodium concentration, history of	Categorised into whether treated by a cardiologist (N=1523), by a generalist (including internists, family physicians/general practitioners, hospitalists, and internists with a non-cardiology subspecialty) with cardiology consult (N=1210) or by a generalist without cardiology consult (N=4901)	factors: % Angina 36.2; arrhythmia 4.7; atrial fibrillation 36.3; diabetes 38.8; hypertension 65.9; peripheral arterial disease 12.1; previous acute myocardial infarction 41.0; previous CABG 20.2; previous PCI 11.2 Do not resuscitate % 10.2 <u>Generalists with cardiology consult</u> – age mean (Sd) 76 (12); female % 51.3; Cardiovascular comorbitities/risk factors %: Angina 31.1; arrhythmia 3.1; atrial fibrillation 35.5; diabetes 38.4;		generalist without cardiology consult			135/1523 (23.2) Generalist with cardiology consult: 30 day: 102/1210 (8.4%) OR 0.70 (95% CI 0.42-1.18) 1 year: 374/1210 (30.9%) 1.03 (95% CI 0.83-1.28)	from CIHR and Ontario Ministry of Health and Long-term Care	was a bit difficult to decipher what the confounders were that were adjusted for.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
	cerebrovascular disease, dementia, chronic obstructive pulmonary disease, cirrhosis, and cancer. A sensitivity analysis was carried out using patients without a	Inclusion: All patients admitted to one of 81 acute care hospital corporations with a diagnosis of heart failure in the follow-up phase of the EFFECT study. Discharge Abstract Database Exclusion: Patients with a previous heart failure admission within the past 3 years and those with missing	hypertension 66.9; peripheral arterial disease 15.2; previous acute myocardial infarction 35.4; previous CABG 14.1; previous PCI 6.3 Do not resuscitate % 20.9 <u>Generalists without cardiology consult</u> – age mean (Sd) 78 (11); female % 53.2; Cardiovascular comorbidities/risk factors %: Angina 32.3; arrhythmia 2.5; atrial fibrillation 36.0; diabetes 17.9; hypertension 65.2; peripheral arterial disease 13; previous acute myocardial infarction 34.7;					Generalist with cardiology consult: 30 day: 564/4901 (11.5 %) 1.34 (95% CI 0.94-1.91) 1 year: 1676/4901 (34.2 %) 1.22 (95% CI 1.02-1.44)		
							Outcome 2 Readmission for heart	Rates not prese		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
	'do not resuscitate' order	clinical data that were required to calculate risk adjusted outcomes (N=616 or 7.5%)	previous CABG 12; previous PCI 4.7 Do not resuscitate % 23.7 In short patients of cardiologists were younger more frequently male were the least likely to have a do not resuscitate order. They were also more likely to have a cardiovascular related comorbidity including previous myocardial infarction, angina, arrhythmia and prior cardiac surgery.				failure	nted. Compared to cardiologists Generalists with cardiology consult: 30 days 0.95 (95% CI 0.70-1.30); 1 year 1.00 (95% CI 0.83-1.23); Generalists without cardiology		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								consult: 30 days 0.81 (95% CI 0.64-1.04); 1 year 0.97 (95% CI 0.83-1.14)		

Table 54: Evidence extraction for Cleland et al, 2012 National Heart Failure Audit[30]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Cleland et al, 2012[30]	Audit report of 142 out of 155 NHS	N=32,906 index admissions and N=4,170 readmissions	Acute patients discharged from hospital with a primary diagnosis of heart failure	48% treated in cardiology wards	41% treated on general medical wards and 11% on other wards.	3 years for mortality (multivariate	Mortality: In-hospital (adjusted for age, NYHA class III/IV and previous AMI)	HR 1.66 (1.52-1.81)	Healthcare quality improvement Partnership	Multivariate adjustment a bit limited.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
	Trusts in England and Health Boards in Wales		Inclusion criteria: A primary diagnosis of heart failure on discharge designated by any of the following ICD-10 descriptions – hypertensive heart disease with (congestive) heart failure; ischaemic cardiomyopathy; cardiomyopathy unspecified; congestive heart failure; left ventricular failure; heart failure unspecified Exclusions: It states that '….patients admitted for elective procedures ought not to be included.'			analysis)				
							1 year mortality: (adjusted for age, NYHA class III/IV and previous AMI; ACE/ARB on discharge; beta blockers on discharge; diuretics; cardiology follow-up)	HR 1.10 (1.03-1.17)		
							3 year mortality: (adjusted for age, NYHA class III/IV and previous AMI; ACE/ARB on discharge; beta blockers on discharge; diuretics; cardiology follow-up)	HR 1.11 (1.08-1.15)		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
			54.1% of men were treated on cardiology wards, compared with 39.5% of women. Women were more likely to be treated on general medical wards (47.9% vs. 36.0%) and other wards (12.4% vs. 9.5%). The likelihood of being treated on a cardiology ward decreased with age: 76.3% of patients who were 16-44 were treated on cardiology wards, compared with 47.1 of patients in the 74-84 age group, and 32.1% of patients over 84 years of age.							

Table 55: Evidence extraction for Howlett et al, 2003[76]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Howlett et al, 2003[76]	Retrospective review of consecutive patients admitted to a tertiary care facility with a primary diagnosis of congestive heart failure To determine independen	Total N =185 (N=65 seen by cardiologist (CARD group) and N=120 seen by internist (IM group)) Inclusion criteria: all patients with a primary diagnosis of CHF as indicated on a discharge summary sheet (only first admissions) Exclusion: Congestive Heart Failure as a secondary diagnosis,	Age mean (sd): CARD 70 (11) – IM 77 (11) Male/Female: CARD 35/30 – IM 54/66	Cardiologist care	Internist care	Retrospective review of charts no follow-up	Independent predictors of beta blocker therapy at discharge	Coexisting ASA Acetylsalicylic acid) therapy (OR 4.2 (2.29 to 6.71); Lack of oedema OR 1.60 (1.26 to 2.00); Cardiologist attending OR 1.30 (1.07 to 1.64); Coexistent hypert	Canadian Institute of Health Research and individual investigator awards (studentship grants)	Retrospective data only, study only indirectly addressing the protocol question

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
	t predictors, variables from the univariate analysis with p<0.1 were then including in multiple logistical regression analysis	acute myocardial infarction, patients transferred from another hospital Those patients seen by cardiologists were younger and had larger left ventricular end-diastolic diameter by echocardiography.						ension OR 1.24 (1.02 to 1.54)		

Table 56: Evidence extraction for Joynt et al. 2013[81]

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

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Joynt et al. 2013	Retrospective review of all Medicare fee-for-service beneficiaries discharged from acute care hospital in the USA, with a primary discharge diagnosis of HF. To determine the effect of physician specialis	81, 136 cared for by physicians with a 'medium volume' of HF patients, which is the group chosen by the systematic reviewer as the most relevant for data extraction. In addition there were also 390,066 patients cared for by physicians with 'lowest', 'low', high' and 'highest' volumes of HF patients,	Inclusion: All Medicare fee-for-service beneficiaries discharged from acute care hospital in the USA, with a primary discharge diagnosis of HF. Exclusion: Patients discharged from Federal hospitals, the district of Columbia, and hospitals outside 50 US states. For the 81.136 patients in the medium volume quintile, median (IQR) age was 82(75-87); 44.6% were female; 25.5% had uncomplicated diabetes mellitus,	Cardiologist care OR Internist care	Generalist care	Retrospective review of charts; no follow-up	30 day risk adjusted mortality rate for Cardiologists versus generalists	Cardiologists: 891/14604 (6.1%) Generalists: 2688/24665 (10.9%)	Academic grants only (Clinical Research Program Grant from American Heart Association and Lerner Research Award from a Local hospital). No conflicts of interest.	Retrospective data only. Although not explicitly reported in the paper, the re-admission rates are likely to represent the proportion of patients with at least one re-admission, rather than the actual number of admissions (which may include multiple re-admissions per person). This assumption is based on
							30 day risk adjusted mortality rate for Internists versus generalists	Internists: 4061/41866 (9.7%) Generalists: 2688/24665 (10.9%)		
							30 day risk adjusted re-admission rate for Cardiologists versus generalists	Cardiologists: 3241/14604 (22.4%) Generalists: 5648/24665 (22.9%)		
							30 day risk adjusted re-admission rate for Internists versus generalists	Internists: 9964/14604 (23.8%) Generalists: 5648/24665 (22.9%)		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
	ation on mortality and readmiss ion levels.	and detailed results for these have not been extracted.	53.6% had hypertension and 29.1% had CKD; and 68.9% were emergency admissions.				The above mortality and re-admission rates were for the quintile of physicians with a medium volume of HF patients. Very similar results for mortality were observed for physicians in the other 4 quintiles (lowest, low, high and highest). For re-admission rates, the volume influenced the relationship between groups, with lowest volumes tending to favour generalists over cardiologists and internists, but the highest volumes tending to favour cardiologists over internists and generalists.			the way the data is presented, as percentages of patients.

1

2 **Table 57: Evidence extraction for Lowe et al, 2000[97]**

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Lowe et al, 2000[97]	Prosp ective cohort	N=256 patients admitted to	All patients admitted over a 7-months period in	Specialist	Generalist (General physicians	2 year	Outcome 1 Adjusted Length of stay	If a specia list	New South Wales	2 year follow-up rate

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
	study of patients admitted to hospital with congestive heart failure multivariate analysis adjusting for factors including co-morbidity, use of ACE inhibitors, NYHA grade and wheth	hospital with congestive heart failure (N=102 care for by cardiologists and N=154 care for by generalists) Inclusions: Patients aged 60 or more with congestive heart failure defined by the Framingham criteria admitted as medical emergencies	whom Congestive Heart Failure was considered to be the main reason for hospitalization. Patients admitted under general physicians were older and more likely to have impaired renal function and chest infections. The prevalence of diabetes mellitus was higher in the patintes care for by generalists but this difference did not reach statistical significance. 47% of patients admitted under the cardiologists had a co-morbidity score greater than one, whereas 70% of		who have extended training in internal medicine as well as medical speciality and invite consultation from fellow specialists as necessary.			cardiologist was the principal care giver adjusted LOS was reduced by 5% (95% CI -23-17% not significant) Univariate LOS Specialist mean (sd) Specialist 9.6 (7.8) Gener	Department of Health; Merck, Sharpe and Dhome Limited	reported as 99% of the whole cohort which seems incredibly high.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
	er or not the admission was the first with heart failure.		patients admitted under the gernal physicians had an elevated score. 16% of patients admitted under the general physicians had either previously seen a cardiologist or were seen by one during or after admission.					alists 12.3 (12.9)		
							Outcome 2 Adjusted mortality In hospital 28 day 1 year	In hospital: Specialist 12/102- Generalists 6/154 adjusted OR 3.1 (1.1-8.6); 28 day Specialist 16/102; Generalists 8/154 adjusted OR 4.3 (1.5-12.2);		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								1 year: Specialist 38/102 - Generalists 47/154adjusted OR 1.6 (0.85-3.2)		

Appendix H: Economic evidence tables

H.1 Natriuretic peptides

Table 58: Economic evidence tables

Adelaide Health Technology Assessment. B-type natriuretic peptide assays in the diagnosis of heart failure. Part A: in the hospital emergency setting. Part B: in the non-hospital setting. Merlin, T. Adelaide: Adelaide Health Technology Assessment (AHTA). 2007.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CEA (health outcome = deaths) **Study design:** A cost effectiveness analysis of care costs and mortality of patients in the BASEL study[110]. Mortality and resource use was compared in patients randomised to a management strategy guided with or without B-typeNP. All patients underwent an initial clinical assessment then an adjudicating diagnosis at the end of the follow-up period **Approach to analysis:** Analysis of averaged individual level resource use, with Australian unit costs applied	**Population:** Patients presenting to ED with acute dyspnoea **Cohort settings:** N = 452 Mean age = 71 years M = 58% **Intervention 1:** Conventional diagnostic assessment[+] **Intervention 2:** Conventional assessment supplemented and guided by B-type natriuretic peptide testing. (<100pg/mL guides rule-out; >500pg/mL guides rule-in[++])	**Total costs:** mean per patient cost of care at 30-days Intervention 1: £1,876 Intervention 2: £1,721 Incremental (2-1): -£155 (CI -£1, -£318; p=NR) **Currency & cost year:** 2001 Australian dollars presented here as 2001 UK pounds‡ **Cost components incorporated:** Emergency care and admitted patient care including cardio-pulmonary investigations, outpatient care, and B-typeNP test	**Primary outcome measure:** 30-day all-cause deaths per patient Intervention 1: 0.12 Intervention 2: 0.10 Incremental (2-1): -0.26 (CI -0.32, 0.83; p=0.45) **Other outcome measures:** *Median days hospitalised (initial)* Intervention 1: 11 Intervention 2: 8 Increment (2-1): -3 (p=0.001) *Initial hospitalisation rate* Intervention 1: 0.85 Intervention 2: 0.75 Increment (2-1): -0.10 (p=0.008) *30-day re-admission rate* Intervention 1: 0.10	**Primary ICER:** Intervention 2 dominates Intervention 1 The estimated probability of the incremental cost-effectiveness obtained from bootstrap sampling: Intervention 2 vs 1: less costly/lower mortality = 78.8% Intervention 2 vs 1: less costly/higher mortality = 18.8% Intervention 2 vs 1: more costly/lower mortality = 1.9% Intervention 2 vs 1: more costly/higher mortality = 0.5% **Analysis of uncertainty:** At 30-days the primary cost saving element is the patient admission rate (initial plus re-admission). If no difference is assumed, and there are identical proportions of HF and other diagnoses in admitted and non-admitted patients, then the additional per patient cost is the B-typeNP test itself

Adelaide Health Technology Assessment. B-type natriuretic peptide assays in the diagnosis of heart failure. Part A: in the hospital emergency setting. Part B: in the non-hospital setting. Merlin, T. Adelaide: Adelaide Health Technology Assessment (AHTA). 2007.				
Perspective: Australian (Payer) **Time horizon:** 30-days **Discounting:** NA			Intervention 2: 0.12 Increment (2-1): 0.02 (p=0.63)	(representing a 5.6% cost increase for ruling out patients suspected of heart failure)
Data sources				
Health outcomes: Mortality rate was acquired from the 30-day published findings of the BASAL trial.[110] **Quality-of-life weights:** NR **Cost sources:** The Australian Refined Diagnosis Related Group cost estimates were used for hospital charges for heart failure and alternative diagnoses (Department of Health and Aging 2006). The unit cost of B-typeNP testing was obtained through local laboratory benchmarking data (£23[‡]).				
Comments				
Source of funding: Governmental **Limitations:** NP thresholds not adjusted for gender, age, renal function or obesity; short follow-up unlikely to reflect all differences in costs and outcomes				
Overall applicability*: Partially applicable Overall quality: Potentially serious limitations**				

Abbreviations: CEA = cost-effectiveness analysis; ICER = incremental cost-effectiveness ratio; HF = heart failure; ED = emergency department; NA = not applicable; NR = not reported; RCT = randomised clinical trial

[+]Patients in the control group were treated according to the most recent clinical guidelines. [++]Patients scoring >500pg/mL were recommended rapid therapy with diuretics, nitroglycerin, angiotensin-converting-enzyme inhibitors, and morphine.

[‡] Currency converted from US dollars to Australian dollars using purchasing power parities for 2005, then from 2005 Australian dollars to 2005 UK pounds using purchasing power parities for 2005[128]

* Directly applicable / Partially applicable / Not applicable; ** Minor limitations / Potentially serious limitations / Very serious limitations

Table 59

Mueller C, Laule-Kilian K, Schindler C, Klima T, Frana B, Rodriguez D et al. Cost-effectiveness of B-type natriuretic peptide testing in patients with acute dyspnea. Archives of Internal Medicine. 2006; 166(10):1081-1087				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CEA (health outcome = deaths)	**Population:** Patients presenting to ED	**Total costs:** mean per patient cost of care at 180-days	**Primary outcome measure:** 180-day all-cause deaths per	**Primary ICER:** Intervention 2 dominates Intervention 1

Mueller C, Laule-Kilian K, Schindler C, Klima T, Frana B, Rodriguez D et al. Cost-effectiveness of B-type natriuretic peptide testing in patients with acute dyspnea. Archives of Internal Medicine. 2006; 166(10):1081-1087				
Study design: A with-in trial cost effectiveness analysis of care costs and mortality of patients in the BASEL study[110]. Mortality and resource use was compared in patients randomised to a management strategy guided with or without B-typeNP. All patients underwent an initial clinical assessment then an adjudicating diagnosis at the end of the follow-up period **Approach to analysis:** Analysis of averaged individual level resource use with local (Swiss) unit costs applied **Perspective:** Swiss (Payer) **Time horizon:** 180-days **Discounting:** NA	with acute dyspnoea **Cohort settings:** N = 452 Mean age = 71 years M = 58% **Intervention 1:** Conventional diagnostic assessment[+] **Intervention 2:** Conventional assessment supplemented and guided by B-type natriuretic peptide testing (<100pg/mL guides rule-out; >500pg/mL guides rule-in[++])	Intervention 1: £6734 Intervention 2: £5084 Incremental (2-1): -£1650 (p=0.004) **Currency & cost year:** 2003 US dollars presented here as 2003 UK pounds‡ **Cost components incorporated** Emergency and admitted patient care (except medication for non-cardiac and non-pulmonary conditions) including cardio-pulmonary investigations, outpatient care, and B-typeNP test	patient Intervention 1: 0.229 Intervention 2: 0.196 Incremental (2-1): -0.034 (p=0.42) **Other outcome measures:** *Median days hospitalised (initial)* Intervention 1: 10 Intervention 2: 8 Increment (2-1): -2 (p=0.002) *Median days hospitalised (total)* Intervention 1: 14 Intervention 2: 10 Increment (2-1): -4 (p=0.005) *Median days hospitalised for dyspnoea (total)* Intervention 1: 13 Intervention 2: 9 Increment (2-1): -4 (p=0.003) *Median days hospitalised (initial, if admitted)* Intervention 1: 13 Intervention 2: 11 Increment (2-1): -2 (p=0.06)	The estimated probability of the incremental cost-effectiveness obtained from bootstrap sampling: Intervention 2 vs 1: less costly/lower mortality = 80.6% Intervention 2 vs 1: less costly/higher mortality = 19.3% Intervention 2 vs 1: more costly/lower mortality = 0.04% Intervention 2 vs 1: more costly/higher mortality = 0.02% **Analysis of uncertainty:** The primary driver of lower costs in the B-typeNP group is reduced time in hospital, emanating equally from the initial stay and re-admissions (2 fewer days each). Also fewer admissions and less intensive care. In comprehensive one-way DSA, only this cost component (specifically the reduction of re-hospitalised days in the B-typeNP arm only) revealed sensitivity: cost neutrality beyond 3 additional hospital days given to B-typeNP. Duration of initial hospitalisation (both groups), cost per day in hospital, cost of outpatient visit, cost of intensive care, cost of B-typeNP test, time in ICU (BNP group only) and cost of long-term medication (B-typeNP group only) were all robust to reasonable one-way variation. Sub-group analysis showed that the 180-day

Mueller C, Laule-Kilian K, Schindler C, Klima T, Frana B, Rodriguez D et al. Cost-effectiveness of B-type natriuretic peptide testing in patients with acute dyspnea. Archives of Internal Medicine. 2006; 166(10):1081-1087				
				cost-reduction benefit of B-typeNP testing was enhanced in patients with a history of coronary artery disease (p=0.005) and those with pulmonary disease (p=0.01)
Data sources				
Health outcomes: 180-day published findings of the BASAL trial[110]. **Quality-of-life weights:** NR. **Cost sources:** Local hospital charges, except for medication (Swiss standard charging rates) and BNP testing (Swiss standard reimbursement rate, £30 unit cost[‡]).				
Comments				
Source of funding: Swiss National Science Foundation, Swiss Heart Foundation, Novartis Foundation, Krokus Foundation, University of Basel. **Limitations:** NP thresholds not adjusted for gender, age, renal function or obesity ; not all relevant costs were included				
Overall applicability*: Partially applicable Overall quality: Minor limitations**				

Abbreviations: CEA = cost-effectiveness analysis; ICER = incremental cost-effectiveness ratio; HF = heart failure; ED = emergency department; NA = not applicable; RCT = randomised clinical trial; DSA= deterministic sensitivity analysis; ICU = intensive care unit

[+]Patients in the control group were treated according to the most recent clinical guidelines. [++]Patients scoring >500pg/mL were recommended rapid therapy with diuretics, nitrogylcerin, angiotensin-converting-enzyme inhibitors, and morphine.

[‡] *Currency converted from 2003 US dollars to 2003 UK pounds using purchasing power parities for 2003*[128]

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations / Potentially serious limitations / Very serious limitations*

Table 60

Breidthardt T, Laule K, Strohmeyer AH, Schindler C, Meier S, Fischer M et al. Medical and economic long-term effects of B-type natriuretic peptide testing in patients with acute dyspnea. Clinical Chemistry. 2007; 53(8):1415-1422				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CEA (health outcome = deaths) **Study design:** A with-in trial cost effectiveness analysis of care costs and mortality of patients in the BASEL study[110]. Mortality and resource use was	**Population:** Patients presenting to ED with acute dyspnoea **Cohort settings:** N = 452 Mean age = 71 years	**Total costs:** mean per patient cost of care at 360-days Intervention 1: £8173 Intervention 2: £6504 Incremental (2-1): -£1669 (p=0.008)	**Primary outcome measure:** 720-day all-cause deaths per patient Intervention 1: 0.36 Intervention 2: 0.37 Incremental (2-1): 0.01 (p=0.582)	**Primary ICER:** Not reported as the authors concluded that there was no difference in mortality The estimated probability of the incremental cost-effectiveness obtained from bootstrap sampling: Intervention 2 vs 1: less costly/lower

Breidthardt T, Laule K, Strohmeyer AH, Schindler C, Meier S, Fischer M et al. Medical and economic long-term effects of B-type natriuretic peptide testing in patients with acute dyspnea. Clinical Chemistry. 2007; 53(8):1415-1422				
compared in patients randomised to a management strategy guided with or without B-typeNP. All patients underwent an initial clinical assessment then an adjudicating diagnosis at the end of the follow-up period **Approach to analysis:** Analysis of averaged individual level resource use with local (Swiss) unit costs applied **Perspective:** Swiss (Payer) **Time horizon:** Health: 720-days; Costs: 360-days **Discounting:** None	M = 58% **Intervention 1:** Conventional diagnostic assessment[+] **Intervention 2:** Conventional assessment supplemented and guided by B-type natriuretic peptide testing (<100pg/mL guides rule-out; >500pg/mL guides rule-in[++])	**Currency & cost year:** 2003 US dollars presented here as 2003 UK pounds‡ **Cost components incorporated** Emergency and admitted patient care (except medication for non-cardiac and non-pulmonary conditions) including cardio-pulmonary investigations, outpatient care, and B-typeNP test	**Other outcome measures:** *Median days hospitalised (total)* Intervention 1: 16 Intervention 2: 12 Increment (2-1): -4 (p=0.025) *Median days hospitalised for dyspnoea (total)* Intervention 1: 14 Intervention 2: 11 Increment (2-1): -3 (p=0.009)	mortality = 39.5% Intervention 2 vs 1: less costly/higher mortality = 59.1% Intervention 2 vs 1: more costly/lower mortality = 0.5% Intervention 2 vs 1: more costly/higher mortality = 0.9% **Analysis of uncertainty:** The reduction in initial mortality observed in frail elderly patients[109] was no longer evident at 720-days. The reduction in days hospitalised was the major driver for a significant reduction in total treatment cost at 360-days.
Data sources				
Health outcomes: Acquired from the 720-day published findings of the BASAL trial[110]. **Quality-of-life weights:** NR. **Cost sources:** Local hospital charges, except for medication (Swiss standard charging rates) and BNP testing (Swiss standard reimbursement rate, £30 unit cost[‡]).				
Comments				
Source of funding: Swiss National Science Foundation, Swiss Heart Foundation, Novartis Foundation, Krokus Foundation, University of Basel. **Limitations:** Natriuretic peptide thresholds not adjusted for gender, age, renal function or obesity; use of different follow-up periods for costs and outcomes would likely bias the cost-effectiveness finding; not all relevant costs were included; some mortality figures reported show contradictory findings which have not been clarified by the authors. **Other:** This is a later analysis of the same RCT and cohort as Mueller2006 but using costs and outcomes from a longer follow-up				
Overall applicability*: Partially applicable Overall quality: Potentially serious limitations**				

Abbreviations: CEA = cost-effectiveness analysis; ICER = incremental cost-effectiveness ratio; HF = heart failure; ED = emergency department; NR = not reported; RCT = randomised clinical trial

[+]Patients in the control group were treated according to the most recent clinical guidelines. [++]Patients scoring >500pg/mL were recommended rapid therapy with diuretics, nitroglycerin, angiotensin-converting-enzyme inhibitors, and morphine
[‡]*Currency converted from 2003 US dollars to 2003 UK pounds using purchasing power parities for 2003*[128]
**Directly applicable / Partially applicable / Not applicable; ** Minor limitations / Potentially serious limitations / Very serious limitations*

Table 61

Moe GW, Howlett J, Januzzi JL, Zowall H. N-terminal pro-B-type natriuretic peptide testing improves the management of patients with suspected acute heart failure: primary results of the Canadian prospective randomized multicenter IMPROVE-CHF study. Circulation. 2007; 115(24):3103-3110				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CCA (health outcome = deaths) **Study design:** A within-trial economic analysis of care costs and mortality of patients in the IMPROVE-CHF study. Patients were randomised to a management strategy guided with or without NT-proBNP. The ED physician scored the likelihood of heart failure at the outset and an adjudicating diagnosis was made at the end of follow-up period **Approach to analysis:** Analysis of averaged individual level resource use with local unit costs applied	**Population:** Patients presenting to ED with acute dyspnoea **Cohort settings:** N = 500 Mean age = 70 years M = 52% **Intervention 1:** Conventional diagnostic assessment[+] **Intervention 2:** Conventional assessment supplemented and guided by NT-proBNP result[+] (Initially the rule-in/out thresholds came from Roche Diagnostics, later from the PRIDE study[79]: <300pg/mL guides rule-out; >450pg/mL for under	**Total costs:** mean per patient cost of care at 60-days Intervention 1: £3899 Intervention 2: £3295 Incremental (2-1): -£604 (p=0.0159) **Currency & cost year:** 2005 Canadian dollars presented here as 2005 UK pounds‡ **Cost components incorporated** Emergency and admitted patient care including cardio-pulmonary investigations, outpatient care, and NT-proBNP test	**Primary outcome measure:** 60-day all-cause deaths per patient Intervention 1: 0.044 Intervention 2: 0.055 Incremental (2-1): 0.01 (p=0.58) **Other outcome measures:** *60-day in-hospital deaths per patient* Intervention 1: 0.024 Intervention 2: 0.045 Increment (2-1): 0.021 (p=0.193) *Hospitalisation rate (initial)* Intervention 1: 0.58 Intervention 2: 0.57 Increment (2-1): -0.01 (p=0.826) *60-day re-hospitalisation rate* Intervention 1: 0.20	**Primary ICER:** Not reported **Analysis of uncertainty:** None

Moe GW, Howlett J, Januzzi JL, Zowall H. N-terminal pro-B-type natriuretic peptide testing improves the management of patients with suspected acute heart failure: primary results of the Canadian prospective randomized multicenter IMPROVE-CHF study. Circulation. 2007; 115(24):3103-3110				
Perspective: Canadian Health System (Payer) **Time horizon:** 60-days **Discounting:** NA	50 years of age, and >900pg/mL for over 50 years of age guides rule-in)		Intervention 2: 0.13 Increment (2-1): -0.07 (p=0.046) *Median days hospitalised (initial)* Intervention 1: 7 Intervention 2: 6 *Median duration of ED visit (hours)* Intervention 1: 6.3 Intervention 2: 5.6 Increment (2-1): -0.7 (p=0.031) Increment (2-1): 1 (p=0.302) *Median days hospitalised in ICU* Intervention 1: 5.5 Intervention 2: 6.0 Increment (2-1): 0.5 (p=0.723)	
Data sources				
Health outcomes Within-trial (IMPROVE-CHF study). **Quality-of-life weights:** NR. **Cost sources:** Canadian Institute of Health Information for ED and hospital costs. Physician fees and costs of outpatient diagnostic and laboratory services from average regional reimbursement fees. NT-proBNP test unit cost estimated (£24[‡])				
Comments				
Source of funding: Industry (Roche Diagnostics) **Limitations:** Natriuretic peptide thresholds not adjusted for gender, renal function or obesity; short follow-up unlikely to reflect all differences in costs and outcomes				
Overall applicability*: Partially applicable Overall quality: Potentially serious limitations**				

Abbreviations: CCA = cost consequence analysis; ICER = incremental cost-effectiveness ratio; HF = heart failure; ED = emergency department; NA = not applicable; NR = not reported; RCT = randomised clinical trial

[+]A specific patient management strategy was not stated

[‡] *Currency converted from2005 Canadian dollars to 2005 UK pounds using purchasing power parities for 2005*[128]

1 ** Directly applicable / Partially applicable / Not applicable; ** Minor limitations / Potentially serious limitations / Very serious limitation*

2 **Table 62**

Rutten JHW, Steyerberg EW, Boomsma F, van Saase JLCM, Deckers JW, Hoogsteden HC et al. N-terminal pro-brain natriuretic peptide testing in the emergency department: beneficial effects on hospitalization, costs, and outcome. American Heart Journal. 2008; 156(7):1-7				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CEA (Health outcome = time to discharge) **Study design:** A within-trial cost-effectiveness analysis of care costs and time to discharge (mortality was a secondary end-point). Patients were randomised to a management strategy guided with or without NT-proBNP. The ED physician scored the likelihood of heart failure at the outset and an adjudicating diagnosis was made at the end of follow-up period **Approach to analysis:** Analysis of averaged individual level resource use with local unit costs applied	**Population:** Patients presenting to ED with acute dyspnoea **Cohort settings:** N = 477 Mean age = 59 years M = 54% **Intervention 1:** Conventional diagnostic assessment+ **Intervention 2:** Conventional assessment supplemented and guided by NT-proBNP result+ (<93pg/mL for males and <144pg/mL for females guides rule-out; >1017pg/mL guides rule-in)	**Total costs:** mean per patient in-hospital cost at 30-days Intervention 1: £4041 Intervention 2: £3171 Increment (2-1): -£870 (p=NS) **Currency & cost year:** 2005 US dollars presented here as 2005 UK pounds‡ **Cost components incorporated** Emergency and admitted patient care including cardio-pulmonary investigations, outpatient care, and NT-proBNP test	**Primary outcome measure:** Median days to discharge Intervention 1: 3.9 Intervention 2: 1.9 Increment (2-1): -2.0 (p=0.04) **Other outcome measures:** *30-day all-cause deaths per patient:* Intervention 1: 0.07 Intervention 2: 0.06 Increment (2-1): -0.01 (p=0.26) *Median duration of ED visit (hours)* Intervention 1: 2.86 Intervention 2: 2.83 Increment (2-1): -0.03 (p=0.12) *Initial hospitalisation rate* Intervention 1: 0.67 Intervention 2: 0.62 Increment (2-1): -0.05 (p=0.26) *Median days of initial hospitalisation*	**Primary ICER:** Intervention 2 dominates Intervention 1 (NT-proBNP reduced the time to discharge with an associated cost saving of £435 per day) **Secondary ICER:** PSA using bootstrap sampling based on the secondary end-point of 30-day all-cause death demonstrated the point-estimate was most likely to lie in the less costly/lower mortality quadrant (probability not reported) **Analysis of uncertainty:** A *post hoc* sub-group analysis indicated that the effect on costs is largest in patients with cardiac dyspnoea compared with non-cardiac dyspnoea (mean saving of £1671 compared with non-cardiac dyspnoea patients £95)

Rutten JHW, Steyerberg EW, Boomsma F, van Saase JLCM, Deckers JW, Hoogsteden HC et al. N-terminal pro-brain natriuretic peptide testing in the emergency department: beneficial effects on hospitalization, costs, and outcome. American Heart Journal. 2008; 156(7):1-7				
Perspective: Dutch (Payer) **Time horizon:** 30-days **Discounting:** NA			Intervention 1: 8.1 Intervention 2: 7.8 Increment (2-1): -0.3 (p=0.48) *ICU admission rate* Intervention 1: 0.16 Intervention 2: 0.16 Increment (2-1): 0.00 (p=0.92) *30-day in-hospital deaths per patient:* Intervention 1: 0.06 Intervention 2: 0.06 Increment (2-1): -0.003 (p=0.89)	
Data sources				
Health outcomes: A within-trial single-centre analysis at patient level for outcome and resource utilisation. **Quality-of-life weights:** NR. **Cost sources:** Hospital admission costs based on national university hospital prices. Diagnostic investigation costs were based on the charge to health insurance companies. NT-proBNP test unit cost estimated (£22[‡])				
Comments				
Source of funding: Erasmus Medical College Medical Research Advisory Committee. **Limitations:** Natriuretic peptide thresholds not adjusted for age, renal function or obesity; short follow-up unlikely to reflect all differences in costs and outcomes.				
Overall applicability*: Partially applicable Overall quality: Potentially serious limitations**				

Abbreviations: CEA = cost effectiveness analysis; ICER = incremental cost-effectiveness ratio; HF = heart failure; ED = emergency department; NS = not significant; NA = not applicable; NR = not reported; ICU = intensive care unit; CCU = coronary care unit; RCT = randomised clinical trial; PSA = probabilistic sensitivity analysis

[+]A specific patient management strategy was not stated

[‡] *Currency converted from2005 US dollars to 2005 UK pounds using purchasing power parities for 2005*[128]

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations / Potentially serious limitations / Very serious limitations*

Table 63

Siebert U, Januzzi JL, Beinfeld MT, Cameron R, Gazelle GS. Cost-effectiveness of using N-terminal pro-brain natriuretic peptide to guide the diagnostic assessment and management of dyspneic patients in the emergency department. American Journal of Cardiology. 2006; 98(6):800-805

Siebert U, Januzzi JL, Beinfeld MT, Cameron R, Gazelle GS. Cost-effectiveness of using N-terminal pro-brain natriuretic peptide to guide the diagnostic assessment and management of dyspneic patients in the emergency department. American Journal of Cardiology. 2006; 98(6):800-805				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CEA (Health outcome = serious adverse events) **Study design:** An economic decision model based on one prospective blinded single-armed NT-proBNP threshold determination study (PRIDE[79]). For the conventional assessment branch costs and outcomes were those reported in PRIDE. For the NT-proBNP branch data was modelled using retrospective classification of patient level data from PRIDE; costs and outcomes were split according to NT-proBNP result. Use of echo was predicted using assumptions **Decision analytic model:** The branch dealing with strategy 1 (control) composed 3 arms representing low, intermediate and high risk of heart failure, as scored at initial assessment. The branch dealing with strategy 2 (NT-proBNP) composed two arms, representing a positive or negative test result. In both strategies, patients in all arms	**Population:** Patients presenting to ED with acute dyspnoea **Cohort settings:** N = 599 (PRIDE study cohort) Mean age = 62 years M = 51% Caucasian: 87% **Strategy 1:** Conventional diagnostic assessment[+] **Strategy 2:** Management directed by NT-proBNP result[+] (>900 pg/mL = positive; <900 pg/mL = negative)	**Total costs:** mean per patient in-hospital cost at 60-days Strategy 1: £3201 Strategy 2: £2900 Increment (2-1): -£301 **Currency & cost year:** 2005 US dollars presented here as 2005 UK pounds ‡ **Cost components incorporated** Emergency and admitted patient care including cardio-pulmonary investigations, outpatient care, and NT-proBNP test	**Primary outcome measure:** Number of SAEs per patient[#] Strategy 1: 0.258 Strategy 2: 0.254 Increment (2-1): -0.004 (CI NR) **Other outcome measures:** *Probability of correct HF diagnosis* Strategy 1: 0.967 Strategy 2: 0.957 Increment (2-1): -0.01 (1.0% reduction) *Proportion of true positive* Strategy 1: 0.320 Strategy 2: 0.328 Increment (2-1): 0.008 (2.5% increase) *Proportion of true negative* Strategy 1: 0.647 Strategy 2: 0.629 Increment (2-1): -0.018 (2.8% reduction) *Proportion of patients initially hospitalised after ED evaluation* Strategy 1: 0.778 Strategy 2: 0.677 Increment (2-1): -0.101 (13%	**Primary ICER (£/SAE):** Strategy 2 dominates Strategy 1 **Analysis of uncertainty** PSA of the incidence of SAEs in true- and false-positives, and true- and false-negatives found the intervention to be dominant in 78% of simulations. DSA of the risk of death after discharge with standard clinical assessment yielded a reduction in per patient risk of death of 0.01 favouring NT-proBNP; however it was not clear how this was determined by the model. DSA of the prevalence of true heart failure demonstrated NT-proBNP dominance to be robust. This remained true when halving or doubling unit costs (NT-proBNP, echo, and hospitalisation). Total cost saving, which was primarily attributable to prevented or shortened hospitalisations, remained favourable when reducing hospital days saved due to prevention of echos from 2.7 days to 1 day. Also when echos were performed in place of positive NT-proBNP tests. Two-way DSA found the cost saving to hold for NT-proBNP sensitivity and specificity across their 95%CIs

Siebert U, Januzzi JL, Beinfeld MT, Cameron R, Gazelle GS. Cost-effectiveness of using N-terminal pro-brain natriuretic peptide to guide the diagnostic assessment and management of dyspneic patients in the emergency department. American Journal of Cardiology. 2006; 98(6):800-805				
were either discharged home with no chance of echo or admitted with a probability of receiving an echo or not. In the base-case it was assumed that NT-proBNP testing had no influence on mortality **Perspective:** USA (Hospital) **Time horizon:** 60-days **Discounting:** NA			reduction) *Mean days hospitalised* Strategy 1: 4.41 Strategy 2: 3.88 Increment (2-1): -0.53 (12% reduction) *Number of echos performed* Strategy 1: 0.251 Strategy 2: 0.105 Increment (2-1): -0.146 (58% reduction)	
Data sources				
Health outcomes: Patient data from the PRIDE study[79] **Quality-of-life weights:** NR. **Cost sources:** Manufacturer costs for NT-proBNP testing (£13 unit cost[‡]) and echocardiography; Massachusetts General Hospital accounting database for hospitalisation costs and professional fees				
Comments				
Source of funding: Part industry (Roche Diagnostics) **Limitations:** Adopted an NT-proBNP rule-out decision only (>900pg/mL); short follow-up unlikely to reflect all differences in costs and outcomes; not all relevant costs were included; use of modelling assumptions relating the use of echo				
Overall applicability*: Partially applicable Overall quality: Potentially serious limitations**				

Abbreviations: CEA = cost-effectiveness analysis; ICER = incremental cost-effectiveness ratio; HF = heart failure; ED = emergency department; NA = not applicable; NR = not reported; SAEs: serious adverse events; CIs = confidence intervals; DS*A = deterministic sensitivity analysis; PSA = probabilistic sensitivity analysis*

[+] A specific patient management strategy was not stated

[#] Urgent care visit, ED presentation, re-hospitalisation

[‡] *Currency converted from2005 US dollars to 2005 UK pounds using purchasing power parities for 2005*[128]

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations / Potentially serious limitations / Very serious limitations*

H.2 Non-invasive ventilation

Table 64: GRAY et al., 2009

Gray AJ, Goodacre S, Newby DE, Masson MA, Sampson F, Dixon S et al. A multicentre randomised controlled trial of the use of continuous positive airway pressure

and non-invasive positive pressure ventilation in the early treatment of patients presenting to the emergency department with severe acute cardiogenic pulmonary oedema: the 3CPO trial. Health Technology Assessment. 2009; 13(33):1-106.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome = QALYs) **Study design:** Within trial analysis based on the 3 CPO trial[67]. **Approach to analysis:** economic analysis done as part of a NIHR HTA (GRAY2009[67]). **Perspective:** UK NHS **Time horizon:** lifetime[(a)] **Treatment effect duration:** lifetime. **Discounting:** Costs = 3.5%; Outcomes = 3.5%	**Population:** Patients presenting with severe acute cardiogenic pulmonary oedema (ACPO) in 26 emergency departments in the UK. **Cohort settings:** N=1069 Start age = 77.8 M = 43% ***Interventions*** **Intervention 1:** Standard oxygen therapy **Intervention 2:** CPAP (5 – 15 cmH_2O) **Intervention 3:** BiPAP (inspiratory pressure 8-20 cmH_2O, expiratory pressure 4-10 cmH_2O) All patients in every intervention were treated for a minimum of 2 days.	**Total lifetime costs without data imputation (mean per patient):** Intvn 1: £15,659 Intvn 2: £16,115 Intvn 3: £16,350 Incremental (2-1): £456 (CI = NR) Incremental (3-1): £691 (CI = NR) **Total lifetime costs with data imputation (mean per patient):** Intvn 1: £15,764 Intvn 2: £17,525 Intvn 3: £17,021 Incremental (2-1): £1,761 (CI = NR) Incremental (3-1): £1,257 (CI = NR) **Currency & cost year:** 2005-6 UK pounds **Cost components incorporated:** standard emergency department care for ACPO, CPAP, BiPAP, medical staff costs, emergency department attendance, minor injuries	**Total lifetime QALYs without data imputation (mean per patient):** Intvn 1: 1.329 Intvn 2: 1.503 Intvn 3: 1.337 Incremental (2-1): 0.174 (CI = NR) Incremental (3-1): 0.008 (CI = NR) **Total lifetime QALYs e with data imputation (mean per patient):** Intvn 1: 1.597 Intvn 2: 1.841 Intvn 3: 1.707 Incremental (2-1): 0.244 (CI = NR) Incremental (3-1): 0.11 (CI = NR)	***ICERs (without data imputation)*** • **Intvn 2 vs Intvn 1:** £2,621 per QALY gained Probability Intvn 2 cost-effective (£20K threshold): 71% • **Intvn 3 vs Intvn 1:** £86,375per QALY gained Probability Intvn 3 cost-effective (£20K threshold): NR ***ICERs (with data imputation)*** • **Intvn 2 vs Intvn 1:** £7,217 per QALY gained Probability Intvn 2 cost-effective (£20K threshold): 74% • **Intvn 3 vs Intvn 1:** £11,427 per QALY gained Probability Intvn 3 cost-effective (£20K threshold): NR **Analysis of uncertainty:** PSA: in the base case, the estimation of lifetime costs and QALYs uses a fixed annual cost and utility. Random variables were estimated for them using: • distributions around the cost parameter • the variability in the UK population norms of the EQ-5D. Using this approach the probability that CPAP is cost-effective is reduced, from 71%

		unit, outpatient attendances (cardiology), inpatient days (ICU, CCU, HDU), prescriptions (per month).		to 63%. [(b)] Using the RCT follow-up time (6 months) for the analysis had a large impact on the ICERs: • Without data imputation: Intvn 2 vs 1: £92,000 per QALY gained • Intvn 3 vs 1: £10,923 per QALY gained With data imputation: • Intvn 2 vs 1: £18,273 per QALY gained • Intvn 3 vs 1: £23,125 per QALY gained
Data sources				
Health outcomes: the 3 CPO trial [67]. **Quality-of-life weights:** EQ5D UK tariff. **Cost sources:** Resource use and costs were obtained from the 3 CPO trial, national or published sources and published literature.				
Comments				
Source of funding: The HTA programme. **Limitations:** Other trials were included in our clinical review while this analysis is based only on one of them. This analysis was published in two papers and discrepancies were noted between papers. Inconsistent results when a 6-month time horizon is considered were not explained.. **Other:** none.				
Overall applicability*: Partially applicable Overall quality: Minor limitations**				

Abbreviations: BiPAP = Bilevel positive airway pressure; CCU = Coronary Care Unit; CI = 95% confidence interval; CPAP = continuous positive airway pressure; 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); HDU = high dependency unit; ICU = Intensive care unit; ICER = incremental cost-effectiveness ratio; NIHR HTA = national institute for health research health technology assessment programme; NR = not reported; pa = probabilistic analysis; QALYs = quality-adjusted life years.

a) This paper reported four sets of data for the cost effectiveness analysis: 6-months data without imputation (n=429), 6-months data with imputation for missing values (n=1069), lifetime data without imputation (n=429) and lifetime data with imputation for missing values (n=1069).Here we only report the lifetime sets of data as they are more in line with the NICE reference case (NICE2008A[117]).

b) Regression imputation of lifetime total costs was undertaken for patients with missing values using age and gender as covariates.

* Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations

H.3 Ultrafiltration

Table 65: DOH 2007

Colechin ES, Bower L, Sims AJ. Ultrafiltration therapy for fluid overload in heart failure. 2007. NHS Purchasing and Supply Agency, Centre for Evidence-based purchasing. Ref ID: DOH2007				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost analysis (CEA conducted by the NCGC on the basis of the clinical evidence) **Study design:** Decision analytic model **Approach to analysis:** Resource use derived from UNLOAD trial which is US setting and costs taken from UK sources **Perspective:** UK NHS **Time horizon:** 90 days from initial hospitalization **Treatment effect duration:** 90 days **Discounting:** Costs were not discounted	**Population:** Patients hospitalized for acute decompensated heart failure. **Cohort settings:** Start age = 63±15 years M = 69% **Intervention 1:** Ultrafiltration **Intervention 2:** Intravenous diuretics	**Total costs (mean per patient):** Intvn 1: £1,379 Intvn 2: £771 Incremental (2-1): £608 (CI NR; p = NR) **Currency & cost year:** 2005/2006 UK pounds **Cost components incorporated:** Preparation, heparin, furosemide, ultrafiltration equipment and consumables, haematocrit testing, hospital care, readmission and emergency care.	**Deaths (all-cause) at 90-days** Intvn 1: 9/100 Intvn 2: 11/100 Incremental (2-1): 2 per 100 (CI NR; p = NR) Incremental risk: 2% averted (calculated by the NCGC) (CI NR; p = NR)	**ICER (Intvn 1 vs Intvn 2):** £30,400 per death averted (calculated by the NCGC) CI: NA **Analysis of uncertainty:** Alternative care settings (for example, ICU, day case) were addressed in a sensitivity analysis. In the ICU setting, the additional cost of UF was £440 per patient. In an inpatient day-case setting, the additional cost of UF was £101 per patient compared to diuretic treatment in a cardiac ward. For treatment in a cardiac ward, the mean length of stay would have to be reduced to 6 days for UF to become cost-saving. Results were insensitive to change in rate of readmission and rate of emergency visit.

Data sources
Health outcomes: The study did not include health outcomes. We used mortality data from the UNLOAD Randomised Controlled Trial[34] to estimate ICER because costing was based on the same trial. **Cost sources:** Primarily PSSRU Unit costs of health and social care 2006. Also from NHS Trusts, Manufacturers of ultrafiltration equipment and BNF.
Comments
Source of funding: NHS Centre for Evidence-based purchasing. **Limitations:** QALYs not calculated; only 90-day follow-up; mortality was not a primary endpoint (the study was not powered to detect a difference); sensitively analysis not performed on differential cost of treatment between strategies **Other:** The trial on which this model is based used primary endpoints weight loss and dyspnoea assessment at 48 hours after randomization.
Overall applicability*: Partially applicable **Overall quality**:** Potentially serious limitations

- Abbreviations: BNF=British National Formulary; CCA = cost-consequence analysis; CHF= congestive heart failure; CI = 95% confidence interval; CRBSI=catheter-related blood stream infections; HIT=heparin induced thrombocytopenia; ICER = incremental cost-effectiveness ratio; NR = not reported; psa = probabilistic sensitivity analysis; PSSRU=Personal Social Services Research Unit.

H.4 Aortic stenosis

Table 66: Fairbairn 2013

Fairbairn, T.A.; Meads, D.M.; Hulme, C.; Mather, A.N.; Plein, S.; Blackman, D.J.; Greenwood, J.P. The cost-effectiveness of transcatheter aortic valve implantation versus surgical aortic valve replacement in patients with severe aortic stenosis at high operative risk. FAIRBAIRN2013				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome = QALYs) Study design: Probabilistic decision analytic model Approach to analysis: A decision tree simulated patient's costs and benefits from baseline (procedure) to 2 years. A cohort Markov	Population: Patients with aortic stenosis with high operative risk Cohort settings#: Mean age = 84 M = 57% Intervention 1:	Total costs (mean per patient): Intvn 1: £53,943 Intvn 2: £52,593 Increment (2-1): -£1,350 Currency & cost year: 2011 UK pounds	Primary outcome measure (mean per patient): QALYs Intvn 1: 2.75 Intvn 2: 2.81 Increment (2-1): 0.063	Primary ICER (Intvn 2 vs Intvn 1): ICER: TAVI dominates SAVR Analysis of uncertainty: Base case parameters were fairly robust. A broad deterministic analysis of potential sensitivities found TAVI to dominate SAVR under reasonable variations in utility, hospitalisation rate, time horizon and extent of discounting costs and benefits. In

Fairbairn, T.A.; Meads, D.M.; Hulme, C.; Mather, A.N.; Plein, S.; Blackman, D.J.; Greenwood, J.P. The cost-effectiveness of transcatheter aortic valve implantation versus surgical aortic valve replacement in patients with severe aortic stenosis at high operative risk. FAIRBAIRN2013				
model of 1-year cycles simulated outcomes from 2 years through to a 10-year time horizon. Perspective: UK NHS Time horizon: 10-years Treatment effect duration: 10-years Discounting: Costs = 3.5%; Outcomes = 3.5%	SAVR Intervention 2: TAVI (TF or TA)	Cost components incorporated: Initial hospitalisation Clinical investigation TAVI procedure TAVI device Complications Medicines inc. long term Rehabilitation Readmissions		a 'worst case' complications scenario, TAVI was cost-effective at £11,307 per QALY gained. When TAVI procedure cost is increased by 15% to £19,000 (£10,000 more than SAVR) the ICER approached £20,000 per QALY gained. Up to 2 additional intensive care bed days for TAVI patients maintained cost effectiveness.
Data sources				
Health outcomes: PARTNER trial Cohort A (RCT) for TAVI and SAVR effectiveness. Some procedural outcomes and complications at 2-years were derived through expert opinion. Quality-of-life weights: A UK study of health related quality of life by NYHA class in TAVI patients using EQ5D and SF12. Cost sources: UK costs from: the PSSRU Unit Costs of Health and Social Care Handbook; the NHS national schedule of reference costs; the British National Formulary (BNF). The cost of the TAVI procedure (including device) = £16,500				
Comments				
Source of funding: The British Heart Foundation. Limitations: The increase in QALYs for TAVI versus SAVR in this evaluation for patient group is not supported by the findings of the underlying outcomes study: Partner A showed similar rates of all-cause mortality and no clear difference in health-related quality of life. The PARTNER trial was conducted in a mainly US outcome population/health system and used only the Edwards-Sapien device only (not Medtronic CoreValve); there was also some imbalance in patient characteristics; trial was sponsored by industry; there were a multitude of exclusion criteria which might make it questionable whether this is a representative population; patients did not necessarily have acute heart failure Costs and benefits were extrapolated for the third to the tenth year based on data collected over 2 years of follow-up in the PARTNER trial – it was assumed that the TAVI valves function for the lifetime of the patient, implanted pacemakers do not require replacement, patients with TAVI and SAVR are subject to the same NYHA deterioration rate after 2 years, and utility decrements from complications were experienced for only the first two years The study reports the average CE for TF and TA TAVI approaches (as was the design of PARTNER A; indeed in PARTNER the TF and TA approaches were found to result in quite different QALY gains with TAVI: TA a loss of 0.07 and TF a gain of 0.068) The evaluation did not use the HRQoL scores reported in the PARTNER trial. Utility estimates were derived from differences in NYHA class proportions in the PARTNER trial and HRQoL scores published in a separate study. Utility methods based on disease severity rather than specific clinical outcomes are subject to criticism when				

Fairbairn, T.A.; Meads, D.M.; Hulme, C.; Mather, A.N.; Plein, S.; Blackman, D.J.; Greenwood, J.P. The cost-effectiveness of transcatheter aortic valve implantation versus surgical aortic valve replacement in patients with severe aortic stenosis at high operative risk. FAIRBAIRN2013
more direct sources are available and these show no clear difference between groups. The PARTNER A trial showed no clear difference in HRQoL operable patients who received TAVI versus those who received SAVR Other:
Overall applicability*: Directly Applicable Overall quality: Potentially Serious Limitations**

Abbreviations: AS = aortic stenosis; BAV = balloon aortic valvuloplasty; CI = 95% confidence interval; CUA = cost-utility analysis; ICER = incremental cost-effectiveness ratio; MM = medical management; QALYs =quality-adjusted life years; NYHA = New York Heart Association; SAVR = surgical aortic valve replacement; TAVI = transcatheter aortic valve implantation; TA = transapical; TF = transfemoral; WTP = willingness to pay.

* Directly applicable / Partially-applicable / Not applicable; ** Minor limitations / Potentially serious limitations / Very serious limitations

[#] Baseline characteristics of patients in the PARTNER trial Cohort A

Table 67: Watt 2012

Watt, Maureen; Mealing, Stuart; Eaton, James; Piazza. Cost-effectiveness of transcatheter aortic valve replacement in patients ineligible for conventional aortic valve replacement. WATT2012[180]				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome = QALYs) Study design: Probabilistic decision analytic model Approach to analysis: A 30-day short-term Markov model of 5 health states based on 4 settings of care (ICU, non-ICU, rehabilitation, home, and death). Surviving patient go into a 10-year long-term Markov model of 3 health states (home, re-op and dead). Perspective: UK NHS	Population: Patients with severe aortic stenosis whom surgeons considered ineligible for SAVR. Cohort settings: Mean age = 83 M = 46% Intervention 1: MM including BAV Intervention 2: TAVI (TF)	Total costs (mean per patient, rounded to the nearest £100): Intvn 1: £5,000 (CI: £3,995, £6,005) Intvn 2: £30,200 (CI: £27,828, £32,833) Increment (2-1): £25,200 Currency & cost year: 2010 UK pounds Cost components incorporated:	Primary outcome measure (mean per patient): QALYs Intvn 1: 0.80 (CI: 0.61, 1.02) Intvn 2: 2.36 (CI: 2.19, 2.43) Increment (2-1): 1.56	Primary ICER (Intvn 2 vs Intvn 1): ICER: £16,200 per QALY gained Analysis of uncertainty: There is a reported 100% probability of TAVI being more cost-effective than MM at a cost-effectiveness WTP threshold of £20,000/ QALY. Scenario analyses showed the ICER was insensitive to pooled parameters values from the literature (when retaining the PARTNER survival data, and when using alternative sources for medical management mortality). However, probabilistic sensitivity analysis showed the ICER was sensitive to the length of the time

Watt, Maureen; Mealing, Stuart; Eaton, James; Piazza. Cost-effectiveness of transcatheter aortic valve replacement in patients ineligible for conventional aortic valve replacement. WATT2012[180]				
Time horizon: 10-years Treatment effect duration: 10-years Discounting: Costs = 3.5%; Outcomes = 3.5%		Initial hospitalisation TAVI procedure and device Pace-maker implantation Drug Rehabilitation Readmissions		horizon. TAVI became cost-effective at the £30,000/QALY WTP threshold when extrapolated for 2 years, and cost-effective at the £20,000/QALY WTP threshold when extrapolated for 4 years. Systematic one-way deterministic sensitivity analysis altering individual parameters +/- 10% showed sensitivity to short-term treatment effect, length of time-horizon and cost of the operation. It was robust to hospitalisation cost and adverse event rate.
Data sources				
Health outcomes: Mortality and event probabilities from the PARTNER trial Cohort B[91]. Quality-of-life weights: EQ5D decrements were derived from NYHA class mix from the PARTNER trial and published EQ5D preference weights. Cost sources: The cost of TAVI was taken from a recent UK costing study, the unit cost of drugs from the British National Formulary, Hospital costs from NHS Reference costs, and rehabilitation costs from PSSRU Unit Costs of Health and Social Care.				
Comments				
Source of funding: Medtronic International Trading. Limitations: The PARTNER cohort B RCT provided TAVI and MM effectiveness from a mainly US outcome population/health system and used only the Edwards-Sapien device only (not Medtronic CoreValve); there was also some imbalance in patient characteristics; trial was sponsored by industry; there were a multitude of exclusion criteria which might make it questionable whether this is a representative population; patients did not necessarily have acute heart failure Costs and benefits were extrapolated for the third year to the to the tenth year based on data collected over 2 years of follow-up from the PARTNER B trial Device failure rates were not taken from patients undergoing TAVI but from those receiving standard prosthetic valves (3-year observational data has shown no failures) Other:				
Overall applicability*: Directly Applicable Overall quality: Potentially Serious Limitations**				

Abbreviations: AS = aortic stenosis; BAV = balloon aortic valvuloplasty; CI = 95% confidence interval; CUA = cost-utility analysis; ICER = incremental cost-effectiveness ratio; MM = medical management; QALYs =quality-adjusted life years; NYHA = New York Heart Association; SAVR = surgical aortic valve replacement; TAVI = transcatheter aortic valve implantation; WTP = willingness to pay.

* Directly applicable / Partially applicable / Not applicable; ** Minor limitations / Potentially serious limitations / Very serious limitations

Table 68. Murphy 2013

Murphy, A.; Fenwick, E.; Toff, W.D. Transcatheter aortic valve implantation for severe aortic stenosis: the cost-effectiveness case for inoperable patients in the United kingdom. MURPHY2013[113]				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome = QALYs) Study design: Probabilistic decision analytic model Approach to analysis: A decision tree based on a cost-utility framework for two arms in the 30-day operation period was attached to a Markov model of 1-year cycles for lifetime. Health states were functioning valve replacement, persistent AS and death Perspective: UK NHS Time horizon: Lifetime Treatment effect duration: Lifetime Discounting: Not reported	Population: Patients with severe aortic stenosis whom surgeons considered ineligible for SAVR. Cohort settings: Mean age = 83 M = 46% Intervention 1: MM including BAV Intervention 2: TAVI (TF)	Total costs (mean per patient): Intvn 1: £12,176 Intvn 2: £28,061 Increment (2-1): £15 885 Currency & cost year: UK pounds. Cost year not reported Cost components incorporated: Initial hospitalisation TAVI procedure and device Emergency Care Complications Drugs Rehabilitation Readmissions Nursing home	Primary outcome measure (mean per patient): QALYs Intvn 1: 1.19 Intvn 2: 1.63 Increment (2-1): 0.44 Life Years Intvn 1: 2.24 Intvn 2: 2.54 Increment (2-1): 0.3	Primary ICER (Intvn 2 vs Intvn 1): ICER: £35,956 per QALY gained (CI: £24,768, £65,103) Analysis of uncertainty: There is an 18% probability of TAVI being more cost-effective than MM at the £30,000/QALY WTP threshold (66% at £40,000) The authors report that the uncertainty in the difference in costs is driven by the uncertainty surrounding the probability of procedure related events, a parameter thought to have been reduced in with improved TAVI devices. A scenario analysis found a 25% reduction in TAVI procedure related events reduced the ICER to £23,642/QALY with an associated probability of cost-effectiveness of 83% at £30,000/QALY WTP threshold. Re-Run The model was re-run using newly published 2-year follow-up data from Germany[21]. Using the mortality benefit at the end of the year-1 the resultant ICER = £19,000/QALY.
Data sources				

Murphy, A.; Fenwick, E.; Toff, W.D. Transcatheter aortic valve implantation for severe aortic stenosis: the cost-effectiveness case for inoperable patients in the United kingdom. MURPHY2013[113]
Health outcomes: Mortality from the PARTNER trial Cohort B[91] and event rates pooled from PARTNER B and other literature sources. Quality-of-life weights: Utility decrements were derived from the PARTNER trial Cohort B NYHA class findings using conversion rates from the literature. Cost sources: Mainly UK costs from the PSSRU Unit Costs of Health and Social Care Handbook, the NHS National Schedule of reference costs 2006-7. Also from the literature. The cost of TAVI device = £12,000, and TAVI procedure = £2 003
Comments
Source of funding: Not stated however the reported conflicting interests are insignificant. Limitations: The PARTNER cohort B RCT provided TAVI and MM effectiveness from a mainly US outcome population/health system and used only the Edwards-Sapien device only (not Medtronic CoreValve); there was also some imbalance in patient characteristics; trial was sponsored by industry; there were a multitude of exclusion criteria which might make it questionable whether this is a representative population; patients did not necessarily have acute heart failure Costs and benefits were extrapolated for the third year to the to the lifetime horizon based on data collected over 2 years of follow-up from the PARTNER B trial Other:
Overall applicability*: Directly Applicable Overall quality**: Potentially Serious Limitations

Abbreviations: AS = aortic stenosis; BAV = balloon aortic valvuloplasty; CI = 95% confidence interval; CUA = cost-utility analysis; ICER = incremental cost-effectiveness ratio; MM = medical management; QALYs =quality-adjusted life years; NYHA = New York Heart Association; SAVR = surgical aortic valve replacement; TAVI = transcatheter aortic valve implantation; TF = transfemoral; WTP = willingness to pay.

* Directly applicable / Partially applicable / Not applicable; ** Minor limitations / Potentially serious limitations / Very serious limitations

Table 69. Orlando 2013

Orlando, R.; Pennant, M.; Rooney, S.; Khogali, S.; Bayliss, S.; Hassan, A.; Moore, D.; Barton, P. . Cost-effectiveness of transcatheter aortic valve implantation (TAVI) for aortic stenosis in patients who are high risk or contraindicated for surgery: a model-based economic evaluation. ORLANDO2013				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome = QALYs) Study design: Probabilistic decision analytic model Approach to analysis: Estimates cost effectiveness	Secondary analysis Population: Patients with aortic stenosis deemed unsuitable for SAVR	Secondary analysis Total costs (mean per patient): Intvn 1: £3,687 Intvn 2: £27,833 Increment (2-1): £24 147	Secondary analysis Primary outcome measure (mean per patient): QALYs Intvn 1: 0.981 Intvn 2: 2.853	Secondary analysis ICER (Intvn 2 vs Intvn 1): ICER: £12,900 per QALY gained Analysis of uncertainty: Not reported. The exploration of uncertainty focussed on the

Orlando, R.; Pennant, M.; Rooney, S.; Khogali, S.; Bayliss, S.; Hassan, A.; Moore, D.; Barton, P. . Cost-effectiveness of transcatheter aortic valve implantation (TAVI) for aortic stenosis in patients who are high risk or contraindicated for surgery: a model-based economic evaluation. ORLANDO2013				
of TAVI being available versus not available (policy perspective) in the primary analysis. A secondary analysis compared TAVI to MM in patients unsuitable for surgery: A Markov cohort simulation was used to total costs and benefits for resultant the long-term using two health states: Hospital-free survival and Other survival. Cycle length was 1 month. Perspective: UK NHS Time horizon: 25-years Treatment effect duration: 10-years Discounting: Costs = 3.5%; Outcomes = 3.5%	Cohort settings#: Mean age = Unclear but >80 Male = % not reported Intervention 1: MM Intervention 2: TAVI (TF or TA)	Currency & cost year: 2010 UK pounds Cost components incorporated: Initial hospitalisation TAVI procedure TAVI device Adverse events Medicines inc. long term Outpatient visits Readmissions Rehabilitation costs were not included	Increment (2-1): 1.872	primary analysis (the policy strategies) in which 90% of patients are eligible for surgery (low to high risk) and 10% receive MM. However, this scenario is also found to be cost effective (with a PSA probability of 99%) which adds validity to this secondary finding.
Data sources				
Health outcomes: PARTNER trial Cohort B (RCT) for effectiveness of TAVI versus MM (2 year follow-up). As the evaluation preceded the publication of PARTNER A, other data sources for effectiveness of TAVI versus SAVR (Wendt et al. 2009, Leontyev et al 2009). Quality-of-life weights: A Dutch study of health related quality of life by NYHA class in TAVI patients using EQ5D and SF36. Cost sources: UK costing perspective: NHS national schedule of reference costs. The cost of the TAVI procedure (including device) = £24,000				
Comments				
Source of funding: NIHR HTA programme Limitations: The PARTNER cohort B RCT provided TAVI and MM effectiveness from a mainly US outcome population/health system and used only the Edwards-Sapien device only (not Medtronic CoreValve); there was also some imbalance in patient characteristics; trial was sponsored by industry; there were a multitude of exclusion criteria which might make it questionable whether this is a representative population; patients did not necessarily have acute heart failure				

Orlando, R.; Pennant, M.; Rooney, S.; Khogali, S.; Bayliss, S.; Hassan, A.; Moore, D.; Barton, P. . Cost-effectiveness of transcatheter aortic valve implantation (TAVI) for aortic stenosis in patients who are high risk or contraindicated for surgery: a model-based economic evaluation. ORLANDO2013
The effectiveness TAVI and SAVR in inoperable patients was not sourced from a random controlled trial Costs and benefits were extrapolated for the third to the tenth year based on data collected over 2 years of follow-up in the PARTNER trial – it was assumed that the TAVI valves function without failure for the lifetime of the patient, implanted pacemakers do not require replacement, patients with TAVI and SAVR are subject to the same NYHA deterioration rate after 2 years, and utility decrements from complications were experienced for only the first two years The evaluation averages the costs and benefits for TF and TA TAVI approaches. The PARTNER A trial found the TF and TA approaches resulted in quite different QALY gains with TAVI: TA a loss of 0.07 and TF a gain of 0.068 The evaluation did not use the HRQoL scores reported in the PARTNER trial. Utility estimates were derived from differences in NYHA class proportions in the PARTNER trial and HRQoL scores published in a separate study. Utility methods based on disease severity rather than specific clinical outcomes are subject to criticism when more direct sources are available and these show no clear difference between groups. The PARTNER trials showed higher HRQoL in inoperable patients who received TAVI versus MM, but no clear difference in operable patients versus surgery. Other:
Overall applicability*: Directly Applicable Overall quality**: Potentially Serious Limitations

Abbreviations: AS = aortic stenosis; BAV = balloon aortic valvuloplasty; CI = 95% confidence interval; CUA = cost-utility analysis; HRQoL = health related quality of life; ICER = incremental cost-effectiveness ratio; MM = medical management; QALYs =quality-adjusted life years; NYHA = New York Heart Association; SAVR = surgical aortic valve replacement; TAVI = transcatheter aortic valve implantation; TA = transapical; TF = transfemoral; WTP = willingness to pay.

* Directly applicable / Partially applicable / Not applicable; ** Minor limitations / Potentially serious limitations / Very serious limitations

[#] Baseline characteristics of patients in the PARTNER trial Cohort B

H.5 Mitral regurgitation

Table 70. Orlando 2013

Mealing, S; Feldman, E; Eaton, J; Singh, M; Scott, D. EVEREST II high risk study based UK cost-effectiveness analysis of MitraClip in patients with severe mitral regurgitation ineligible for conventional repair/replacement surgery. MEALING2013				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome = QALYs) **Study design:** Probabilistic decision analytic model comparing MitraClip to medical management **Approach to analysis:**	**Population:** Patients with severe MR who are ineligible for conventional surgical repair or at high surgical risk (>12% mortality)	**Total costs (mean per patient):** Intvn 1: £4 610 Intvn 2: £31 593 Increment (2-1): £26 989 **Currency & cost year:**	**Primary outcome measure (mean per patient):** QALYs Intvn 1: 0.62 Intvn 2: 1.84 Increment (2-1): 1.22	**Primary ICER (Intvn 2 vs Intvn 1):** ICER: £22 153 per QALY gained (5 year time horizon) **Secondary ICERs** 2 year time horizon: ICER = £49 917 per QALY gained

Mealing, S; Feldman, E; Eaton, J; Singh, M; Scott, D. EVEREST II high risk study based UK cost-effectiveness analysis of MitraClip in patients with severe mitral regurgitation ineligible for conventional repair/replacement surgery. MEALING2013				
Estimate of cost effectiveness from a two part markov model of short term (30 days) and long term costs, utility and survival. Living health states were Hospital care, Rehabilitation, Home, and MV surgery. Patients started in either an Intervention state or the Home state according to strategy. Cycle lengths were 1 day and 1 month. **Perspective:** UK NHS **Time horizon:** 5 years **Treatment effect duration:** 5 years **Discounting:** Costs = 3.5%; Outcomes = 3.5%	**Cohort settings:** Mean age = 77 years M = 63% **Intervention 1:** Conventional medical management (MM) **Intervention 2:** Percutaneous valvular intervention using MitraClip	2011 UK pounds **Cost components incorporated:** Initial hospitalisation Percutaneous procedure Device (£20 000) Adverse events Medicines inc. long term Readmissions Outpatient costs appear not to be included		10 year time horizon ICER = 13 664 per QALY gained Note the analysis predicted a lifetime survival of 1.9 years in the MM arm and 5.1 years in the intervention arm **Analysis of uncertainty:** A probabilistic sensitivity analysis found the probability of MitraClip being cost effective versus MM to be 37% and 93% at £20 000 and £30 000 thresholds respectively. A deterministic sensitivity analysis showed the base case (5 year) ICER to be sensitive to choice of time horizon, NYHA utility decrements, and the cost of the interventional procedure
Data sources				
Health outcomes: The EVEREST II High Risk Registry Study for effectiveness of MitraClip (single armed cohort study). The outcomes of patients from EVEREST II (United States, n=78) and a concurrent control group receiving conventional medical management (United States, n=36) were reported together by Whitlow *et al*. 2012. **Quality-of-life weights:** From a representative UK sample of patients, applying decrements according to NYHA class. **Cost sources:** Resource utilisation was based on the EVEREST II HRS for MitraClip patients and literature sources for MM patients, but a UK perspective was taken to unit costing: NHS national schedule of reference costs. Expert opinion was elicited for some parameters including the extent of use of background medication.				
Comments				
Source of funding (of evaluation): Abbott Vascular (Manufacturer) and Oxford Outcomes Ltd (Consultancy) **Limitations:** 1. Based on a single arm study compared to a concurrent control, both studies were small in size, and the follow-up was only 12 months 2. All the time horizons presented were reliant on the parametric extrapolation of survival estimates **Other:**				

Mealing, S; Feldman, E; Eaton, J; Singh, M; Scott, D. EVEREST II high risk study based UK cost-effectiveness analysis of MitraClip in patients with severe mitral regurgitation ineligible for conventional repair/replacement surgery. MEALING2013	
Overall applicability*: Directly Applicable	**Overall quality**: Very Serious Limitations**

a) Abbreviations: CI = 95% confidence interval; CUA = cost-utility analysis; HRS = High risk registry study; ICER = incremental cost-effectiveness ratio; MM = medical management; MR = mitral regurgitation; QALY =quality-adjusted life year; NYHA = New York Heart Association;

b) Directly applicable / Partially-applicable / Not applicable; ** Minor limitations / Potentially serious limitations / Very serious limitations

H.6 Mechanical assist devices

Table 71: Moreno 2012

Moreno SG, Novielli N, Cooper NJ. Cost-effectiveness of the implantable HeartMate II left ventricular assist device for patients awaiting heart transplantation. *J.Heart Lung Transplant.* 31 (5):450-458, 2012				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:** A Markov model of monthly cycles estimates survival, utility and resource use of LVADS as a bridge to transplant versus MM. Both strategies used a 3-health state model structure: LVAD/MM-HT-death	**Population:** Patients with ESHF, who were urgent listed cardiac transplant candidates at risk of imminent death from non-reversible left ventricular failure **Cohort settings:** Start age: 50 Male: NR **Intervention 1:** MM as BTT **Intervention 2:**	**Total cost (mean per patient):** Intvn 1: £208 444 Intvn 2: £350 939 Increment (2-1): £142 495 (CI: £116 413, £168 578) **Currency & cost year:** 2011 UK pounds **Cost components incorporated:** LVAD LVAD implantation Post-LVAD implantation care costs Medical management HT	**QALYs (mean per patient):** Intvn 1: 6.38 Intvn 2: 6.93 Increment (2-1): 0.55 (CI: -0.01, 1.11)	**ICER (Intvn 2 versus Intvn 1):** £258 922 per QALY gained (pa) (CI: £140 000, £980 000) **Analysis of uncertainty:** Deterministic sensitivity analysis showed the ICER is driven by incremental life years gained whilst implanted with the LVAD, and device acquisition cost: a) when the bridging interval was extended to 12 months and 18 months, the ICER point estimate decreased to £178 829 and £133 860 per QALY gained, respectively b) when the acquisition cost was reduced to £0 the ICER decreased to £85,897 after 6 months bridging and £24,063 after 18 months bridging

Perspective: UK NHS **Time horizon:** Lifetime **Treatment effect duration[(a)]:** 6 months (the mean bridging period) **Discounting:** Costs: 3.5%; Outcomes: 3.5%	LVAD as BTT (Second generation: HeartMate II)	assessment Peri- and Post-HT care cost		

Data sources

Health outcomes: The survival of patients whilst listed for transplant for LVAD patients was based on an uncontrolled prospective multicentre 18-month US study of HeartMate II in 281 patients (Pagani2009[130]): patients with heart failure who were on a waiting list for heart transplant were required to have NYHA class IV and be ill enough to have high priority for transplantation (UNOS 1a or 1b). The mean waiting time for heart transplant in the base case (in the UK) was 6 months. The comparative survival data for medically managed patients was taken from patients waiting for transplant who were listed in the US registry of Transplant Recipients of UNOS status 1a or 1b. (Lietz2007[93]: the latest published survival rates at the time were 76%, 69% and 63% at 6, 12 and 18 months respectively). Post-transplant survival was assumed to be identical in both strategies, with estimates taken from a US observational study (Russo2009[150]). **Quality-of-life weights: :** From Sharples *et al* UK HTA 2006 (EQ5D from patients and using a UK tariff). **Cost sources:** From Sharples *et* al. UK HTA 2006 (UK perspective: Hospital financial records, NHS reference costs, PSSRU, BNF, UK cost studies, expert opinion for some resource use estimates)

Comments

Source of funding: Not reported. There were no commercial conflicts of interest.

Limitations:

1. Estimates of effectiveness were not taken from RCT evidence. Evidence from the REMATCH RCT suggests VAD implantation improves survival in patients ineligible for transplant; the observational data used here echos this outcome in patients eligible for transplant
2. RCT evidence was not available to inform the choice of correct comparator population
3. The on-going long-term cost of supporting patients with modern VADs is uncertain, in particular the cost of adverse events experienced by recipients of newer generation VADs
4. Survival estimates beyond the observed were reliant upon extrapolation, leading to uncertainty over transition probabilities in the long-term
5. The model does not incorporate the potential benefit of LVADs post-transplantation (theory supports some organ protection from LVADs relative to MM)
6. The probability of transplant was equal in the base case analysis whereas in reality LVAD patients wait considerably longer. Extending the VAD bridging period reduces the comparative cost of MM and yields more QALYs compared to VADs, therefore the base case contain bias in the direction of VADs
7. The survival estimate applied to medically managed patients may overestimate true survival owing to 7% of registry patients receiving LVAD implantation

Other: The design of the economic model in this evaluation was based on that reported in a previous evaluation by Sharples *et al.*[162] A recent study (Starling 2011[165]) reported better survival in LVAD patients than used in this model, which the authors explain may be due to the gathering of experience. However, it is suggested here that the improvement is due to the inclusion patients who were less ill.

Overall applicability[(b)]: Partially applicable	Overall quality[0]: Potentially serious limitations

Abbreviations: BNF: British National Formulary; BTT: bridge to transplant; CI: 95% confidence interval; CUA: cost–utility analysis; da: deterministic analysis; ESHF: end-stage heart failure; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health]; <0.0 means worse than death); HT: heart transplant; ICER: incremental cost-effectiveness ratio; ICU: intensive care unit; LVAD: left-ventricular assist device; MM: medical management; NR: not reported; pa: probabilistic analysis; PSSRU: Personal Social Services Research Unit; QALYs: quality-adjusted life years; SAEs: serious adverse events; UK: United Kingdom; US: United States of America

a) All patients underwent heart transplant after 6 months, the 'treatment period', which is the mean heart transplant waiting time in the UK. After this period and until the end of the time horizon the probability of survival for both implanted and non-implanted patients was assumed to be the same
b) Directly applicable / Partially applicable / Not applicable
c) Minor limitations / Potentially serious limitations / Very serious limitations

Table 72: Sutcliffe 2013

Sutcliffe P, Connock M, Pulikottil-Jacob R, Kandala N-B, Suri G, Gurung T, et al. Clinical effectiveness and cost-effectiveness of second- and third-generation left ventricular assist devices as either bridge to transplant or alternative to transplant for adults eligible for heart transplantation: systematic review and cost-effectiveness model. *Health Technol Assess* 2013; 17(53)

Study details	Population & interventions	Costs	Health outcomes	Cost effectiveness
Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:** A Markov model of 1 month cycles was used to estimate survival, utility and resource use of VADS as a bridge to transplant versus MM. Both strategies used a 3-	**Population:** UK patients with ESHF on eligible for HT. MM patients on inotrope medication **Intervention 1** MM as BTT **Intervention 2** LVAD as BTT (~40% second and ~60% third generation devices) **Cohort settings:** Start age: 51 (BTT)	**Total costs (mean per patient):** Intvn 1: £112 802 Intvn 2: £240 193 Increment (2-1): £127 391 **Currency & cost year:** 2010/11 UK pounds **Cost components incorporated:** LVAD LVAD implantation Post-LVAD implantation care costs Medical management HT	**QALYs (mean per patient):** Intvn 1: 1.94 Intvn 2: 4.32 Increment (2-1): 2.38 **Life years (mean per patient):** Intvn 1: 2.67 Intvn 2: 5.46 Increment (2-1): 2.79	**ICER (Intvn 2 versus Intvn 1):** ICER: £53 527 per QALY gained (CI: £31 802, £94 853) **Analysis of uncertainty:** A DSA of costs, utilities and probability of death and HT found the base case ICER was robust under a range of conditions. The model inputs most influential in affecting the ICER were: 1. The choice of inotrope BTDB patients as the comparator population 2. The equal probability of receiving a donor heart for VAD and MM groups 3. Cost of lifetime treatment for BTT 4. Cost of the VAD

health state model structure: Alive with VAD/MM-Alive after HT-death **Perspective:** UK NHS **Time horizon:** Lifetime **Treatment effect duration:** Median time to HT: 4.8 months **Discounting:** Costs: 3.5%; Outcomes: 3.5%	Male: 84% (BTT)	assessment Peri- and Post-HT care cost		To bring the ICER to £30 000 per QALY would require a reduction in device cost of 76% **'End-of-Life' ICER (Calculated by NCGC)** ICER = (Cost Intvn2 – Cost Intvn1)/(LYs Intvn2 – QALYs Intvn1) = £36 190
Data sources				
Health outcomes: NHS BTDB (both arms). **Quality-of-life weights:** From Sharples *et al* UK HTA 2006 (EQ5D from patients and using a UK tariff). **Cost sources:** Based on Sharples *et* al. UK HTA 2006 (UK perspective: Hospital financial records, NHS reference costs, PSSRU, BNF, UK cost studies, expert opinion for some resource use estimates) with appropriate cost updates				
Comments				
Source of funding: This was a UK NHS R&D HTA. **Limitations:** 1. Estimates of effectiveness were not taken from RCT evidence. Evidence from the REMATCH RCT suggests VAD implantation improves survival in patients ineligible for transplant; the observational data used here echos this outcome in patients eligible for transplant 2. RCT evidence was not available to inform the choice of correct comparator population 3. The on-going long-term cost of supporting patients with modern VADs is uncertain, in particular the cost of adverse events experienced by recipients of newer generation VADs 4. The BTDB did not report HRQoL so values according to NYHA class were derived from the literature and fitted to NYHA proportions in each health state 5. The model does not incorporate the potential benefit of LVADs post-transplantation; theory supports some organ protection from LVADs relative to MM 6. The probability of transplant was equal in the base case analysis whereas in reality LVAD patients wait considerably longer (reported as 45 versus 3.25 months). Extending the LVAD bridging period reduces may yield more QALYs for MM compared to LVADs, therefore the base case contain bias in the direction of LVADs **Other:** The design of the economic model in this evaluation was based on that reported in a previous evaluation by Sharples *et al.*[162]				
Overall applicability[(a)]: Partially applicable Overall quality[0]: Potentially serious limitations				

Abbreviations: ATT = alternative to transplant; BNF: British National Formulary; BTDB = blood and transplant database; BTT: bridge to transplant; CI: 95% confidence interval; CUA: cost–utility analysis; da: deterministic analysis; ESHF: end-stage heart failure; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health]; <0.0 means worse than death); HT: heart transplant; ICER:

incremental cost-effectiveness ratio; ICU: intensive care unit; LVAD: left-ventricular assist device; MM: medical management; NR: not reported; pa: probabilistic analysis; PSSRU: Personal Social Services Research Unit; QALYs: quality-adjusted life years; SAEs: serious adverse events; UK: United Kingdom; US: United States of America

(a) All patients underwent heart transplant after 6 months, the 'treatment period', which is the mean heart transplant waiting time in the UK. After this period and until the end of the time horizon the probability of survival for both implanted and non-implanted patients was assumed to be the same

(b) Directly applicable / Partially applicable / Not applicable

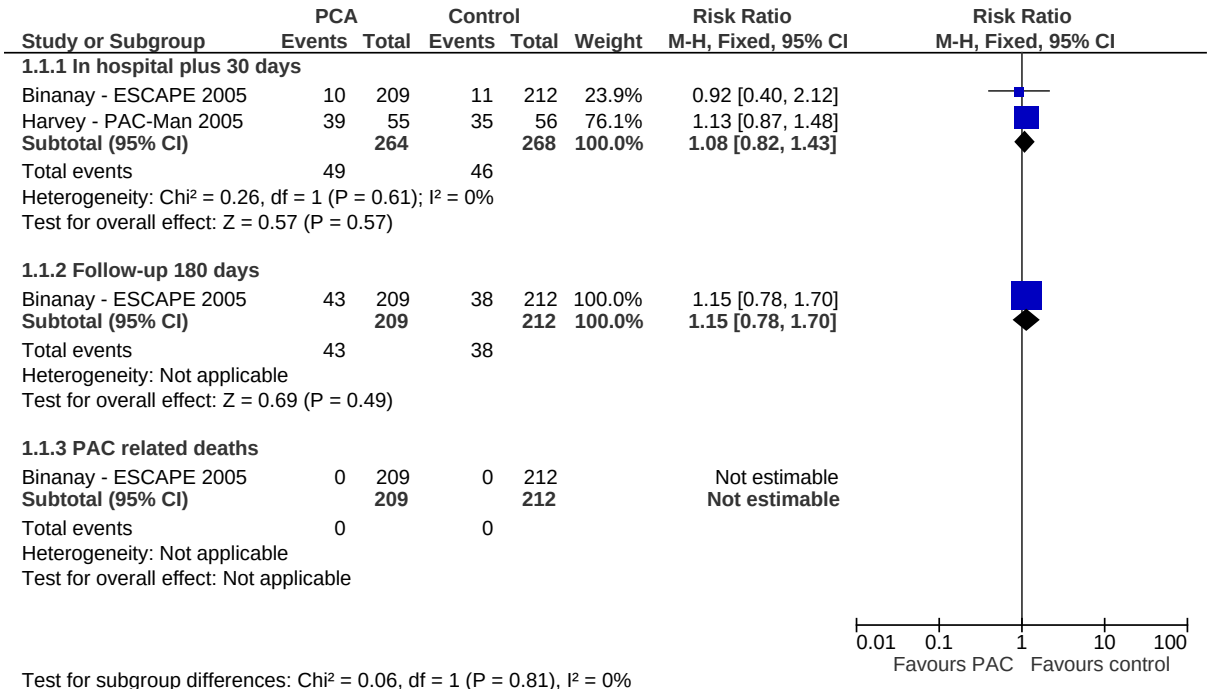
Minor limitations / Potentially serious limitations / Very serious limitations

Appendix I: Forest plots

I.1 Diagnosis, assessment and monitoring

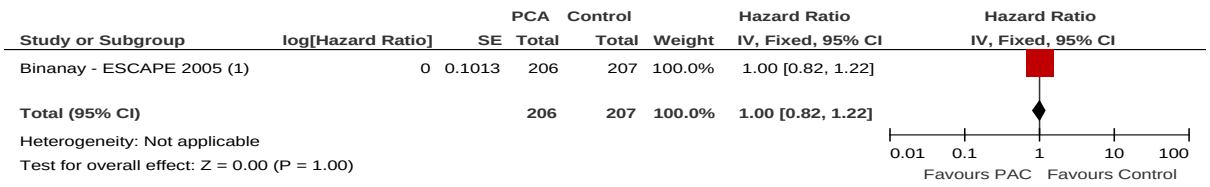
I.1.1 Invasive monitoring

I.1.1.1 Pulmonary artery catheterization vs. clinical assessment



Test for subgroup differences: Chi² = 0.06, df = 1 (P = 0.81), I² = 0%

Figure 19: Days alive and out of hospital



(1) Mean days alive and out of hospital PAC 133 and Control 135

Figure 20: In-hospital mortality –registry data

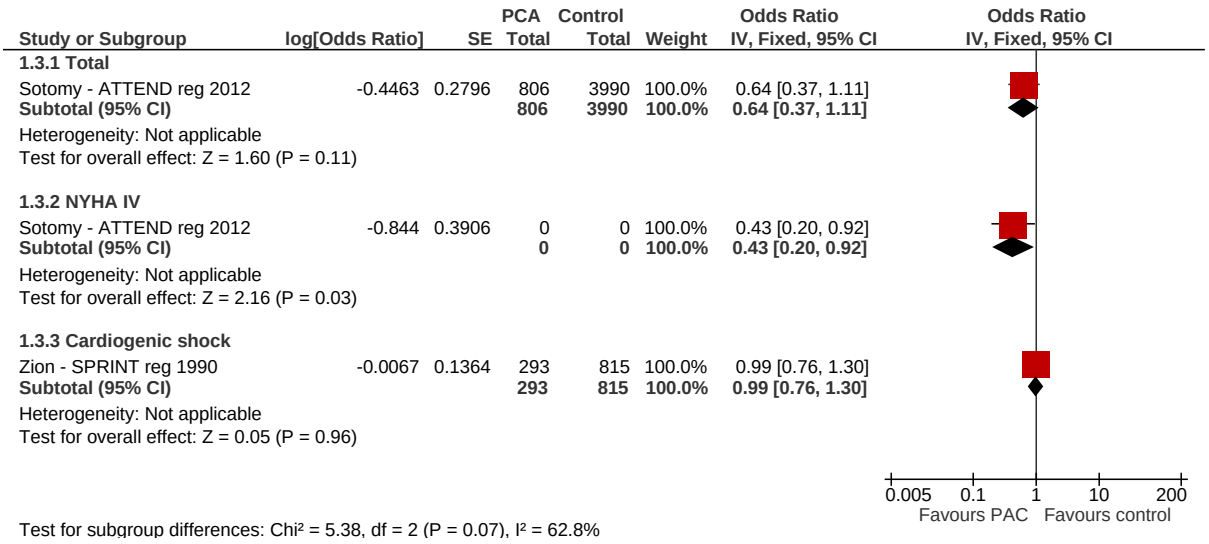


Figure 21: Health related quality of life: Minnesota Living with Heart Failure questionnaire and Time trade-off score (Figure adapted from the Escape trial publication)

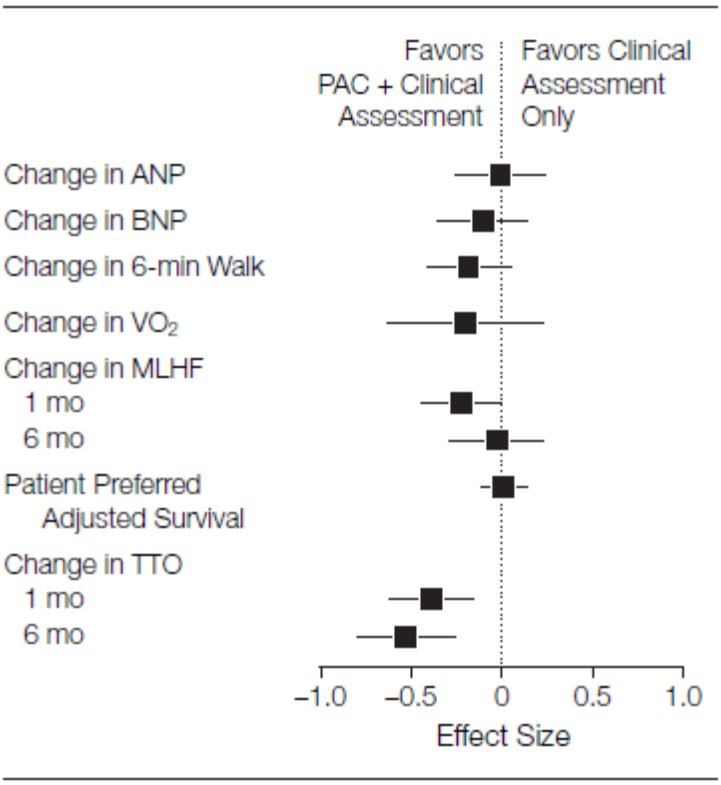


Figure 22: Serious adverse events

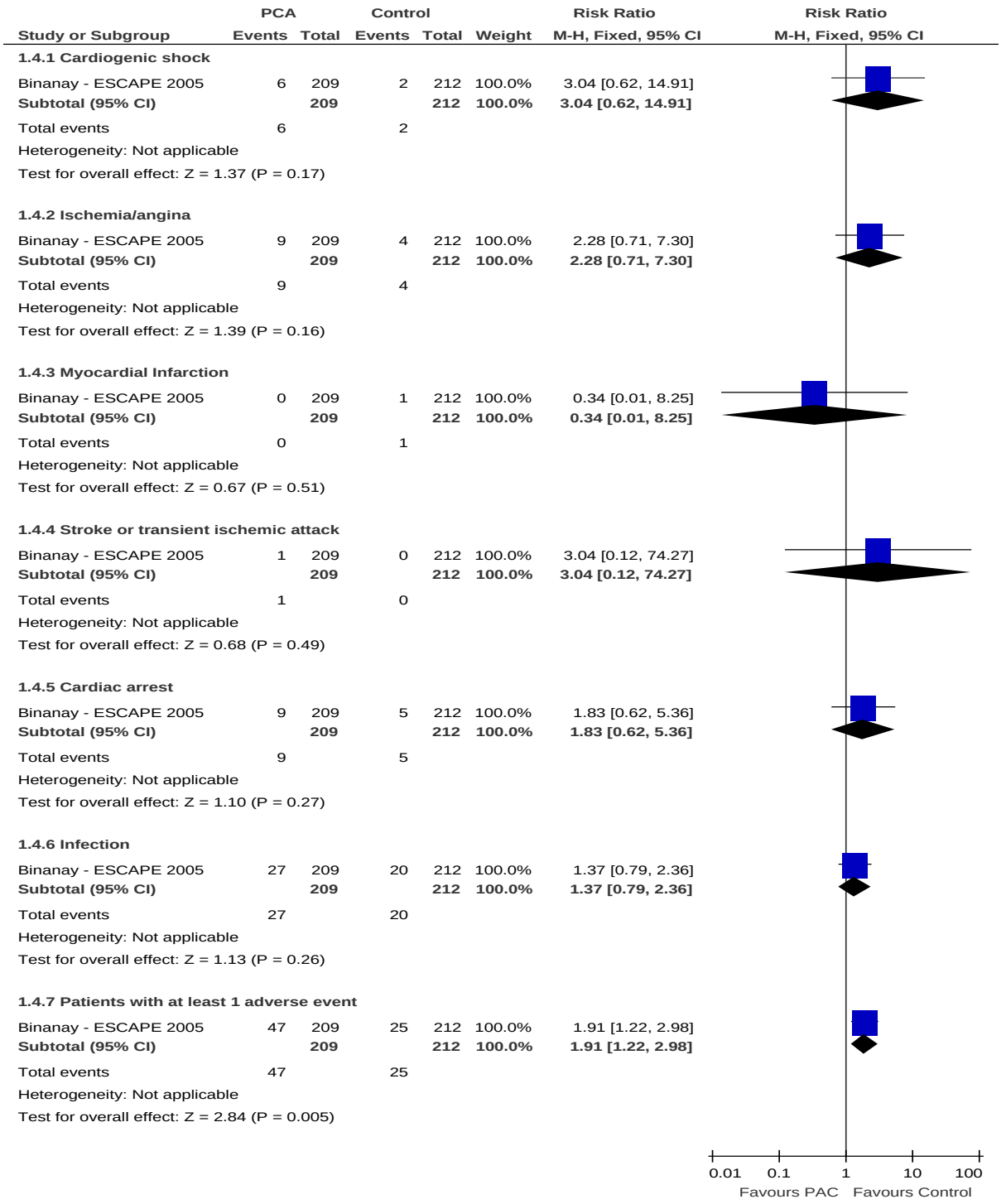
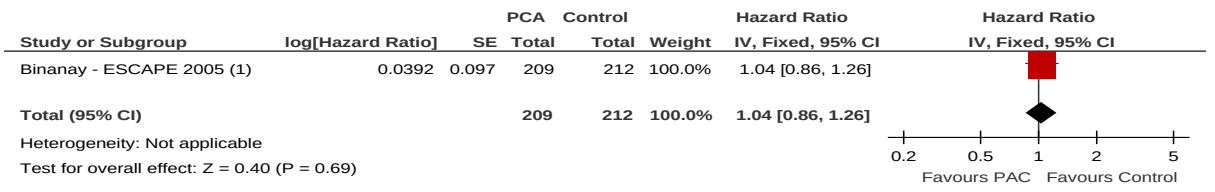
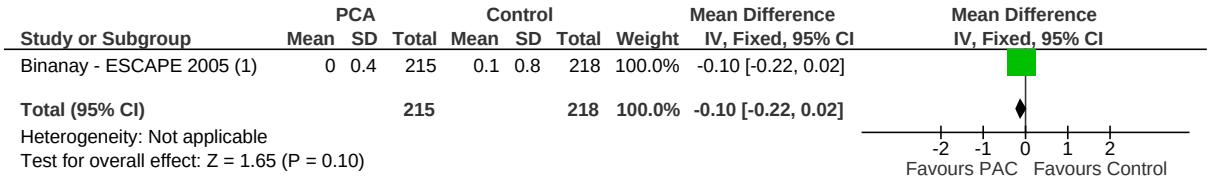


Figure 23: Initial hospitalisation



(1) Mean days of initial hospitalisation: PAC 8.7 / Control 8.3

Figure 24: Serum creatinine level – change from baseline



(1) Numbers represent change from baseline

I.2 Initial pharmacological treatment

I.2.1 Opiates

Figure 25: In hospital and 30-day mortality - Iakobishvili 2011[77]

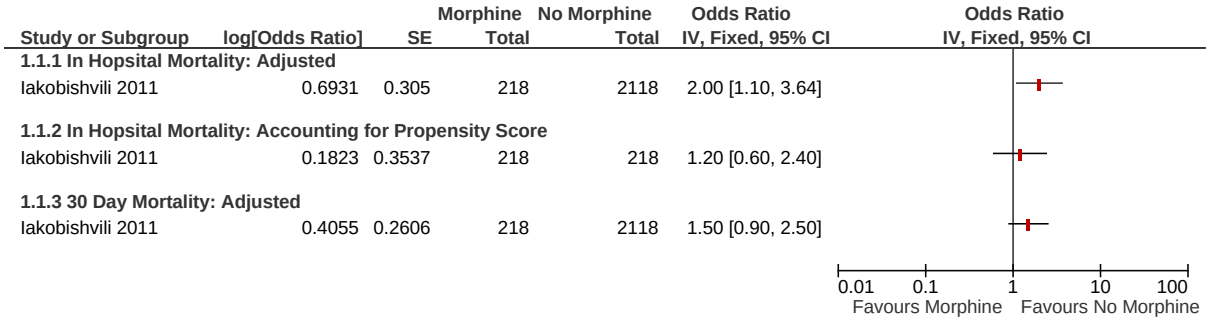


Figure 26: Mortality - Peacock 2008[135]

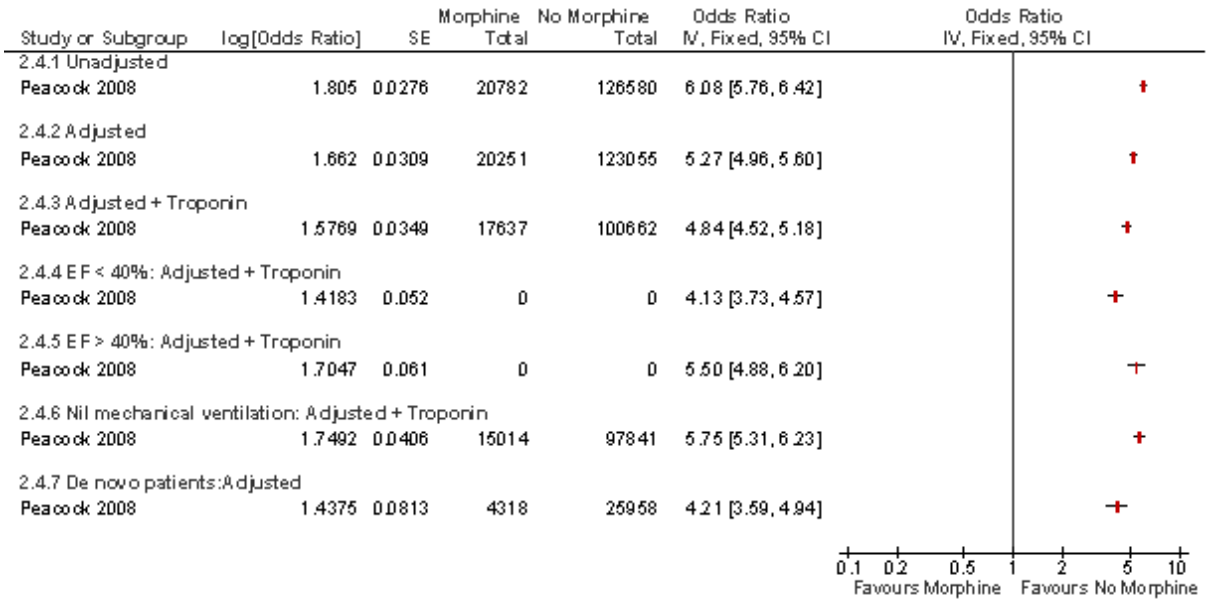


Figure 27: Mortality - Gray 2010[66]

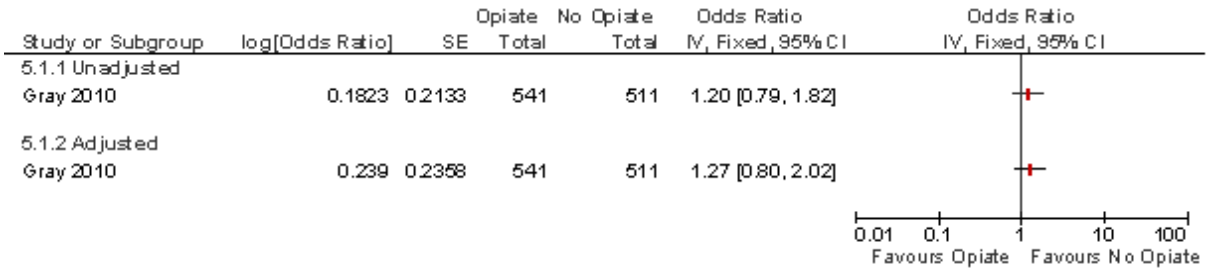


Figure 28: Number of patients progressing to mechanical ventilation - Peacock 2008[135]

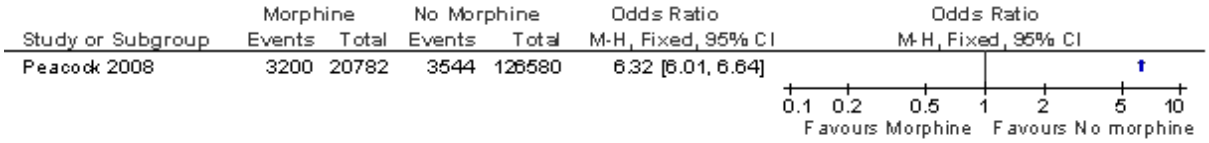


Figure 29: Number of patients progressing to mechanical ventilation - Sacchetti 1999[151]

Figure 30: Number of patients admitted to intensive care unit (ICU) - Peacock 2008[135]

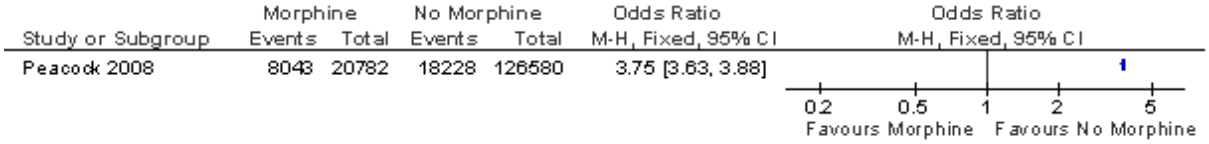
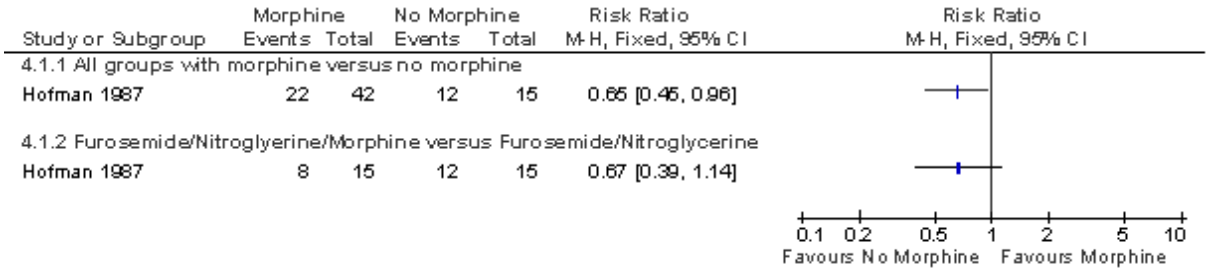


Figure 31: Number of patients admitted to ICU - Sacchetti 1999[151]

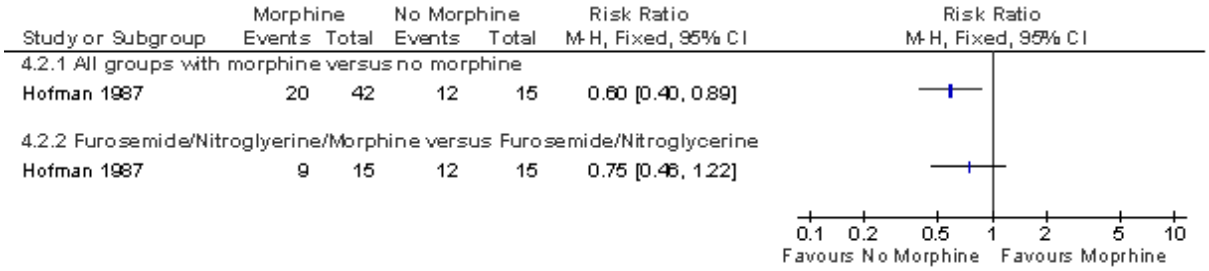
1

Figure 32: Number of patients subjectively reporting an improvement in symptoms - Hoffman 1987[75]



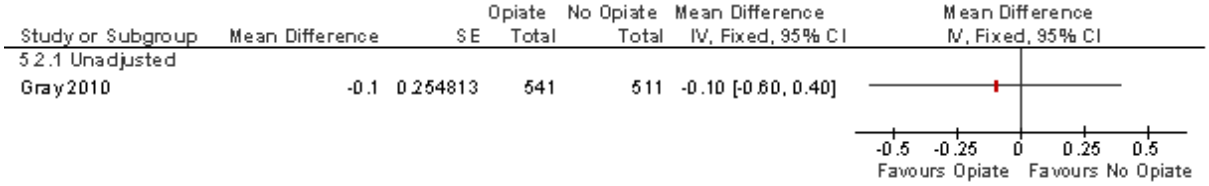
2

Figure 33: Number of patients objectively improved in symptoms - Hoffman 1987[75]



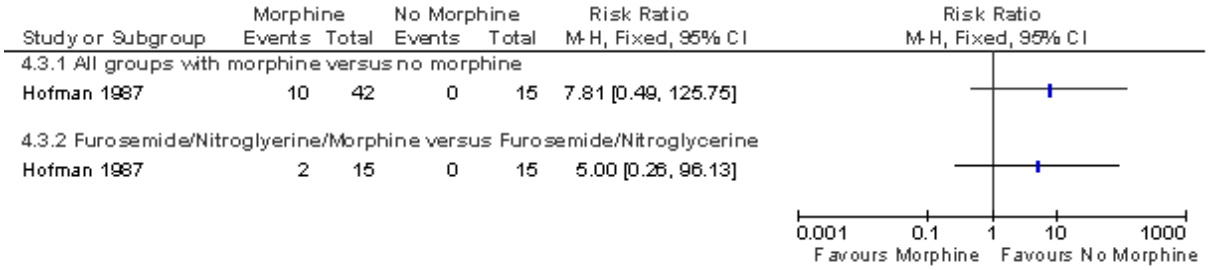
3

Figure 34: Change from baseline in dyspnoea- Gray 2010[66]



4

Figure 35: Number of patients with possible serious adverse events in first hour since therapy - Hofman 1987[75]



I.2.2 Diuretics

I.2.2.1 IV furosemide bolus versus IV furosemide infusion

Figure 36: All-cause mortality at 60 days

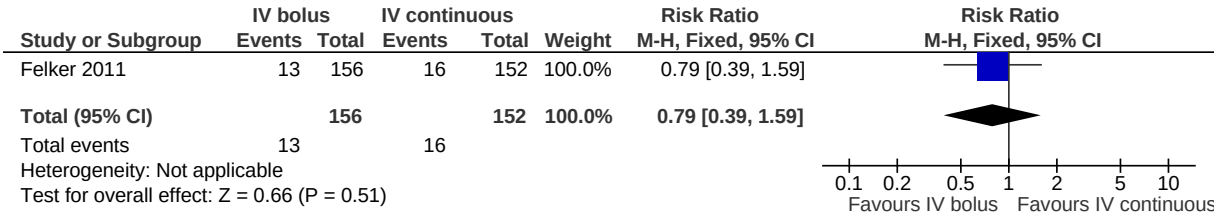


Figure 37: Rehospitalisation at 60 days

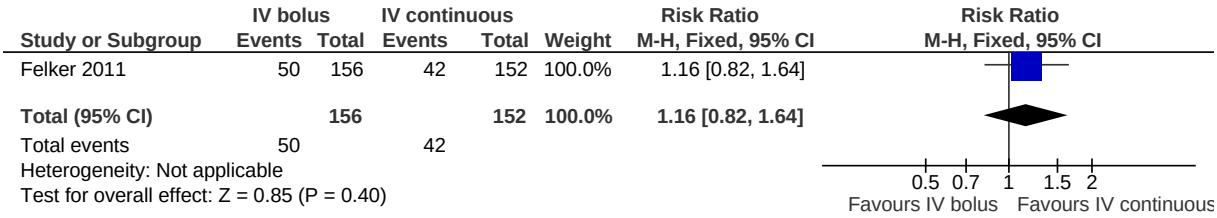


Figure 38: Number of patients visiting the ED at 60 days

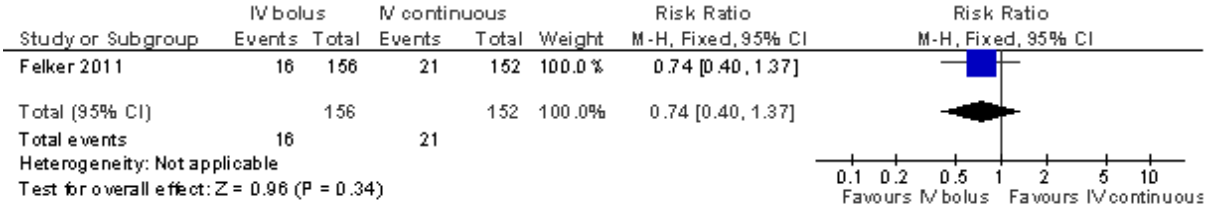


Figure 39: Area under curve (AUC) for dyspnoea at 72 hours

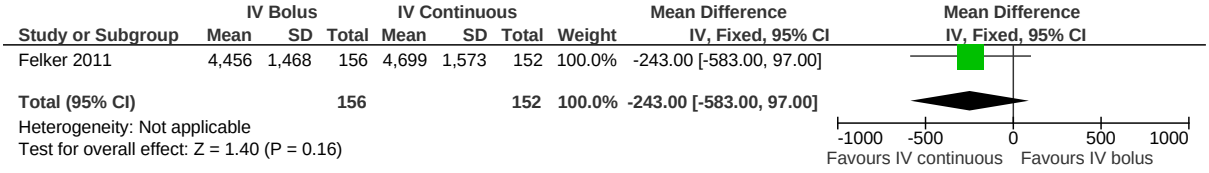


Figure 40: Weight loss (kg) at 72 hours or discharge

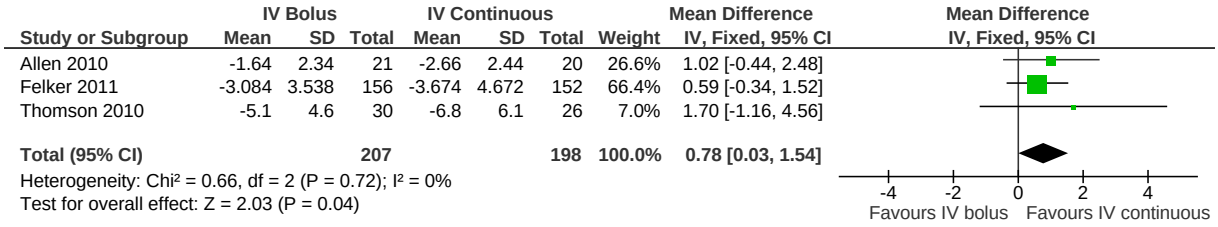


Figure 41: Length of hospital stay (days)

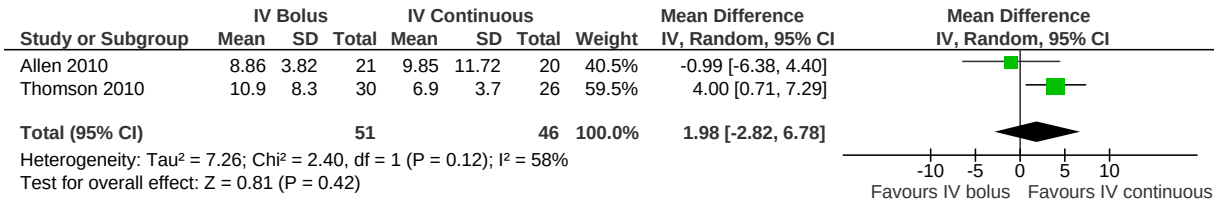


Figure 42: Total Urine Output (ml) 24-72 hours or discharge

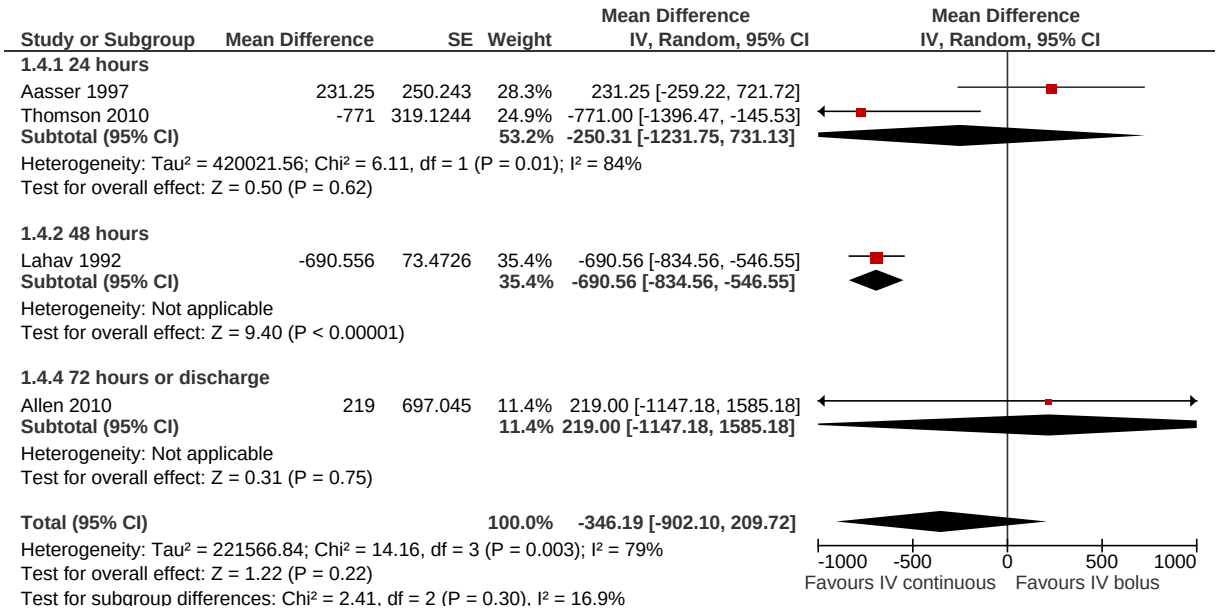


Figure 43: Net Urine Output (ml) 24-72 hours

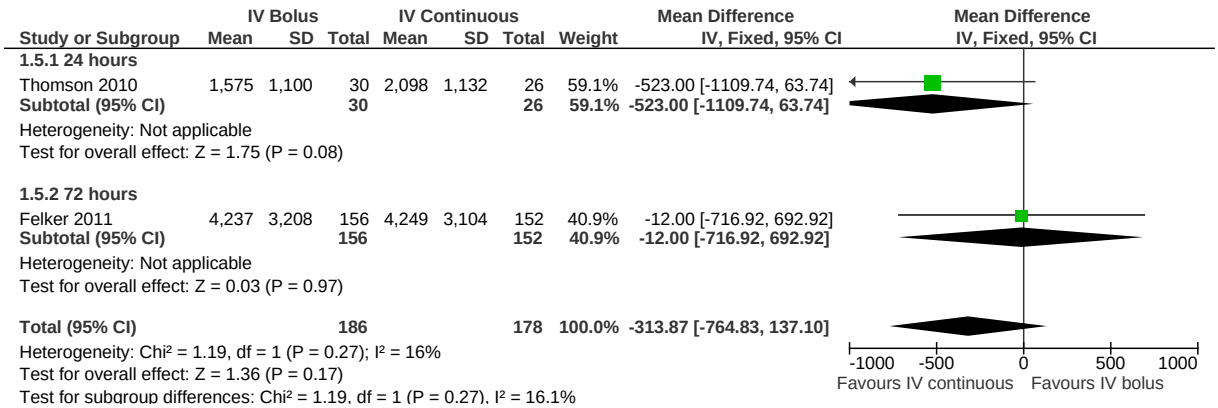


Figure 44: Change in serum creatinine (mg/dl) from baseline at 72 hours or discharge

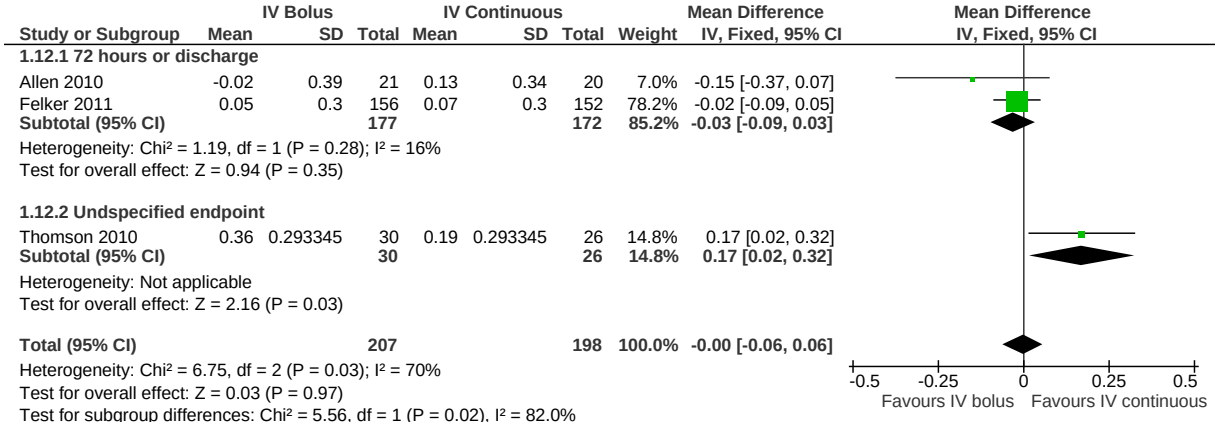


Figure 45: Total number of patients with an increase in serum creatinine of > 0.3mg/dL at 72 hours

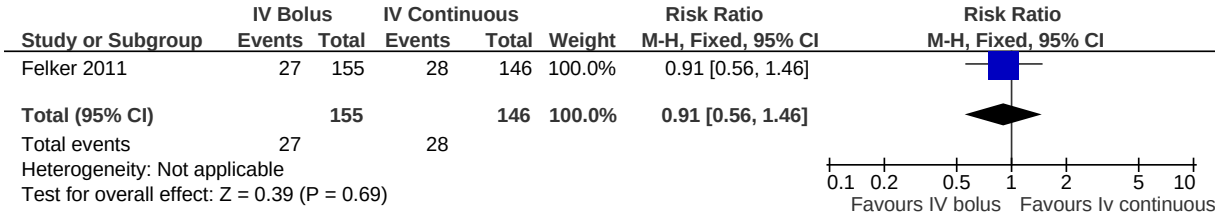


Figure 46: Total number of patients with an increase in serum creatinine of > 0.5mg/dL at unspecified endpoint

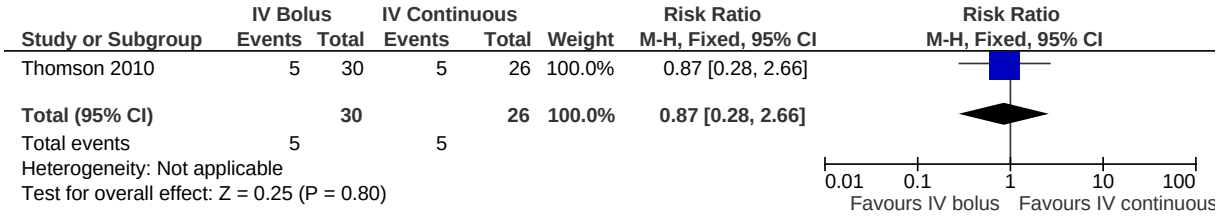


Figure 47: Total number of patients with any SAE at 60 days

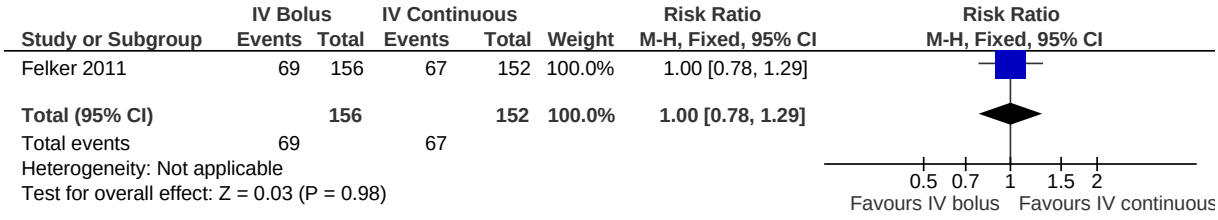


Figure 48: Total number of patients with ventricular tachycardia at 60 days

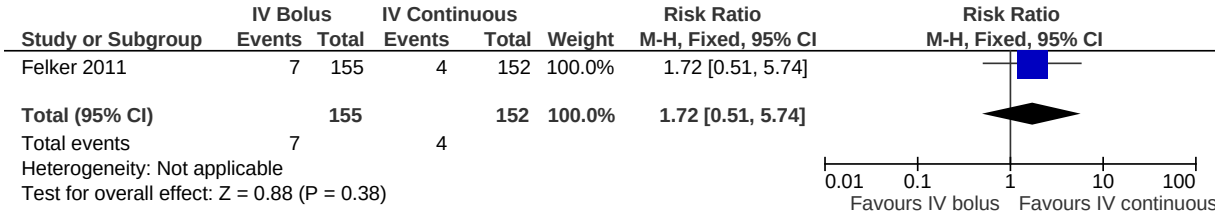
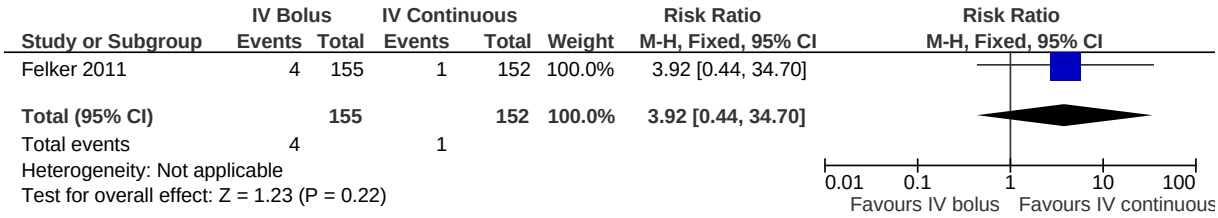


Figure 49: Total number of patients with a new myocardial infarction at 60 days



I.2.2.2 IV furosemide bolus versus IV furosemide infusion with HSS

Figure 50: All cause mortality at 1-48 months

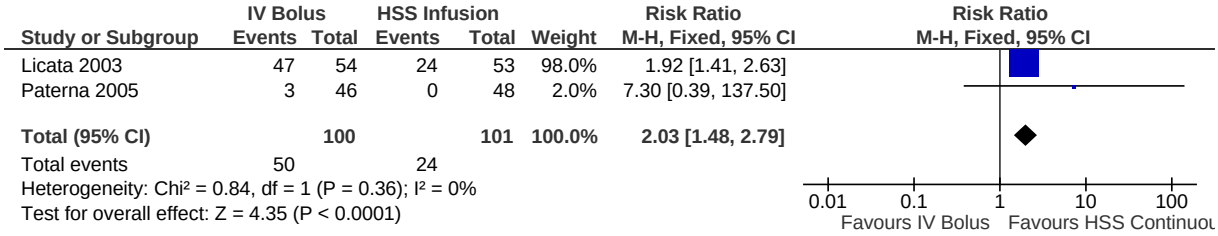


Figure 51: All cause mortality: Hazard ratio at 48 months

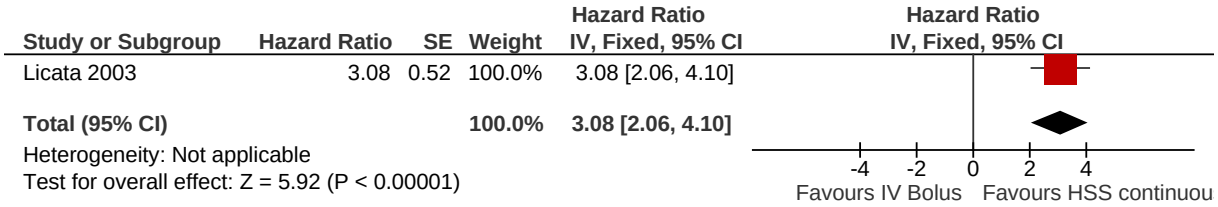


Figure 52: Cardiac mortality at 48 weeks

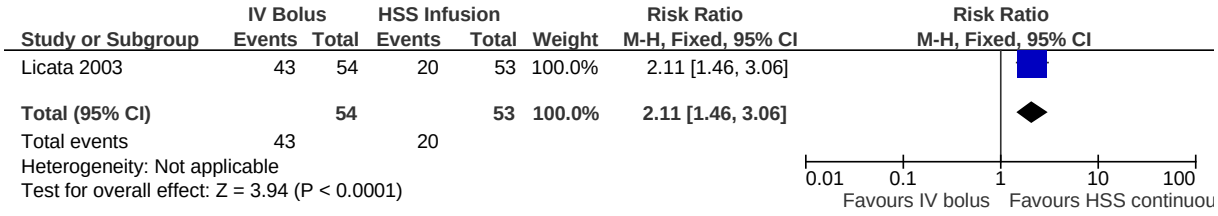


Figure 53: Weight loss (kg) at discharge

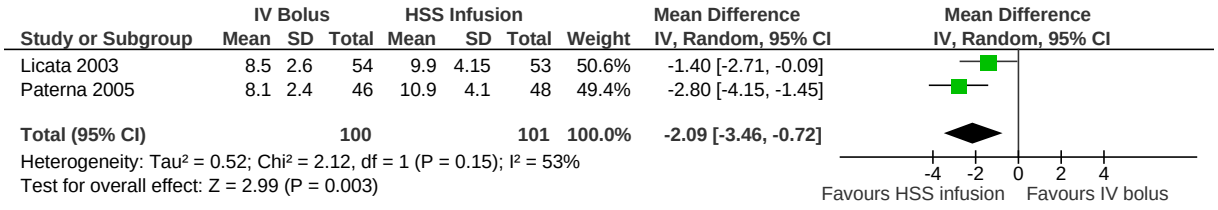


Figure 54: Length of hospital stay (days)

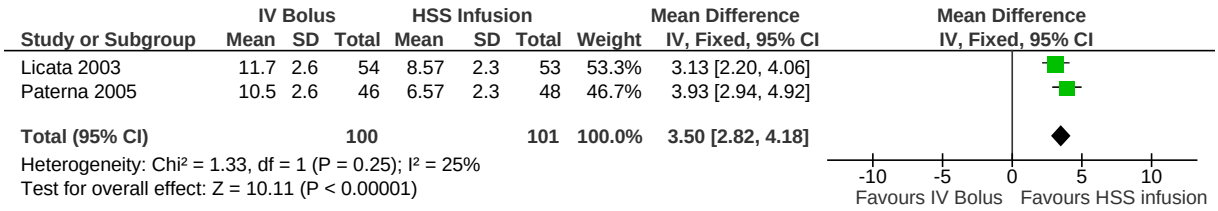


Figure 55: Number of patients admitted during follow up (1-48 months) due to acute heart failure

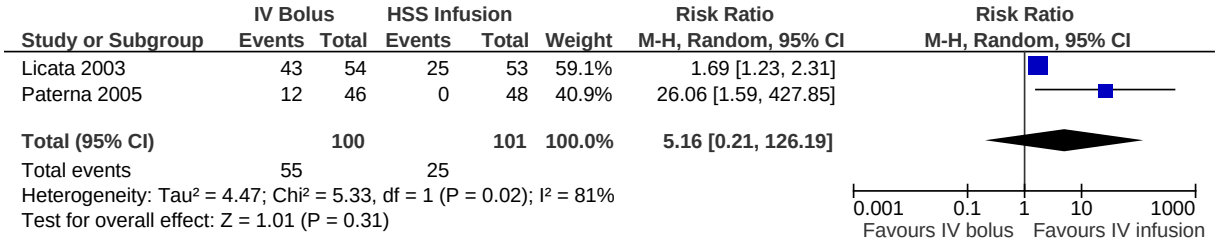


Figure 56: Total urine output (ml)/24 hours

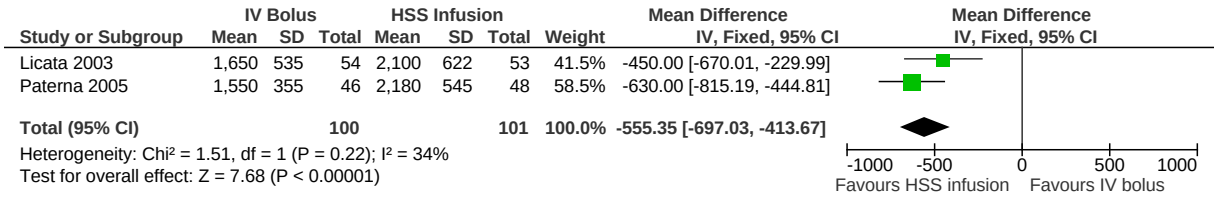
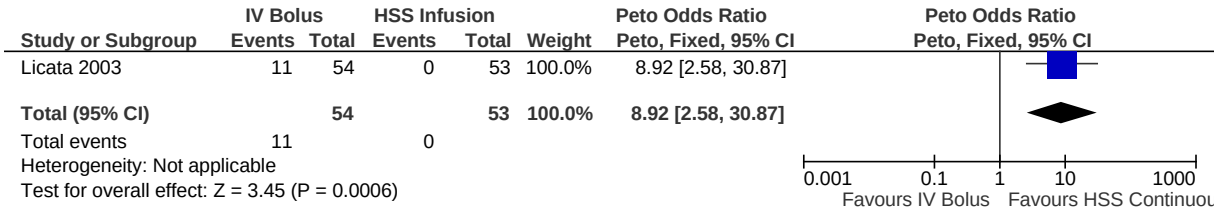
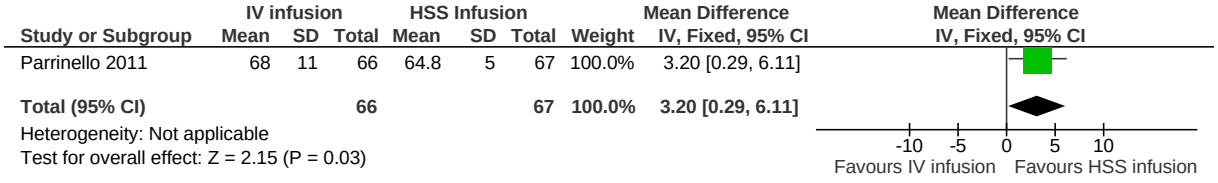


Figure 57: Total number of patients reporting hearing loss or deafness at 48 weeks

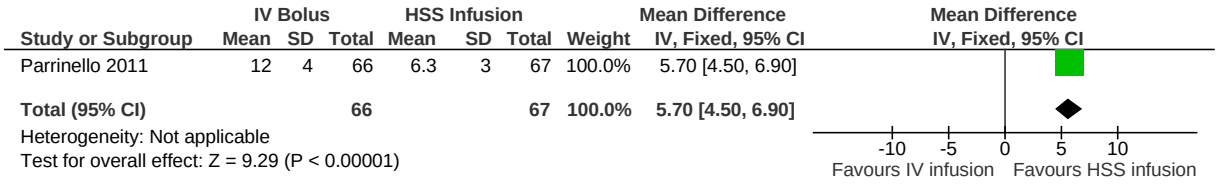


I.2.2.3 IV furosemide infusion versus IV furosemide infusion with HSS

Figure 58: Weight (kg) at 6 days or discharge

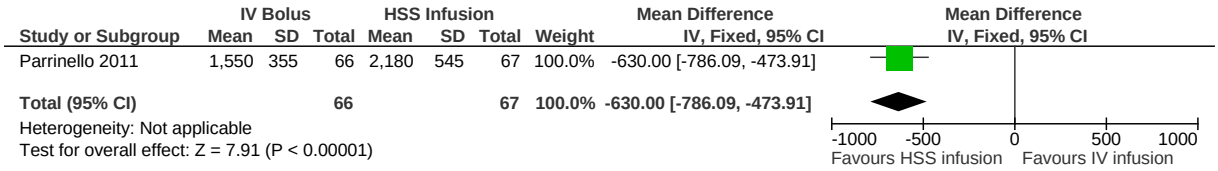


1 **Figure 59: Length of hospital stay (days)**



2

3 **Figure 60: Total urine output (ml)/24 hours**



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I.2.3 Vasodilators

I.2.3.1 Intravenous nitroglycerin versus placebo

Figure 61: Haemodynamic: Mean change in pulmonary capillary wedge pressure (PCWP) (mmHg) from baseline

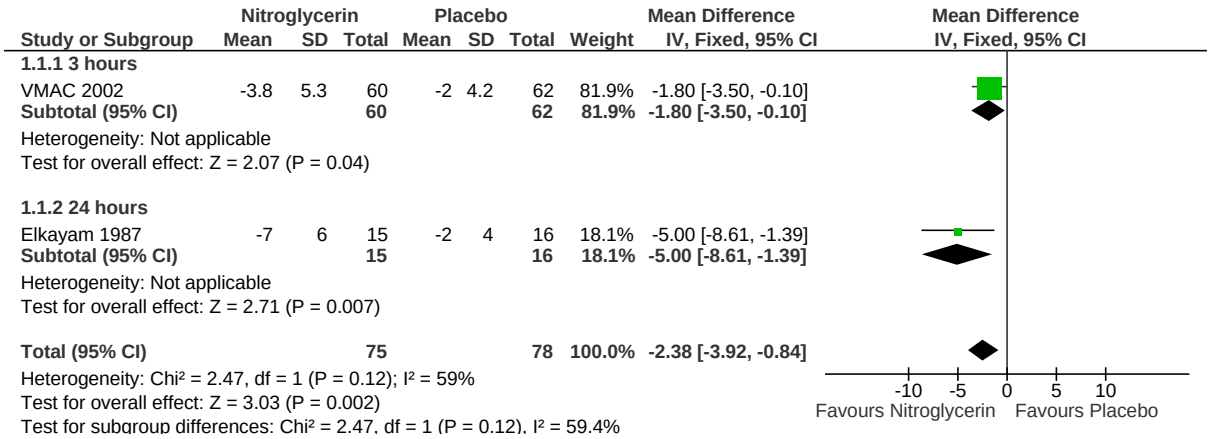


Figure 62: Haemodynamic: Mean change in right atrial pressure (mmHg) from baseline at 3 hours

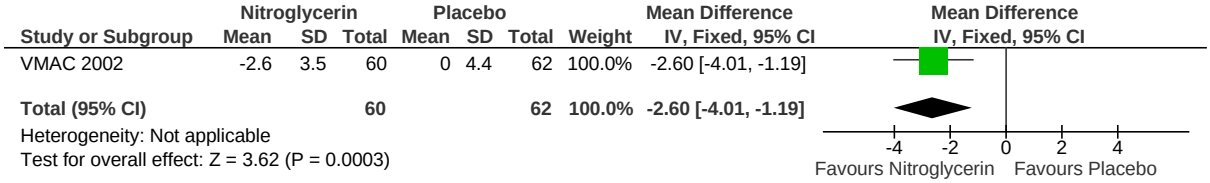


Figure 63: Haemodynamic: Mean change in cardiac index (L/min per m^2) at 3 hours

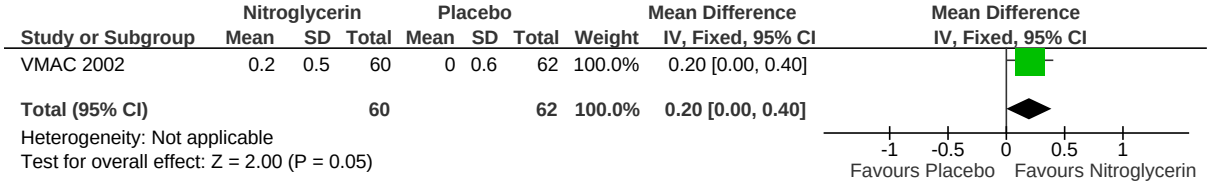


Figure 64: Dyspnoea: Number of patients reporting markedly, moderately or minimally better at 3 hours

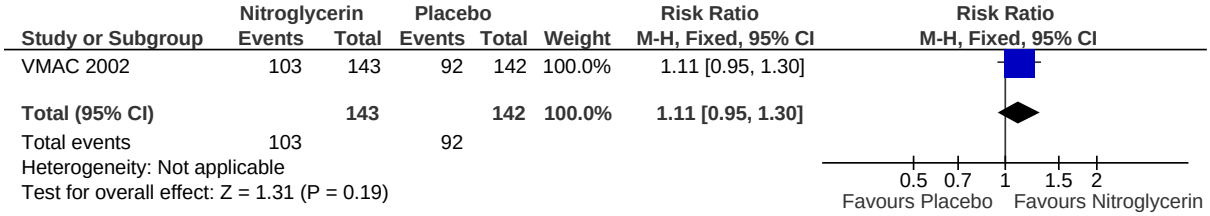


Figure 65: Global clinical status: Number of patients reporting markedly, moderately or minimally better at 3 hours

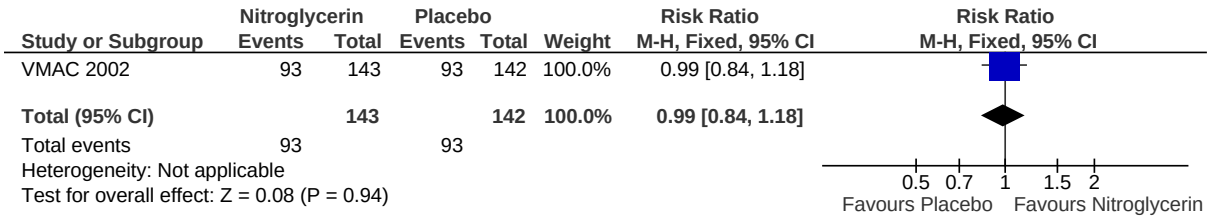


Figure 66: Toxicity: Number of patients with any adverse event

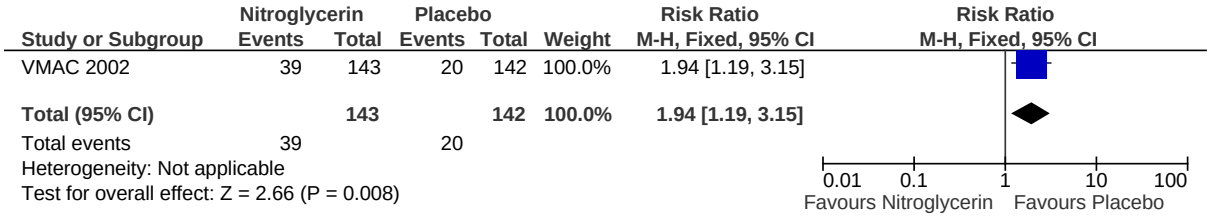


Figure 67: Toxicity: Number of patients discontinuing therapy due to drug

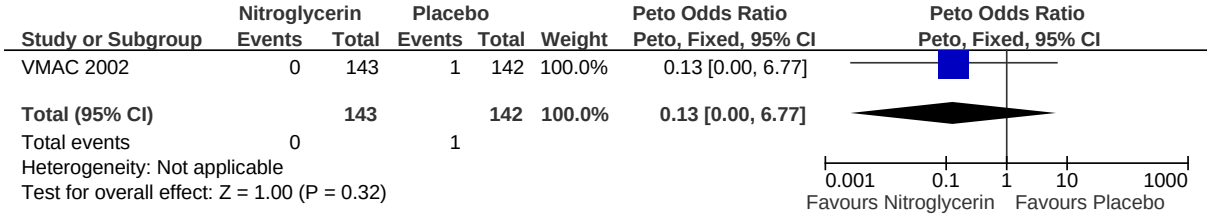
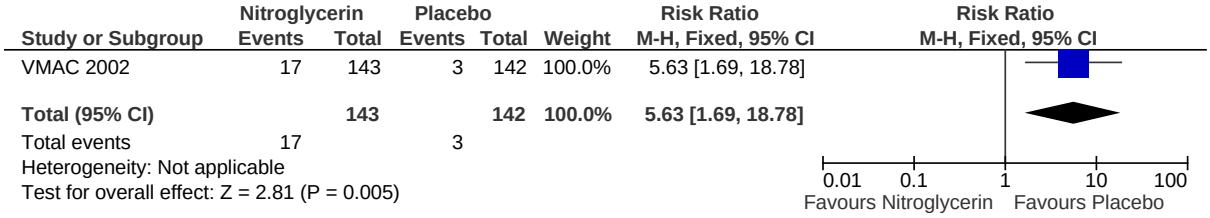


Figure 68: Toxicity: Number of patients with headache



I.2.3.2 Oral isosorbide dinitrate versus placebo

Figure 69: Haemodynamic: End score mean pulmonary arterial pressure (mmHg)

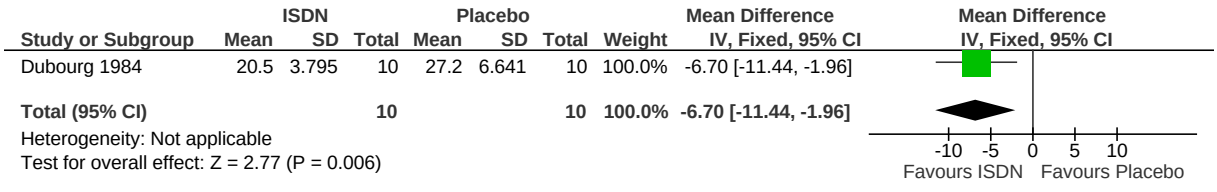


Figure 70: Haemodynamic: End score mean pulmonary capillary wedge pressure (mmHg)

Study or Subgroup	ISDN Mean	ISDN SD	ISDN Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Dubourg 1984	13.1	3.479	10	18.8	6.235	10	100.0%	-5.70 [-10.13, -1.27]
Total (95% CI)			**10**			**10**	**100.0%**	**-5.70 [-10.13, -1.27]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.52 (P = 0.01)

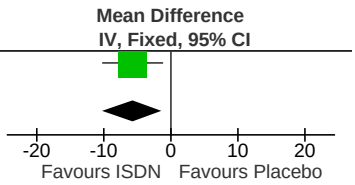
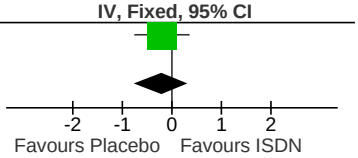


Figure 71: Haemodynamic: End score cardiac index (l/min/m^2)

Study or Subgroup	ISDN Mean	ISDN SD	ISDN Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Dubourg 1984	2.95	0.569	10	3.15	0.664	10	100.0%	-0.20 [-0.74, 0.34]
Total (95% CI)			**10**			**10**	**100.0%**	**-0.20 [-0.74, 0.34]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.72 (P = 0.47)



I.2.3.3 Intravenous sodium nitroprusside versus placebo

Figure 72: Mortality: All-cause

Study or Subgroup	Nitroprusside Events	Nitroprusside Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.1.1 48 hours						
Cohn 1982	11	407	9	405	100.0%	1.22 [0.51, 2.90]
Subtotal (95% CI)		**407**		**405**	**100.0%**	**1.22 [0.51, 2.90]**
Total events	11		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.44 (P = 0.66)						
3.1.2 21 Days						
Cohn 1982	47	407	42	405	100.0%	1.11 [0.75, 1.65]
Subtotal (95% CI)		**407**		**405**	**100.0%**	**1.11 [0.75, 1.65]**
Total events	47		42			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.54 (P = 0.59)						
3.1.3 13 Weeks						
Cohn 1982	69	407	77	405	100.0%	0.89 [0.66, 1.20]
Subtotal (95% CI)		**407**		**405**	**100.0%**	**0.89 [0.66, 1.20]**
Total events	69		77			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.76 (P = 0.45)						

Test for subgroup differences: Chi² = 1.04, df = 2 (P = 0.60), I² = 0%

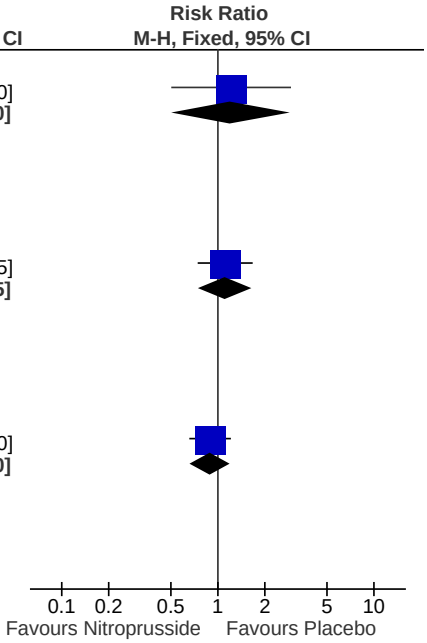
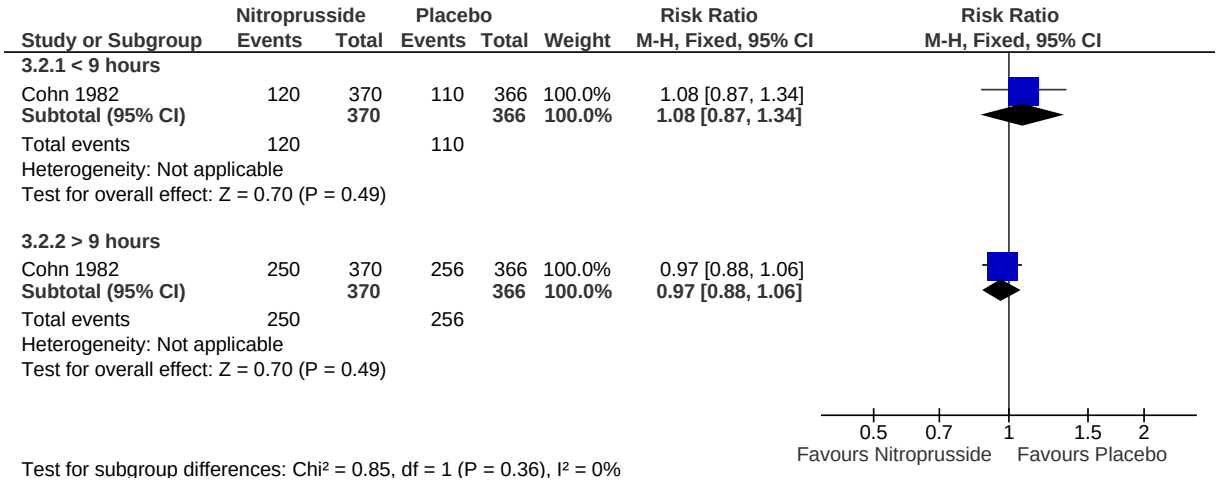


Figure 73: Mortality: 13 week mortality according to time of onset of infarction to start of infusion



Test for subgroup differences: $Chi^2 = 0.85$, df = 1 (P = 0.36), $I^2 = 0\%$

Figure 74: Haemodynamic: Number of patients achieving left ventricular filling pressure (LVFP) reduction by 60%

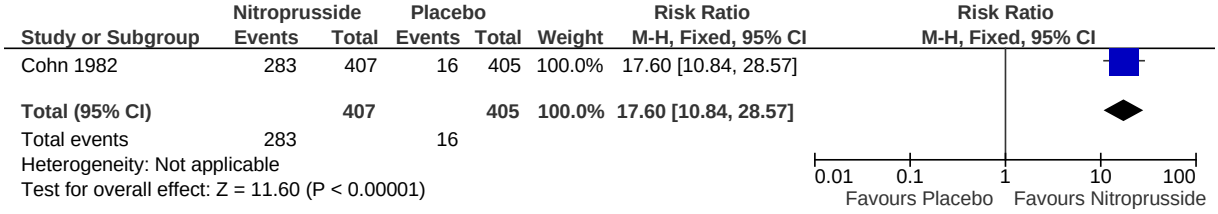


Figure 75: Toxicity: Number of patients reaching hypotensive limit

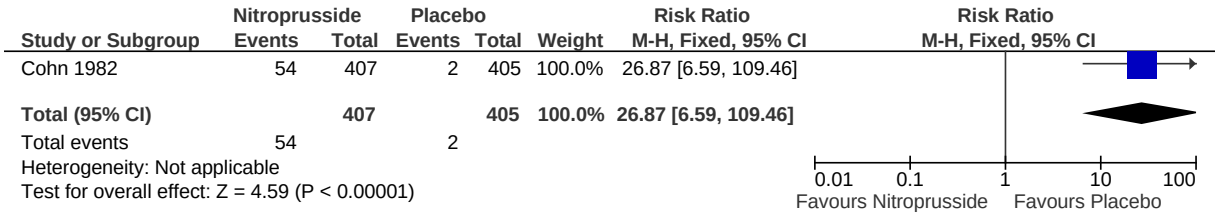


Figure 76: Toxicity: Number of patients reporting headache

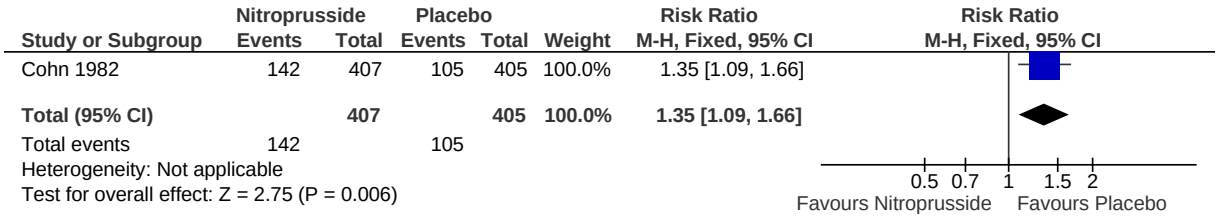


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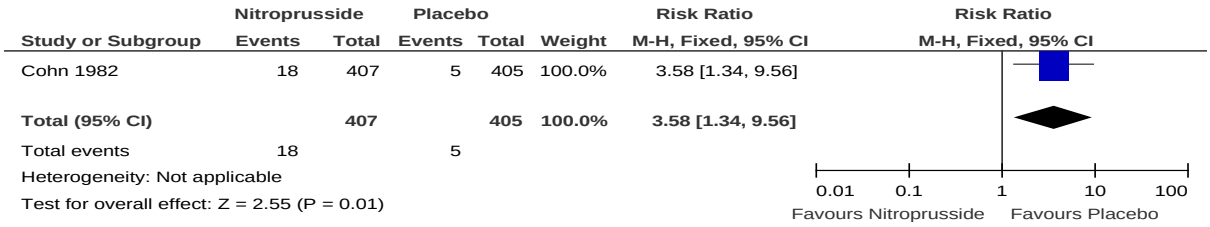
Figure 77: Toxicity: Number of patients with severe headache



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3 **I.2.4 Inotropes and vasopressers**

4 **I.2.4.1 Inotropes vs. placebo**

5 **Milrinone vs. placebo**

Figure 78: Mortality

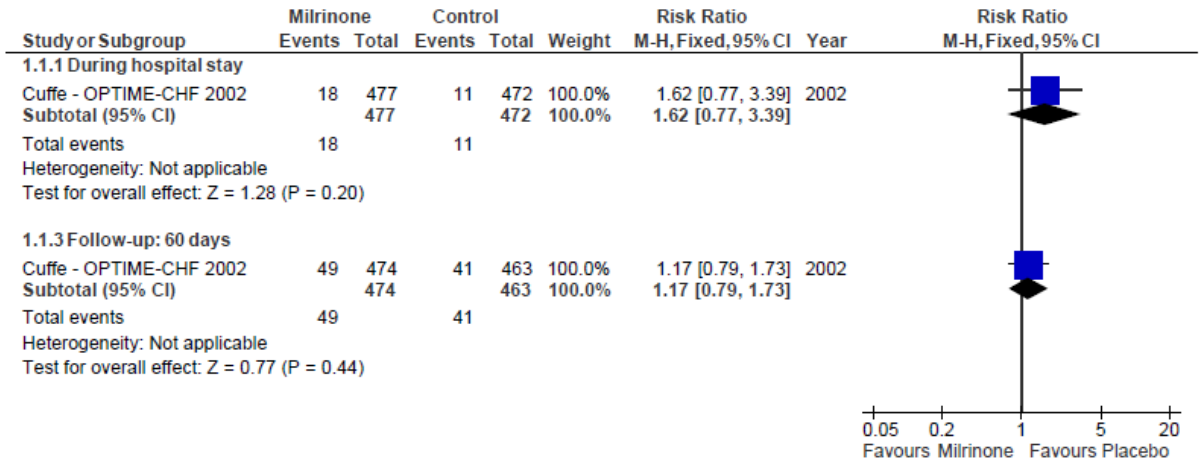


Figure 79: Number of patients improved on a 4 point scale using a combination of subjective ratings of symptoms (e.g. dyspnoea, palpitation) and ratings of physical findings (e.g. moist rales in the lung, gallop)

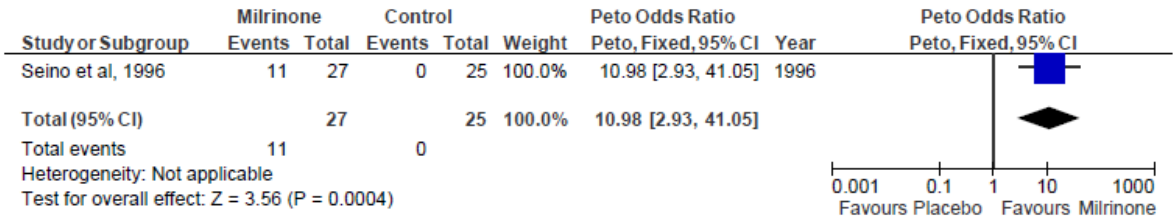


Figure 80: Length of hospital stay (days)

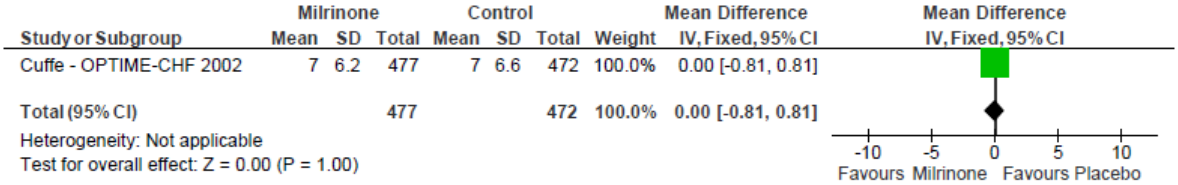


Figure 81: Adverse events: arrhythmia

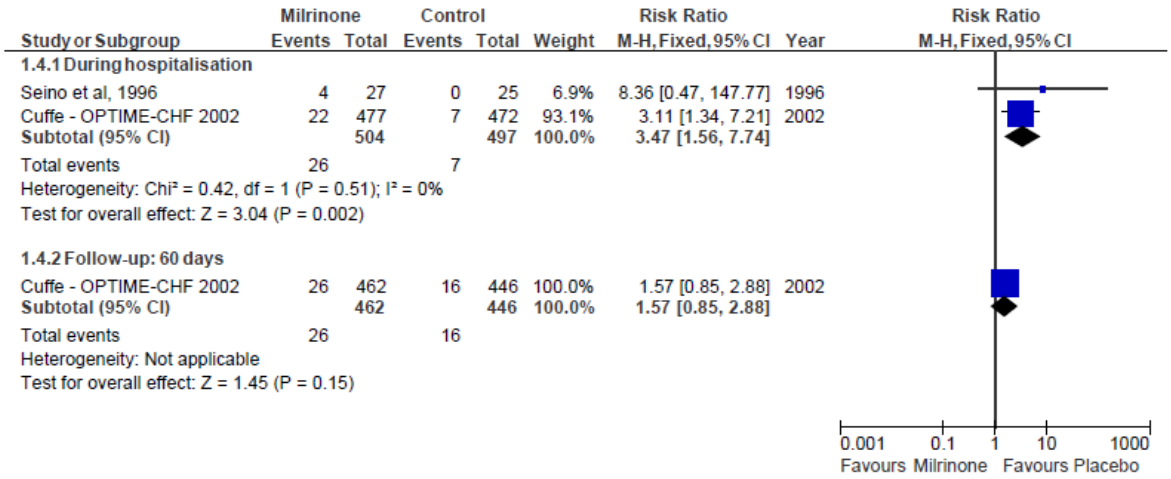
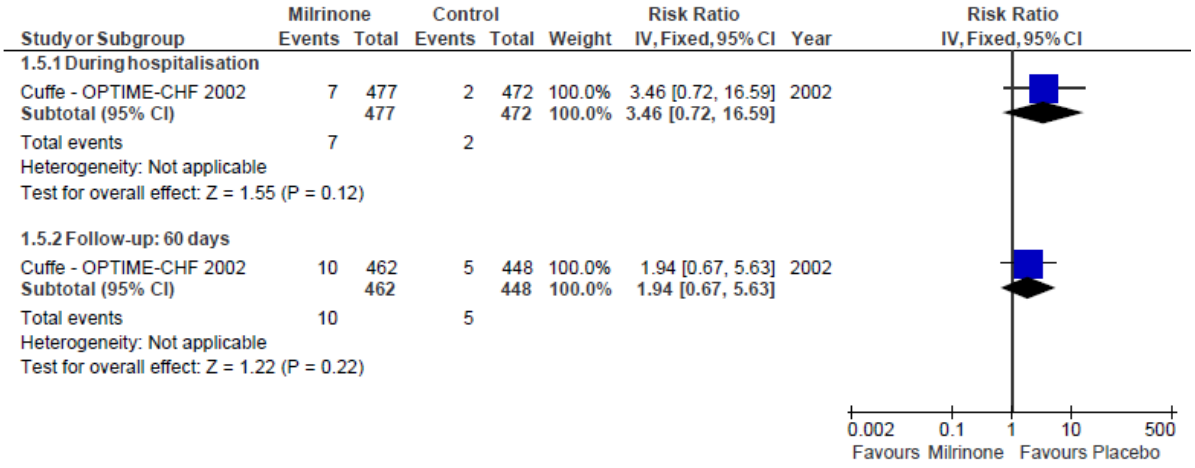
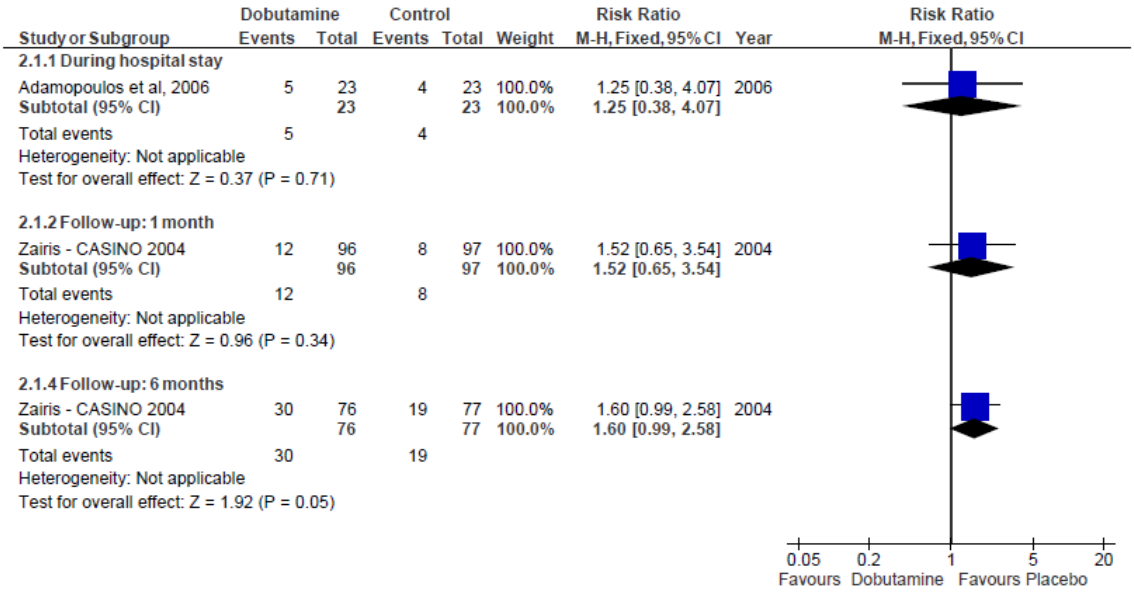


Figure 82: Adverse events: myocardial infarction



I.2.4.2 Dobutamine vs. placebo

Figure 83: Mortality



I.2.4.3 Low dose dopamine/furosemide vs. furosemide

Figure 84: All-cause mortality at 180 days (time-to-event)

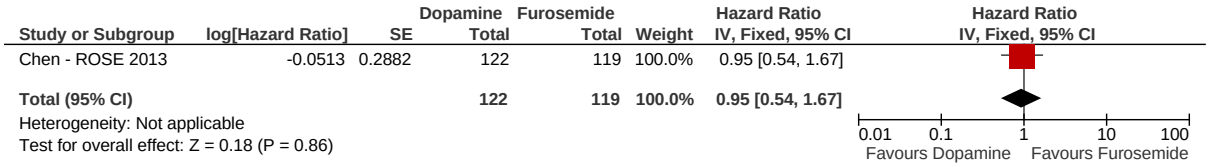


Figure 85: All-cause mortality up to 1 year

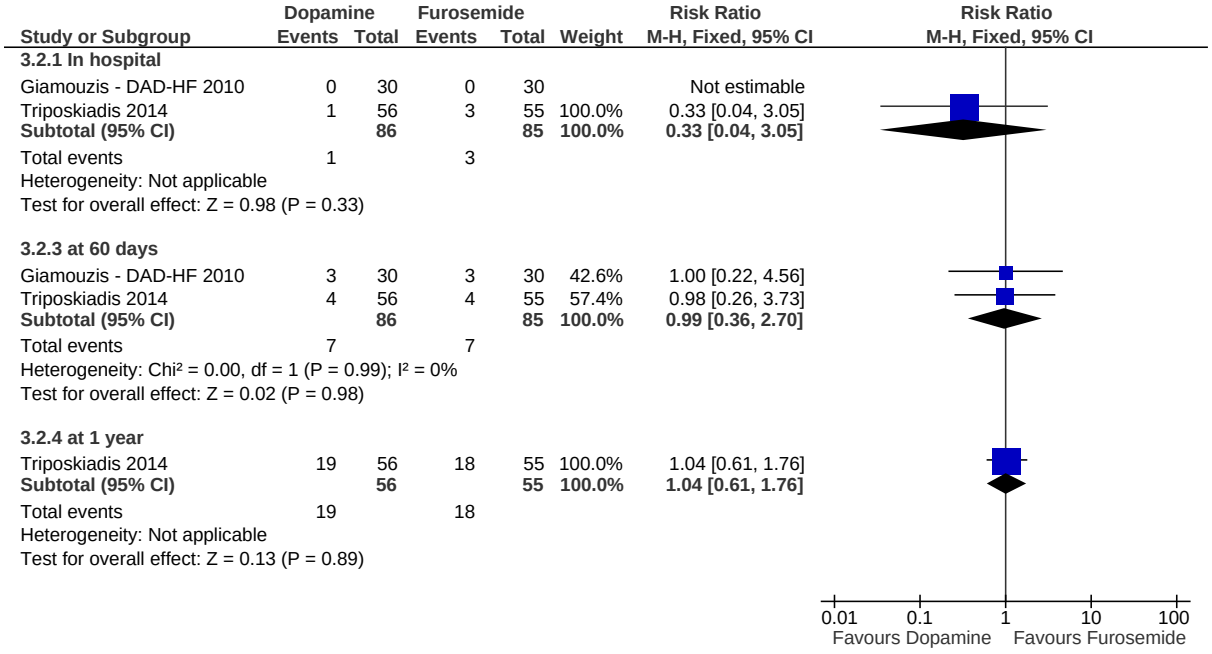


Figure 86: Cardiovascular mortality up to 1 year

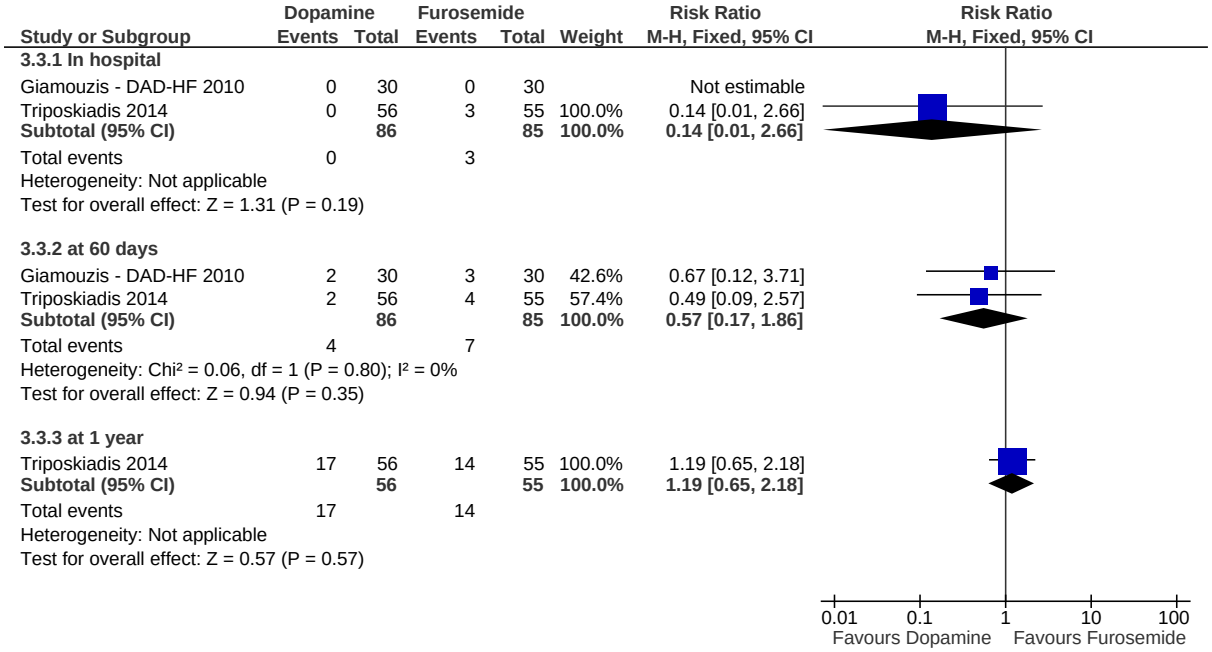
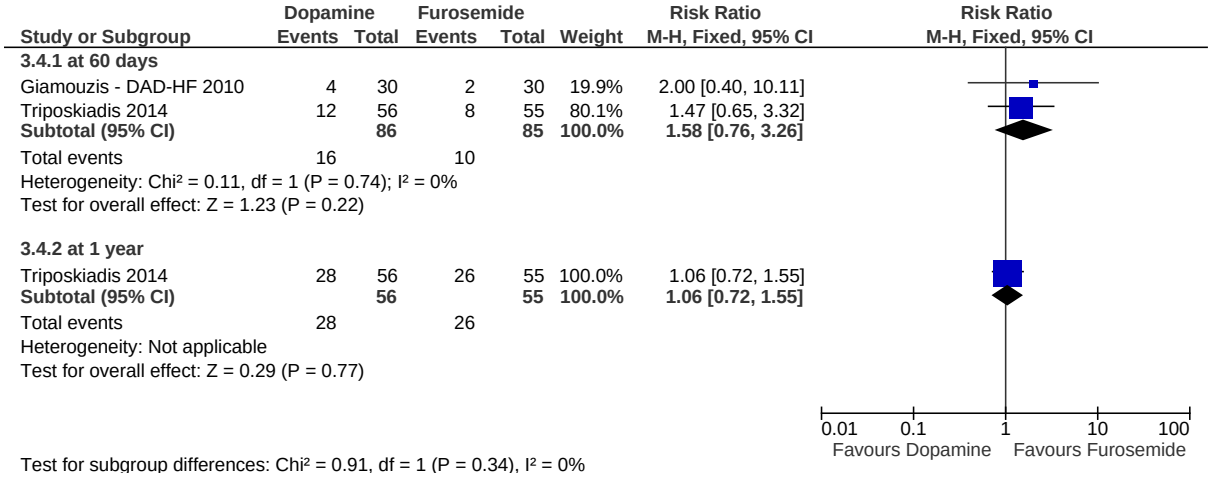


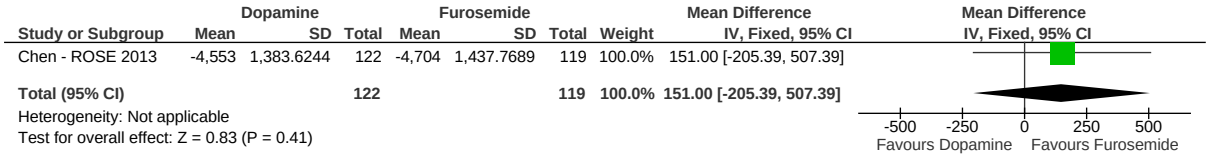
Figure 87: Heart failure hospitalisations up to 1 year



Test for subgroup differences: Chi² = 0.91, df = 1 (P = 0.34), I² = 0%

1

Figure 88: Global well-being score (AUC)



2

Figure 89: Dyspnoea scale (Borg scale and AUC)

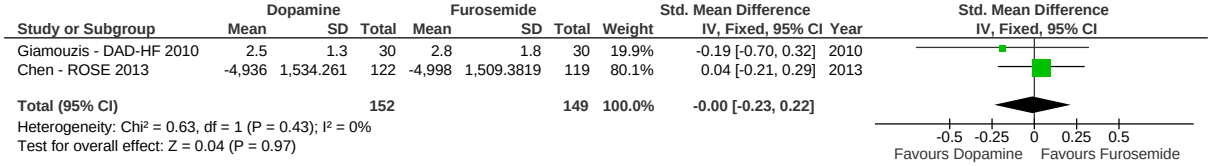
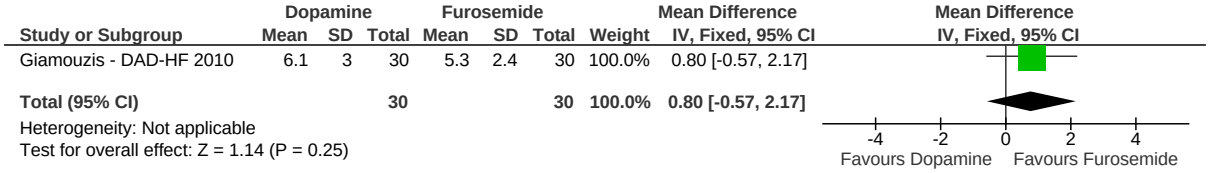


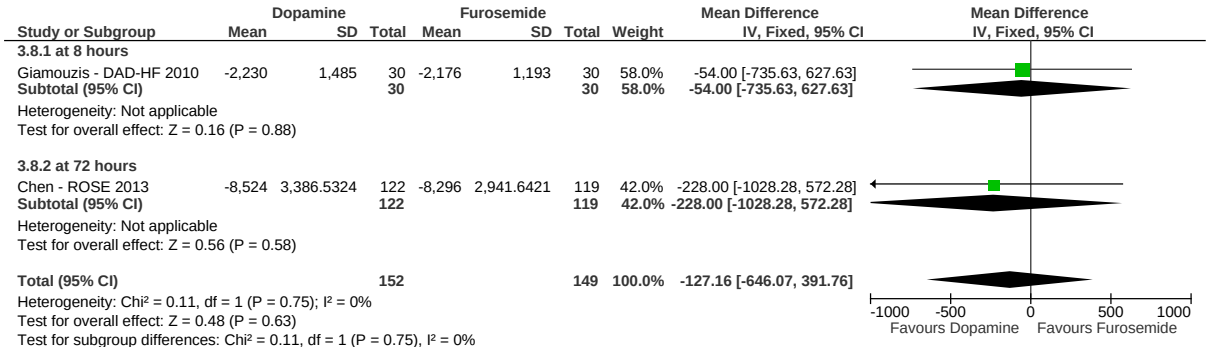
Figure 90: Length of hospital stay (days)



Note. The Triposkiadis et al, 2014 DAD-HF II trial reports medians and interquartile ranges (Dopamine 4.5 (3 - 5.75) Furosemide 4 (3 -5), p=0.342)

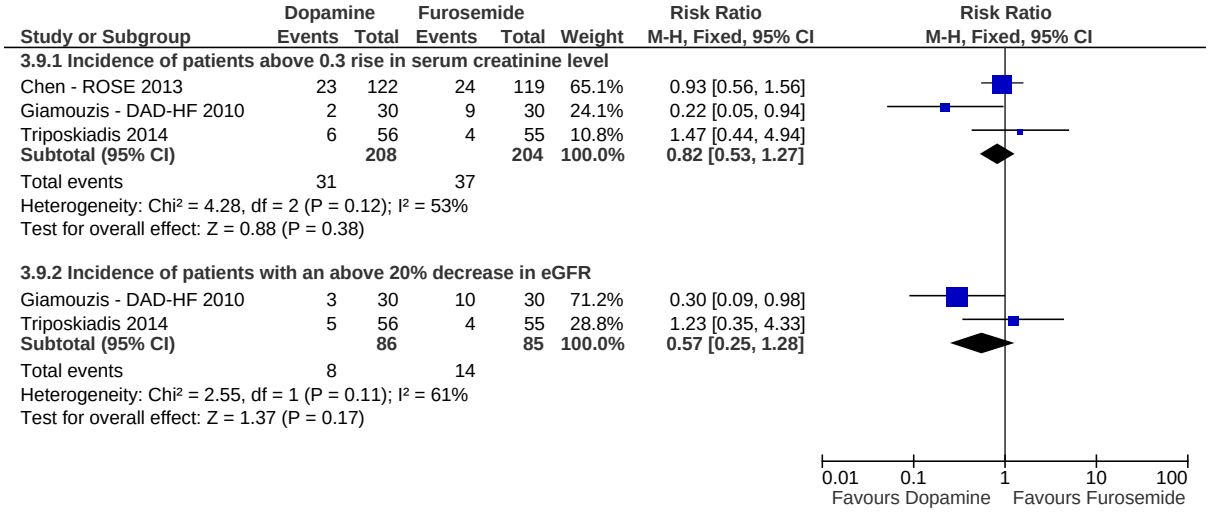
1

Figure 91: Total urine volume



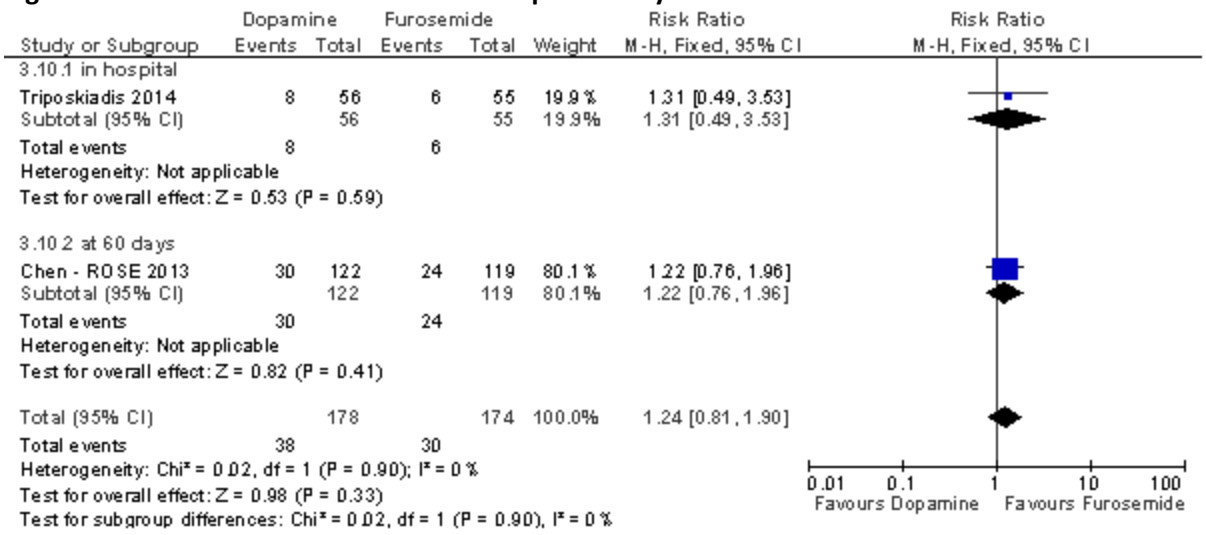
2

Figure 92: Worsening renal function



3

Figure 93: Rate of serious adverse events up to 60 days



I.3 Initial non-pharmacological treatment

I.3.1 Non-invasive ventilation

I.3.1.1 Non-invasive ventilation vs. medical care

Figure 94: In-hospital mortality (including up to 7 days - ordered according to the weight of the study in the analysis)

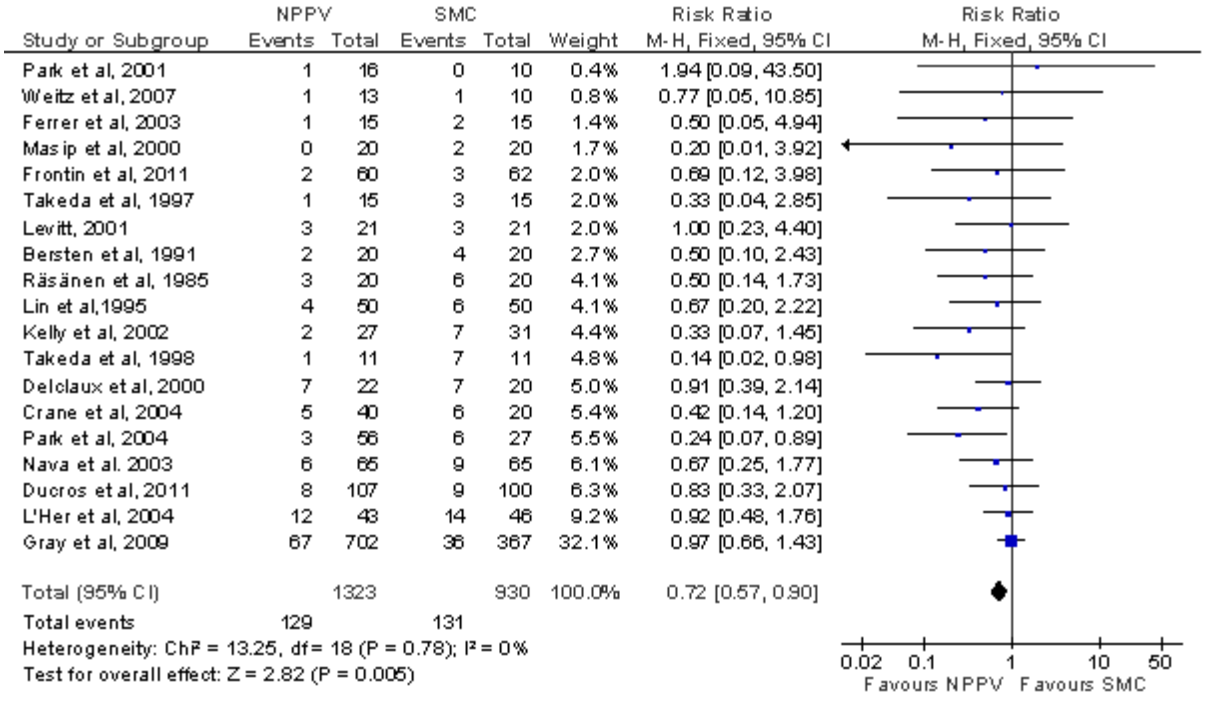


Figure 95: 30-day mortality

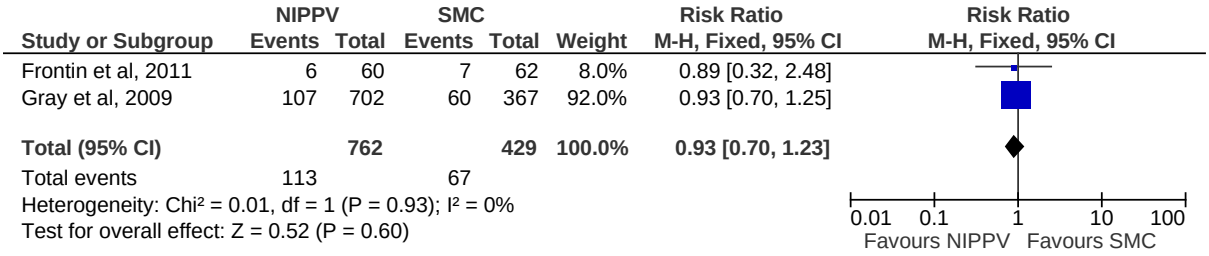
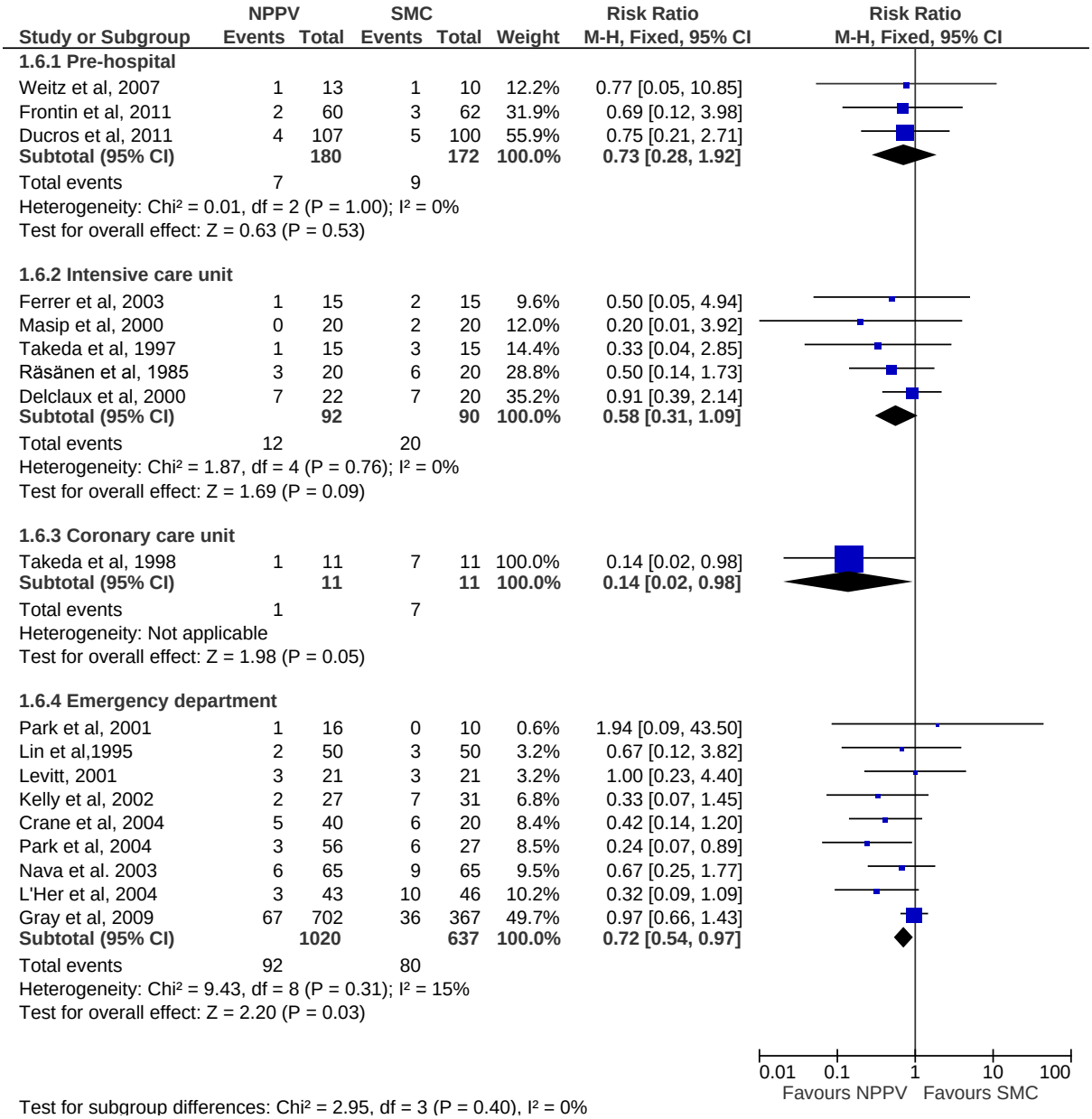
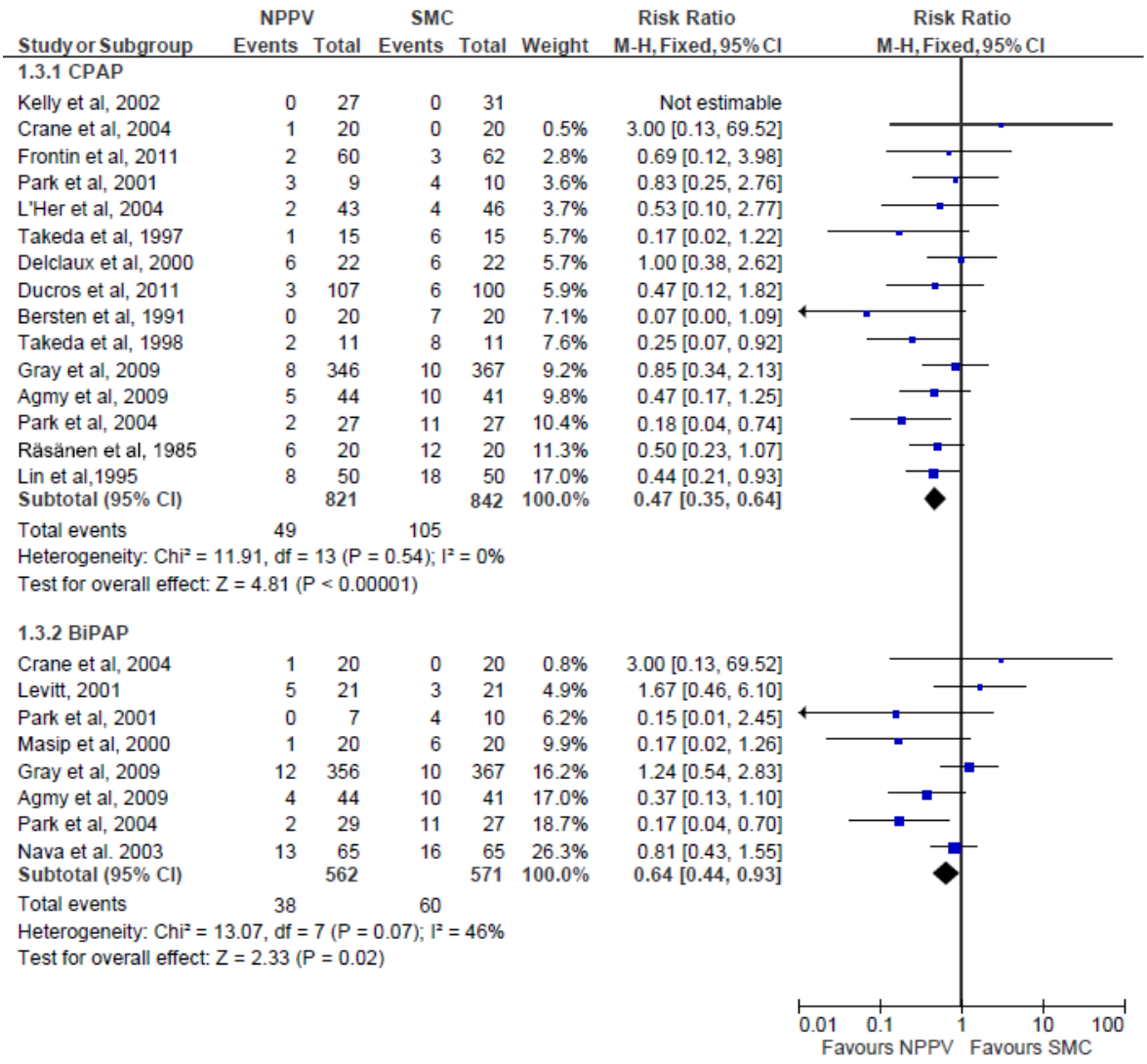


Figure 96: Mortality by setting (ordered according to the weight of the study in the analysis)



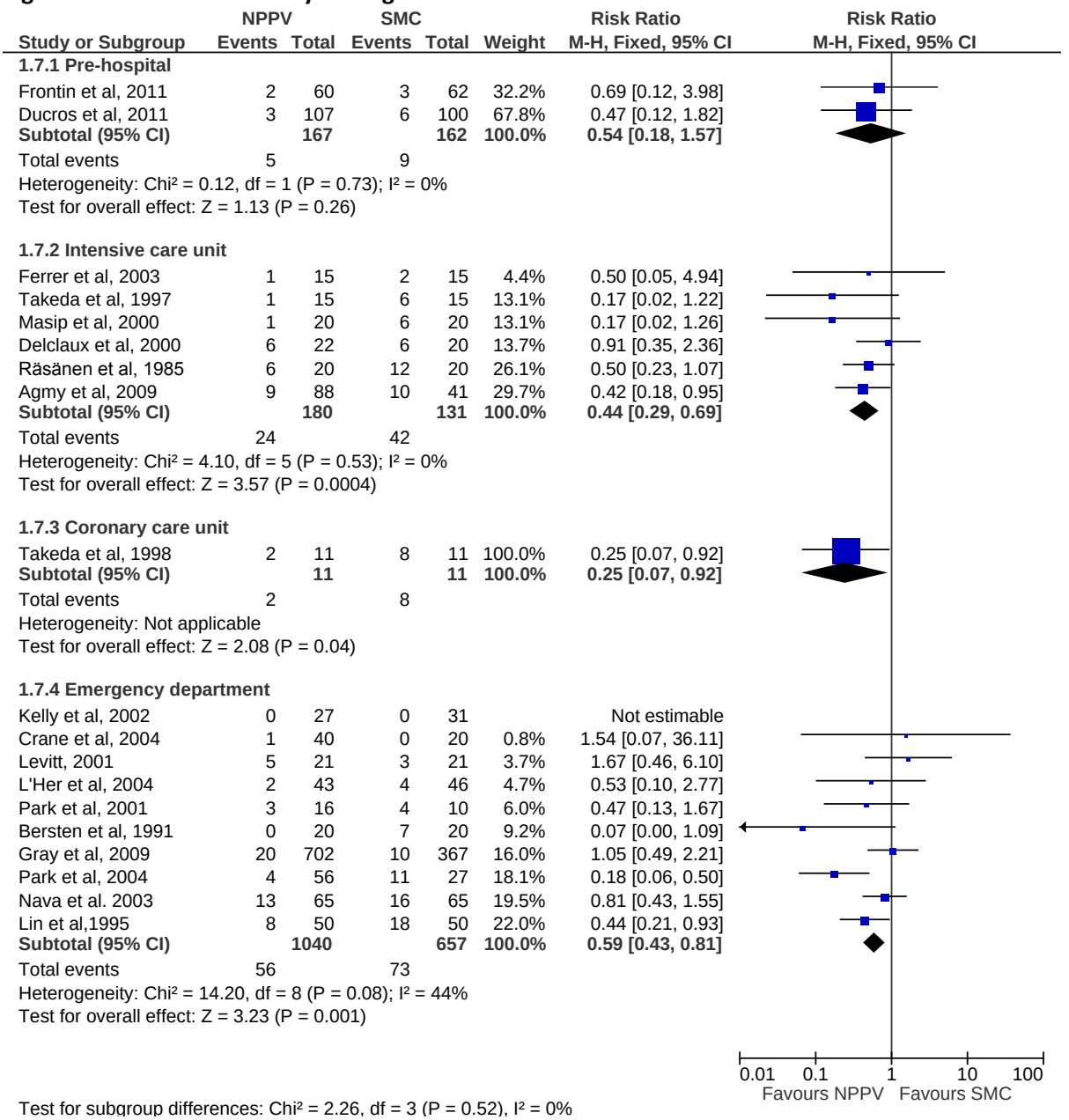
Test for subgroup differences: Chi² = 2.95, df = 3 (P = 0.40), I² = 0%

Figure 97: Intubation rate by type of non-invasive monitoring (ordered according to the weight of the study in the analysis)



1

Figure 98: Intubation rate by setting



1

2

Figure 99: Incidence of new myocardial infarction (ordered according to the weight of the study in the analysis)

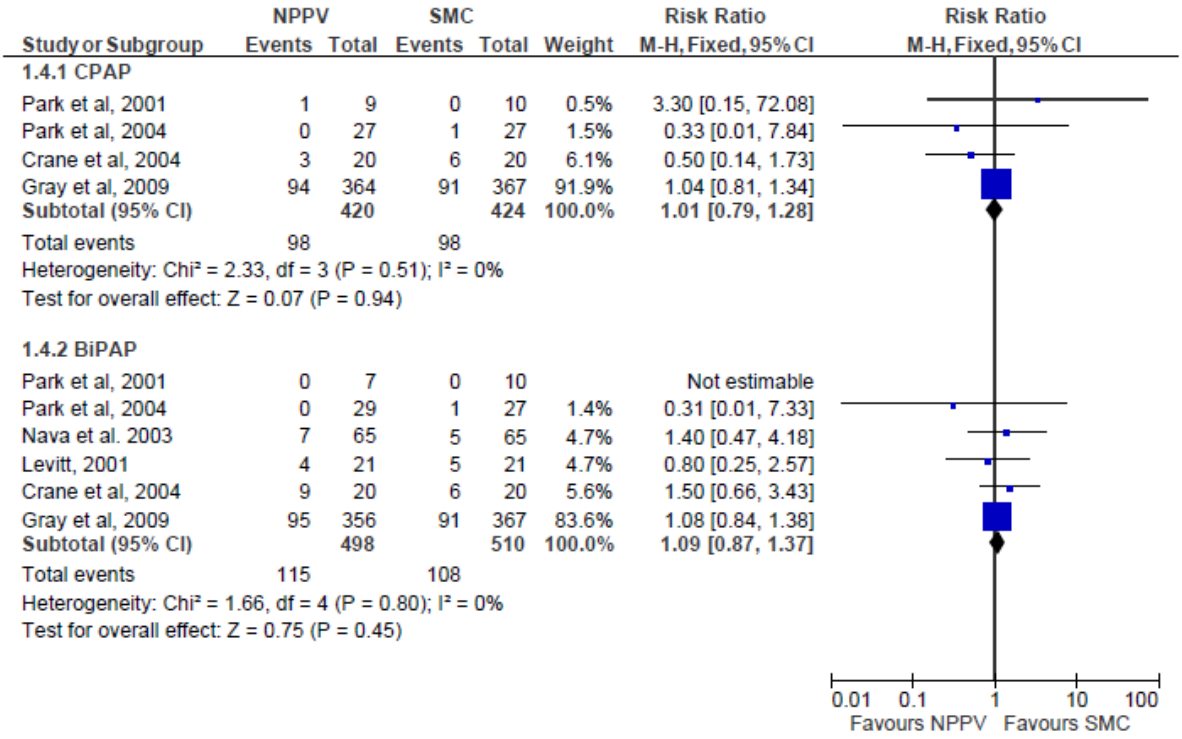
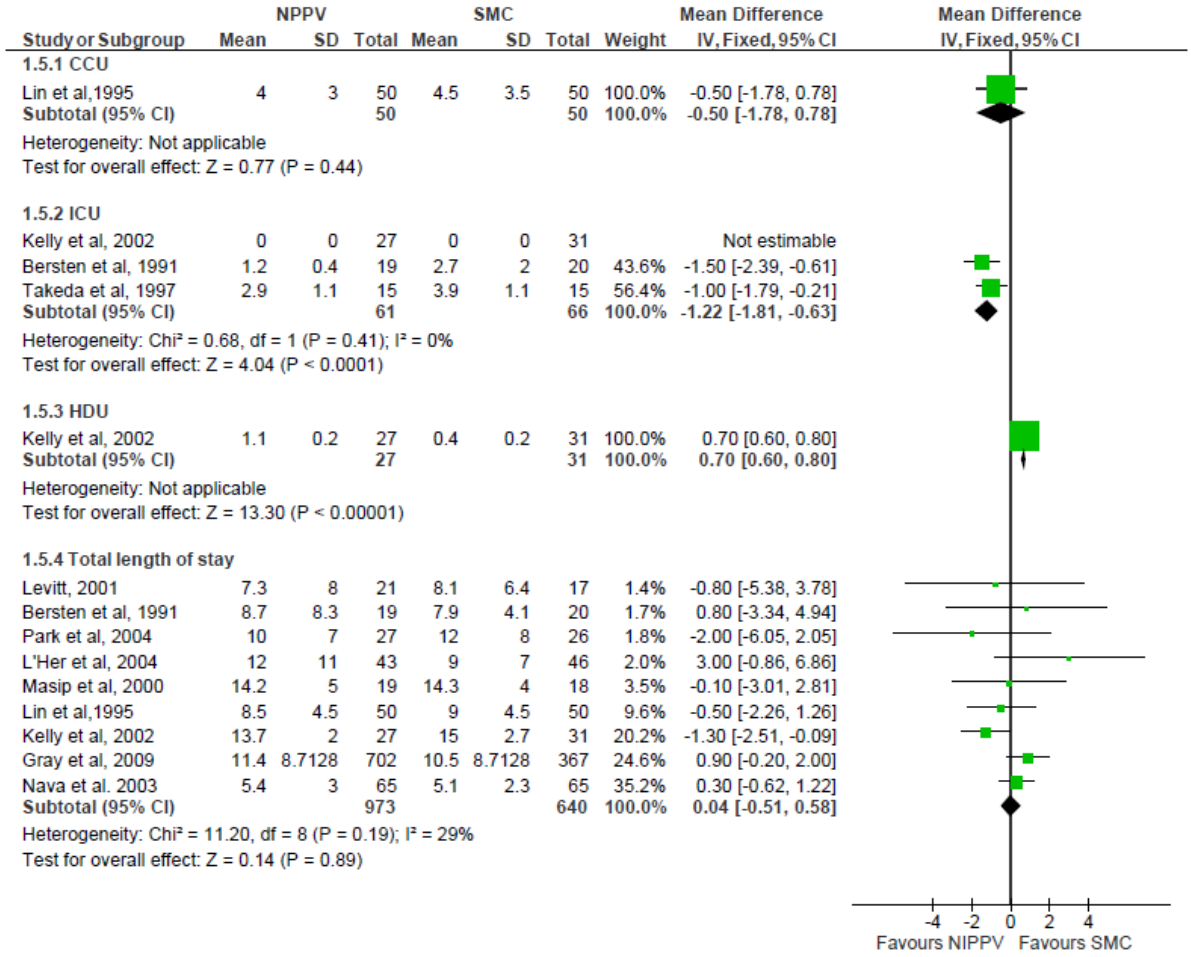
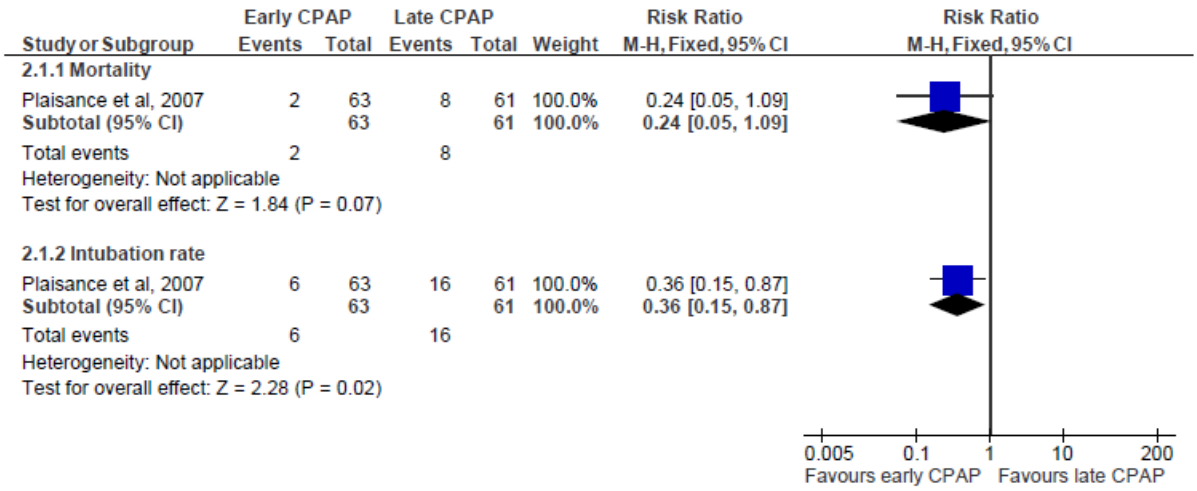


Figure 100: Length of hospital stay by setting (ordered according to the weight of the study in the analysis)



1 **I.3.1.2 Early CPAP vs. late CPAP (after 15 minute delay)**

Figure 101: Relative risks for mortality and intubation rates



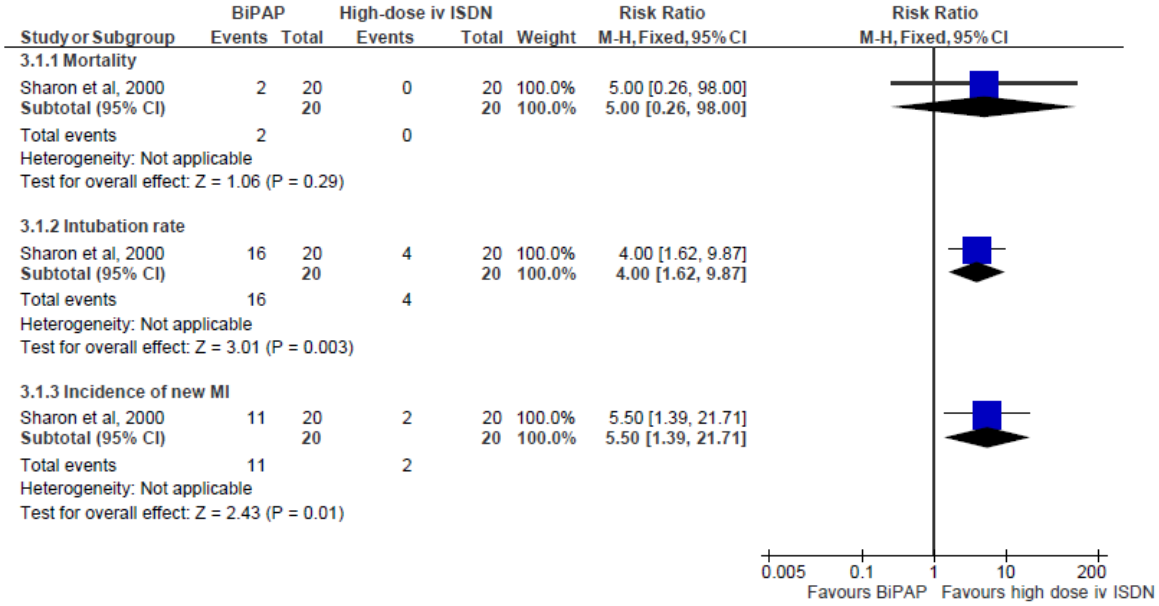
2

3

1

2 **I.3.1.3 BiPAP vs. high-dose intravenous isosorbide dinitrate**

Figure 102: Relative risks for mortality and intubation rates

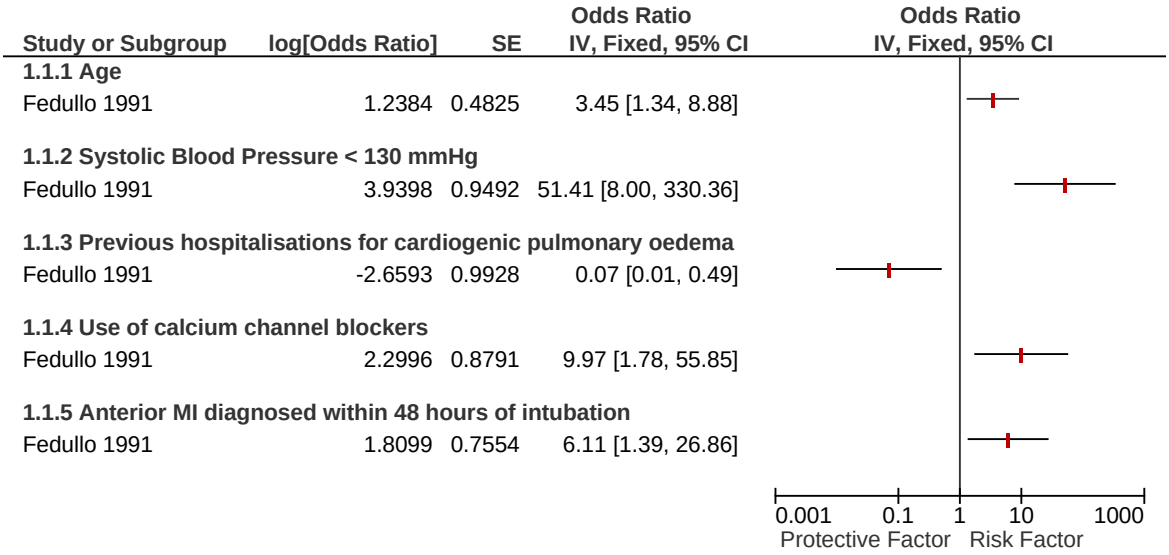


3

4 **I.3.2 Mechanical ventilation**

5 **I.3.2.1 In hospital mortality**

Figure 103: In hospital mortality: Fedullo 1991[51]: Model 1



I.3.2.2 Length of mechanical ventilation and prolonged weaning > 7 days

Figure 104: Linear regression analysis for echocardiographic predictors of length of mechanical ventilation

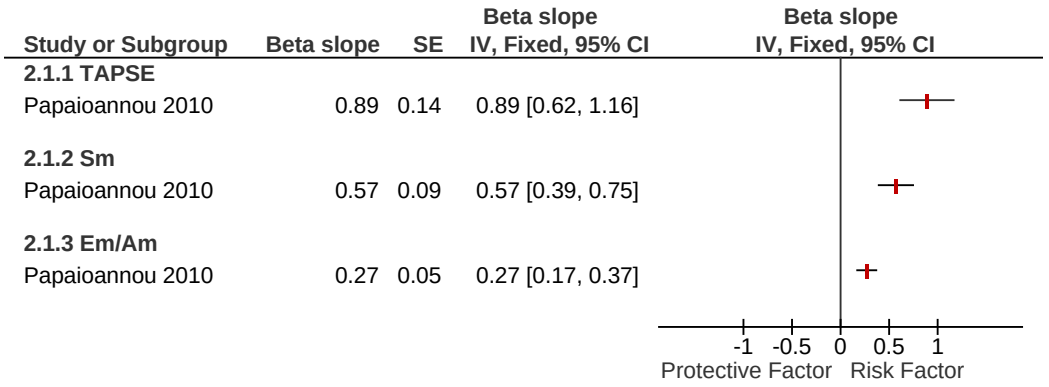
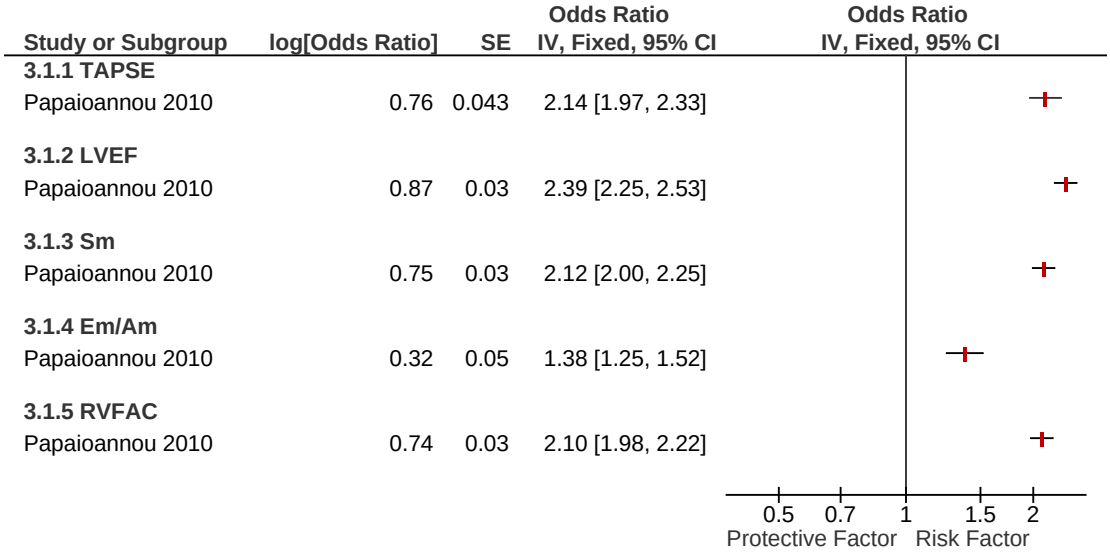


Figure 105: Logistic regression analysis for echocardiographic predictors of weaning > 7 days



I.3.3 Ultrafiltration

I.3.3.1 Ultrafiltration versus diuretic therapy

Figure 106: All-cause mortality at 60 days

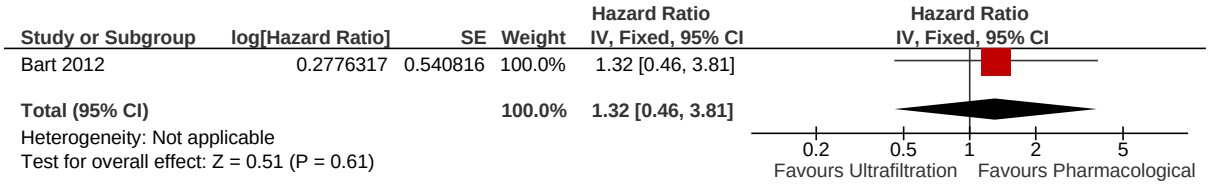


Figure 107: All-cause mortality up to 90 days

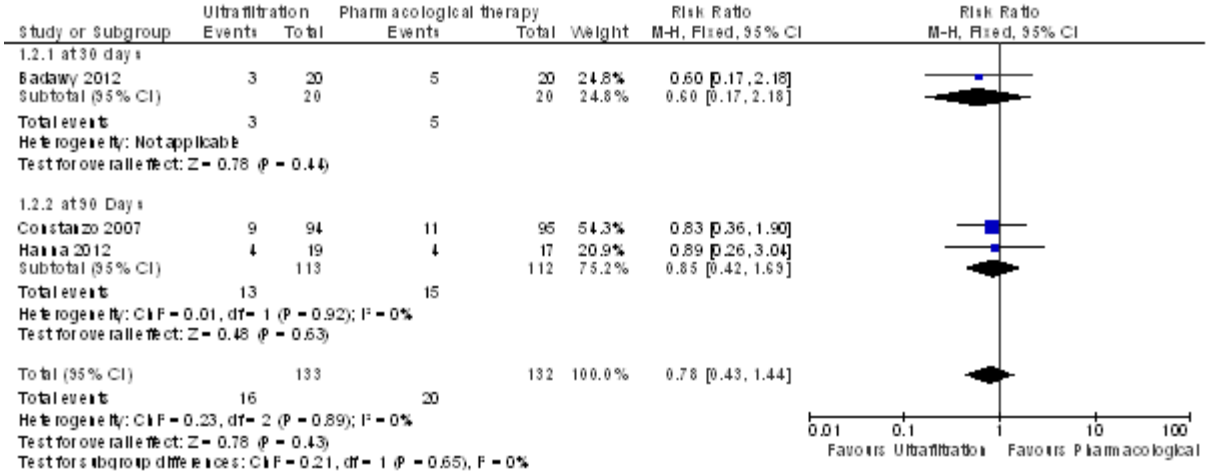


Figure 108: Length of hospital stay

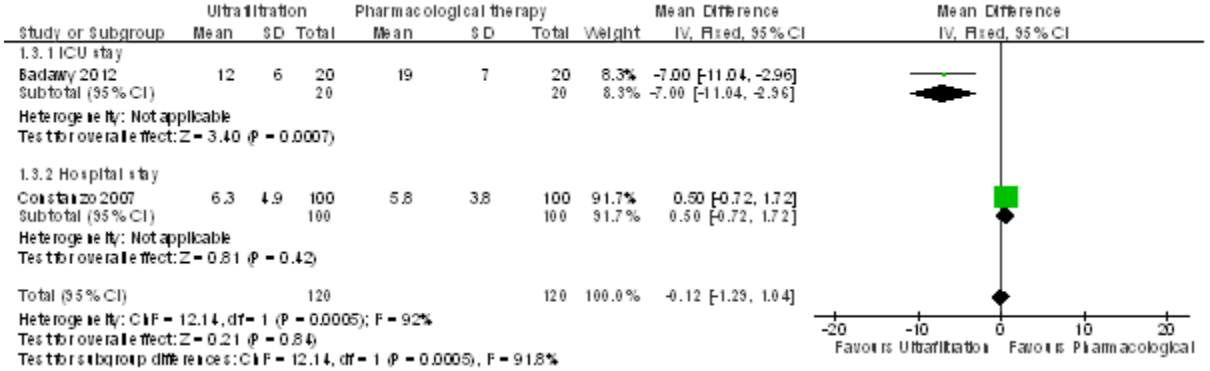
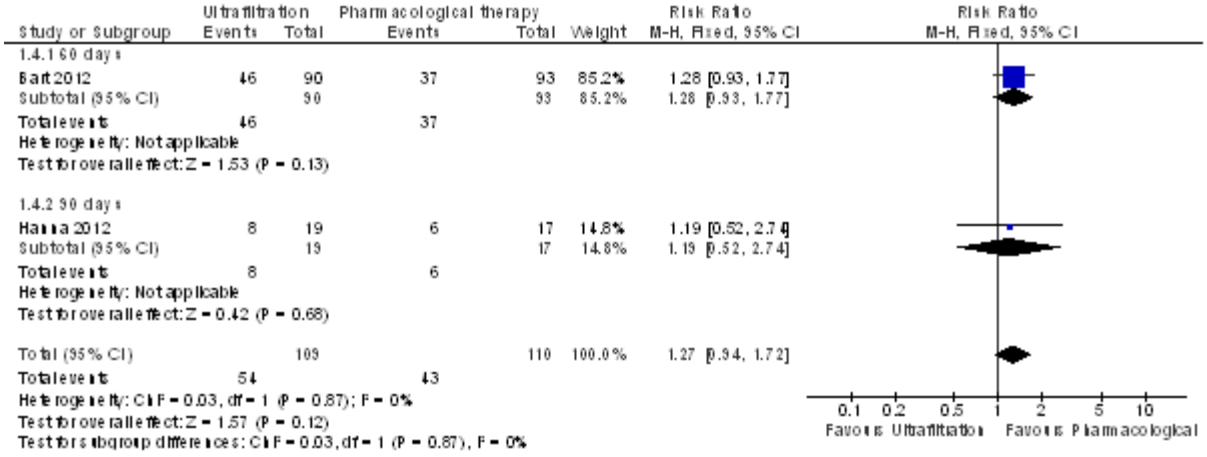
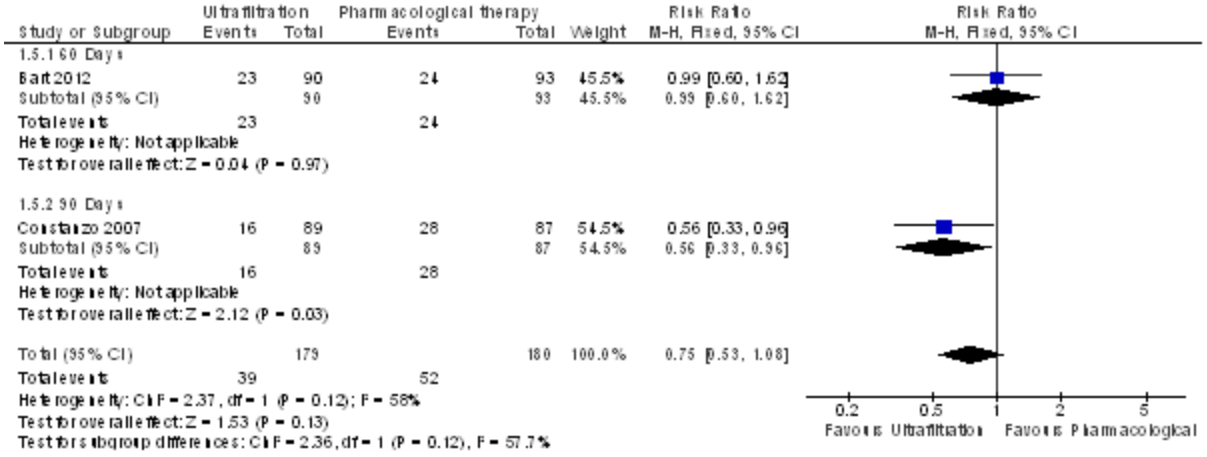


Figure 109: Number of patients readmitted due to any cause grouped according to length of follow-up



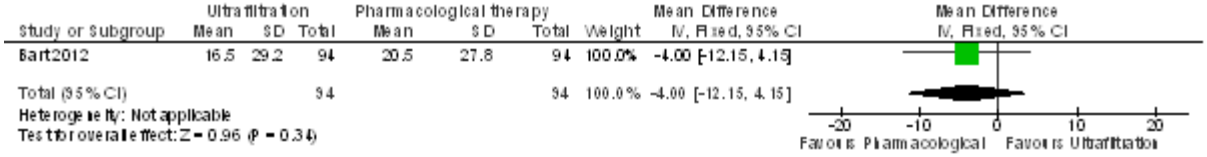
1

Figure 110: Number of patients readmitted due to HF grouped according to length of follow-up



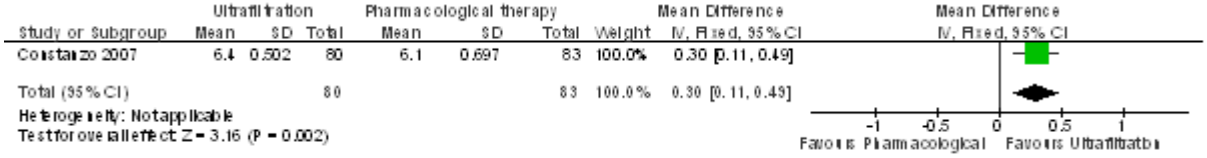
2

Figure 111: Change in score on dyspnoea 100mm VAS from baseline at 96 hours



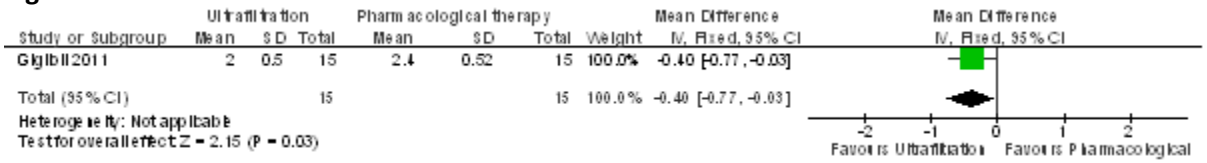
3

Figure 112: Mean dyspnoea score at 48 hours



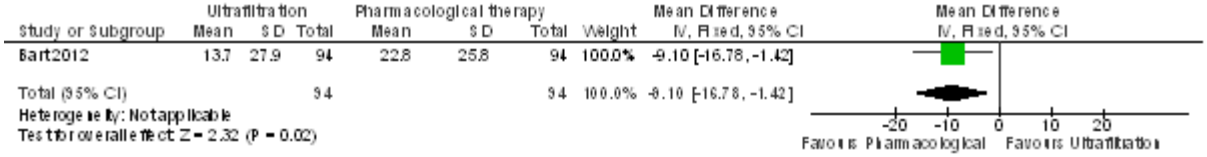
4

Figure 113: End NYHA class at 36 hours



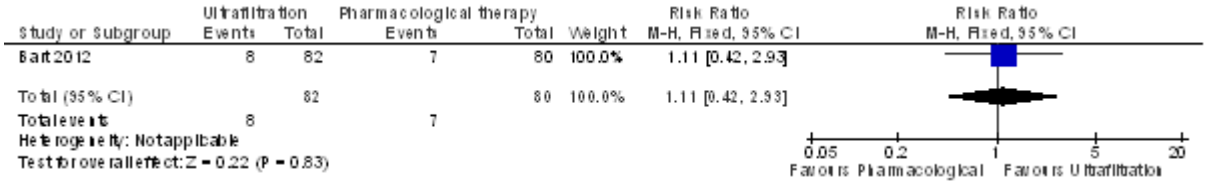
1

Figure 114: Change in score on global well-being scale from baseline at 96 hours



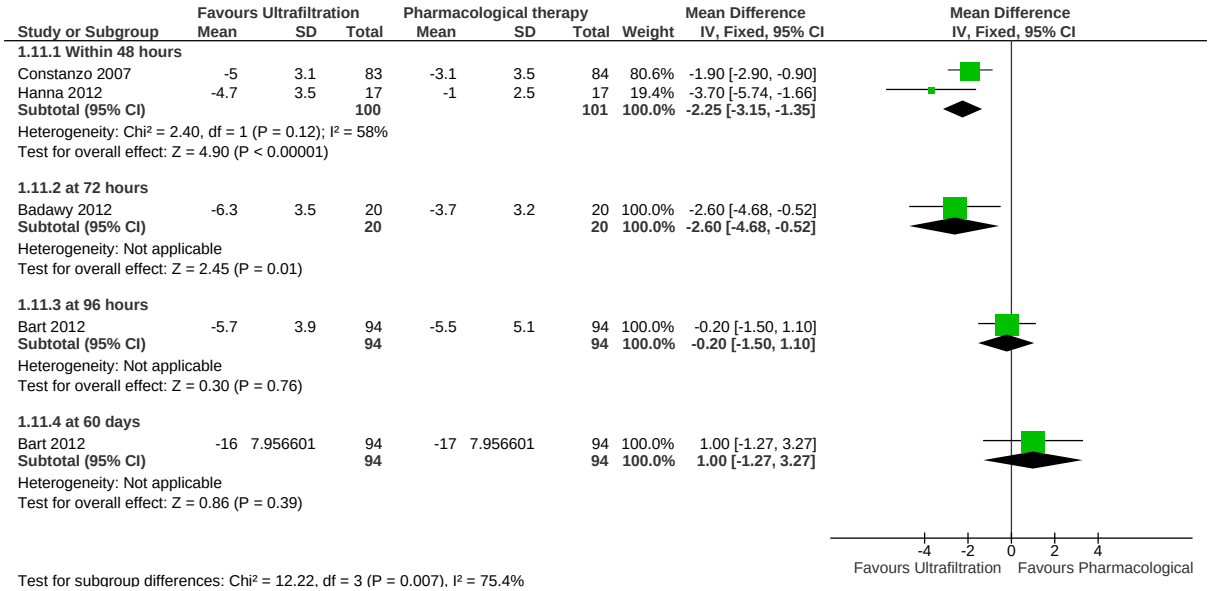
2

Figure 115: Number of patients achieving clinical decongestion at 96 hours



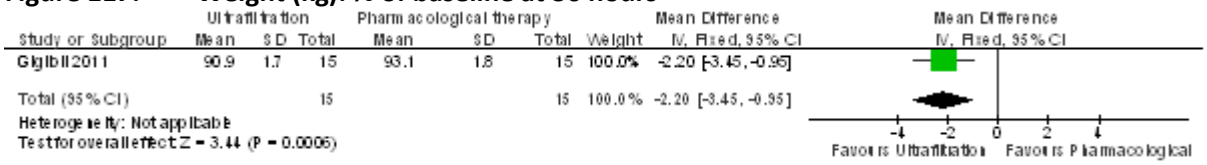
3

Figure 116: Mean change from baseline in body weight (kg) grouped according to follow-up length



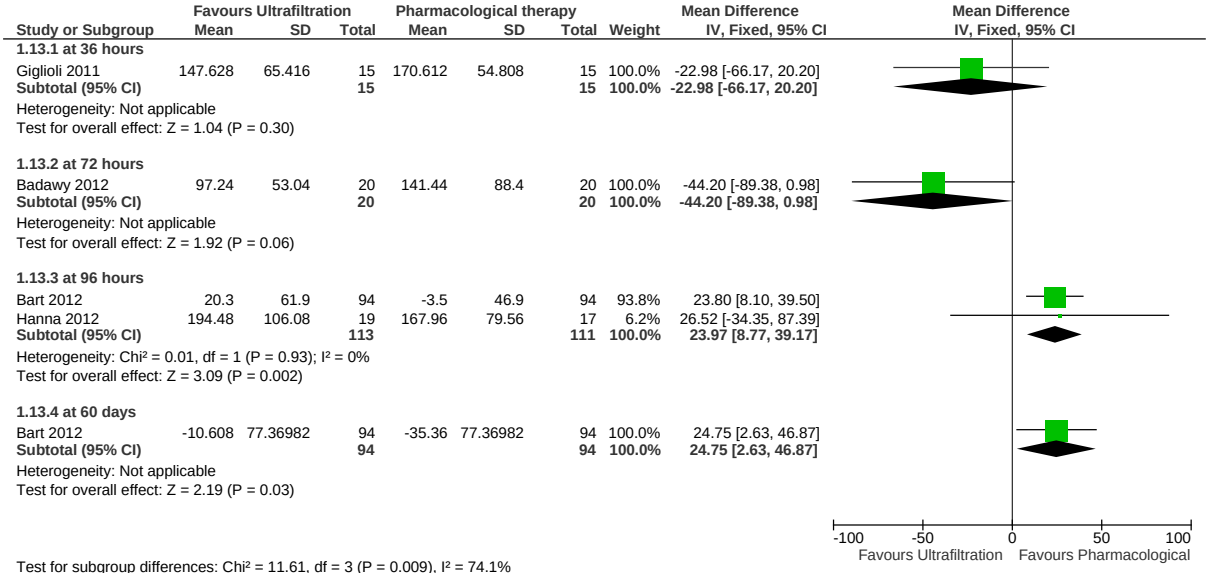
4

Figure 117: Weight (kg): % of baseline at 36 hours



5

Figure 118: Change in serum creatinine 36 hours -90 days (µmol/l) grouped according to length of follow-up



1

Figure 119: Number of patients with rise in serum creatinine 26.5 µmol/l grouped by length of follow-up

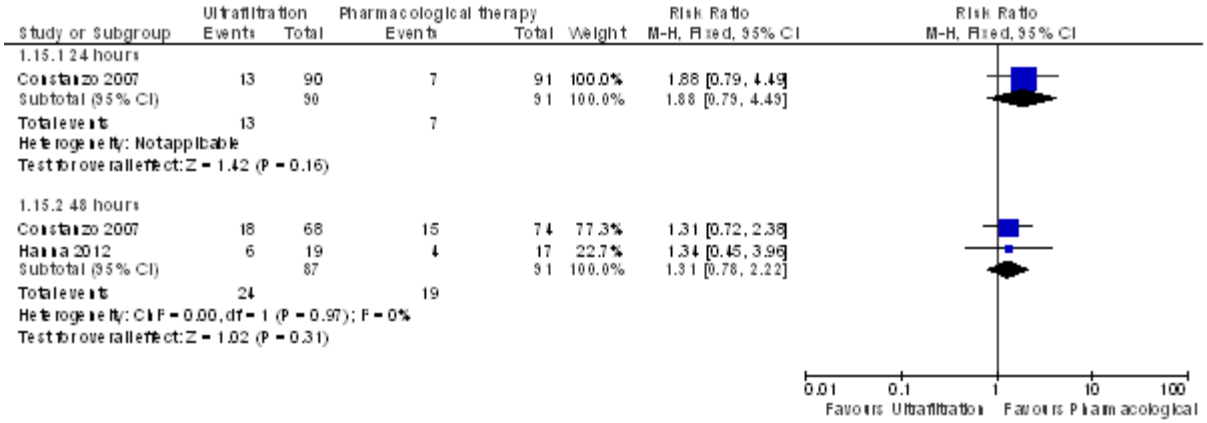
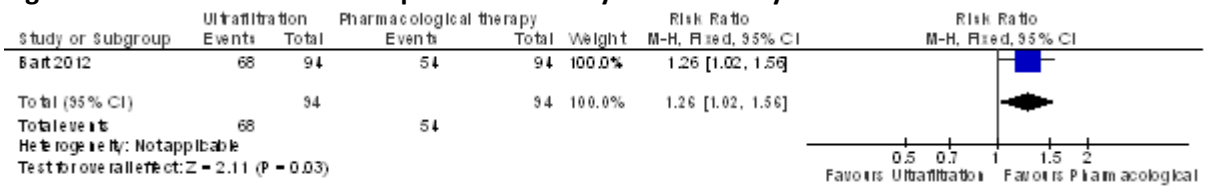
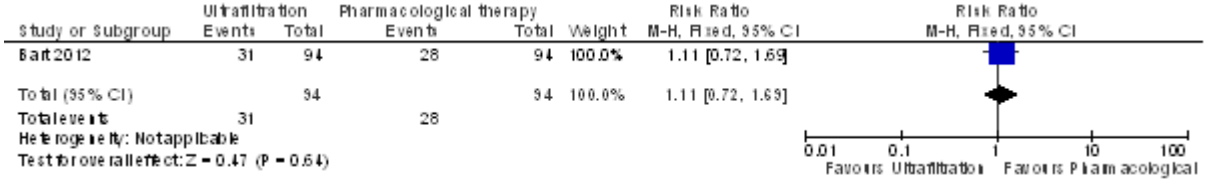


Figure 120: Total number of patients with any SAE at 60 days



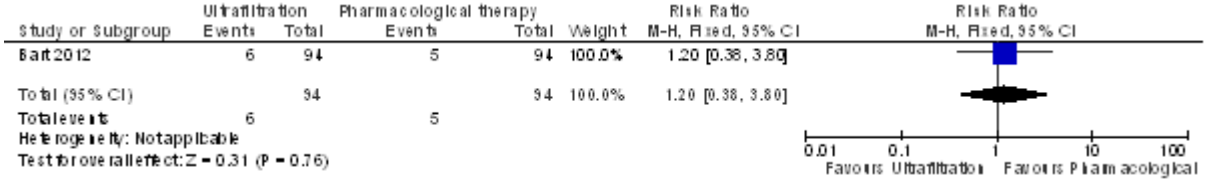
2

Figure 121: Total number of patients with heart failure SAE at 60 days



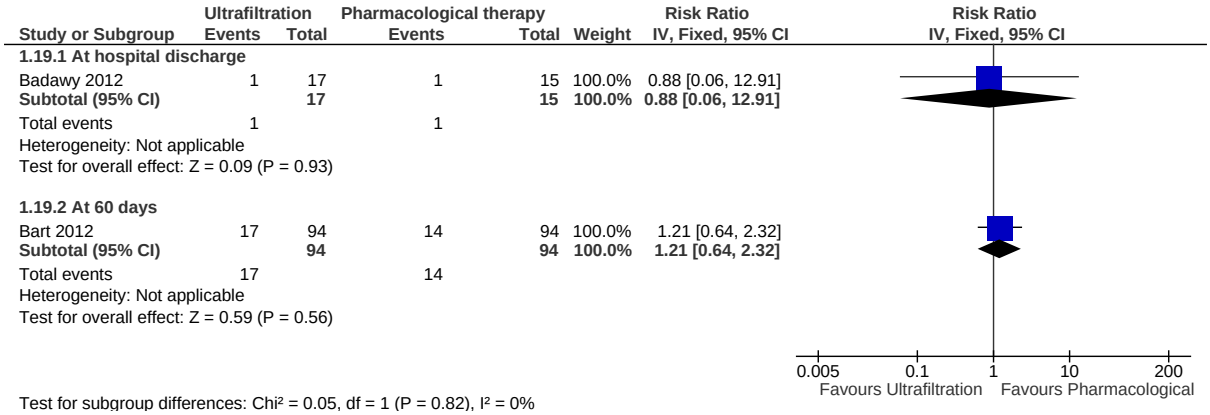
3

Figure 122: Total number of patients with other cardiovascular SAEs at 60 days



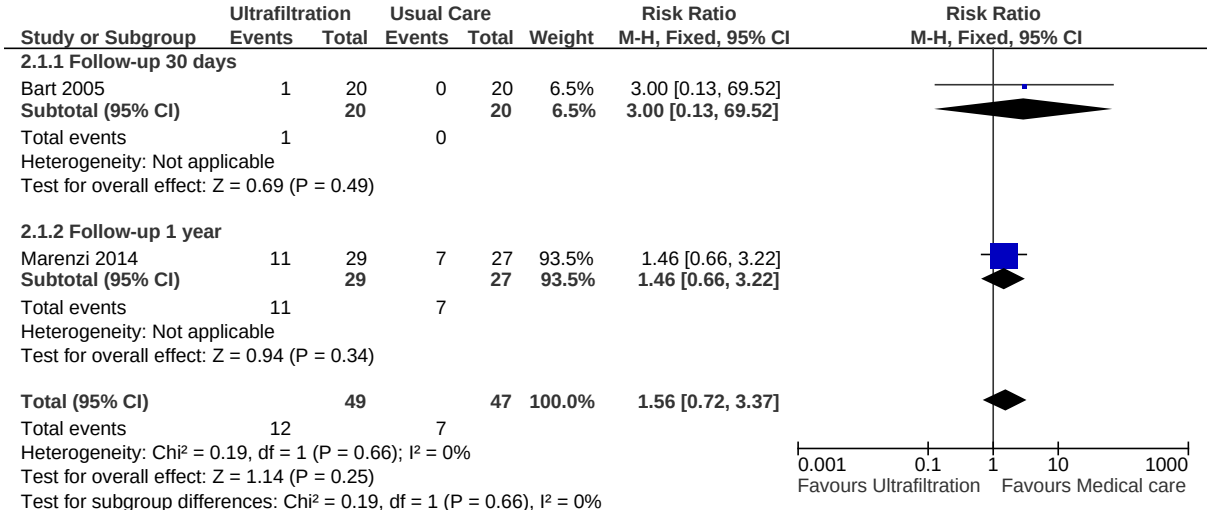
1

Figure 123: Total number of patients with renal failure or dialysis dependence



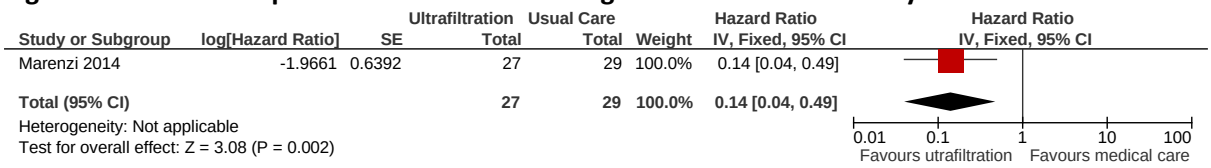
2 **I.3.3.2 Ultrafiltration vs. medical care**

Figure 124: All-cause mortality up to 1 year



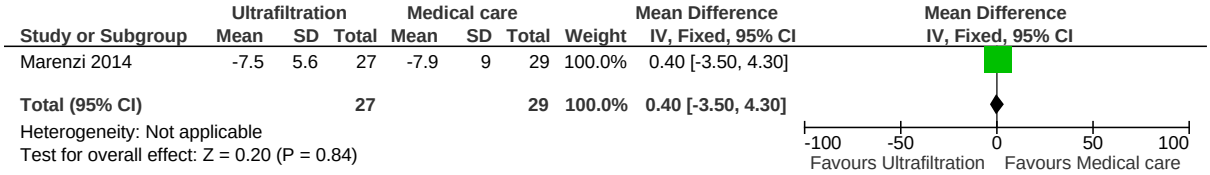
3

Figure 125: Rehospitalisation rate due to congestive heart failure at 1 year



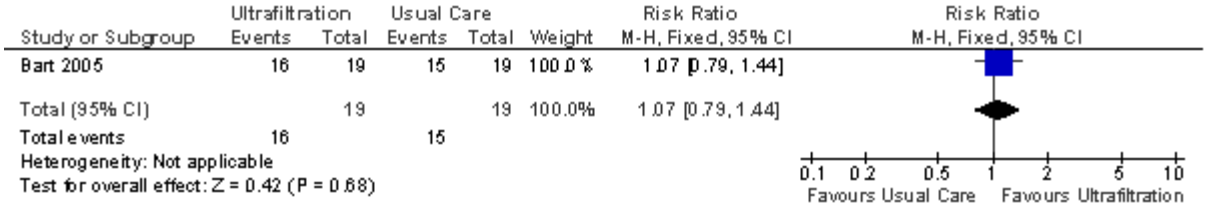
4
5

Figure 126: Mean change from baseline in body weight at hospital discharge



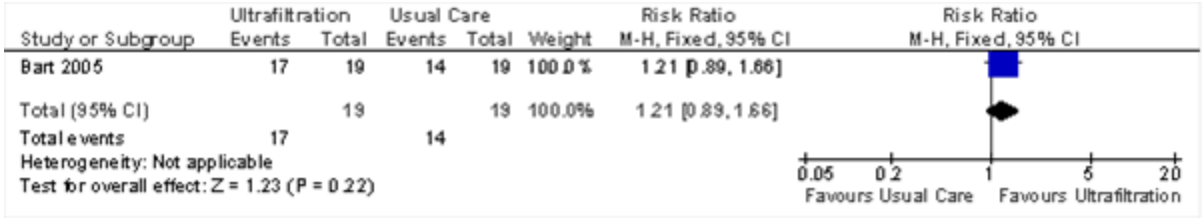
1

Figure 127: Number of patients with marked, moderate or mild improvement in dyspnoea at 24 hours



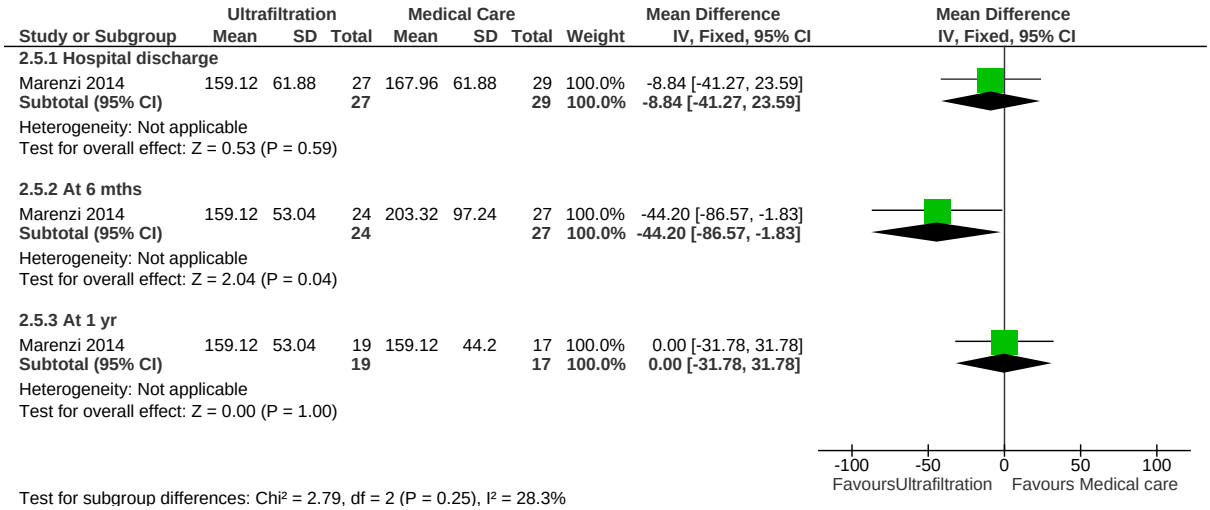
2

Figure 128: Number of patients with marked, moderte or mild improvement in global symptoms at 24 hours



3

Figure 129: Renal function: serum creatinine (µmol/l)

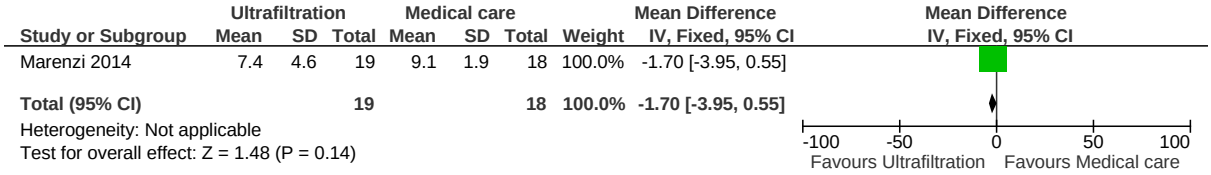


Test for subgroup differences: Chi² = 2.79, df = 2 (P = 0.25), I² = 28.3%

<Insert Note here>

4

Figure 130: Length of hospital stay



I.4 Treatment after stabilisation

I.4.1 Beta blockers

I.4.1.1 Beta-blocker continuation vs. reduction or discontinuation of beta-blocker therapy

Figure 131: Mortality from RCT data

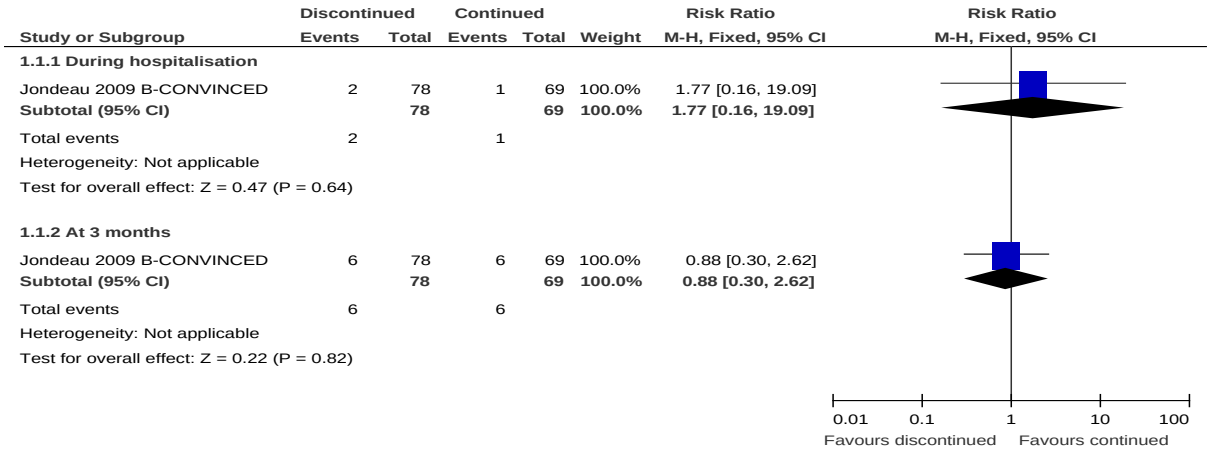


Figure 132: Mortality from observational data (60- to 90-day follow-up)

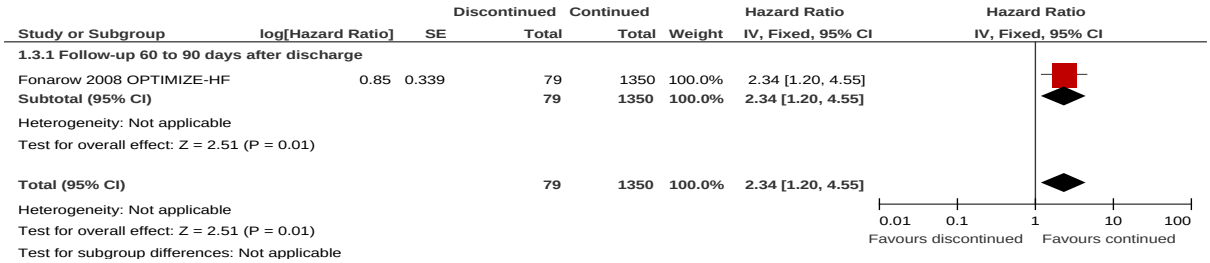
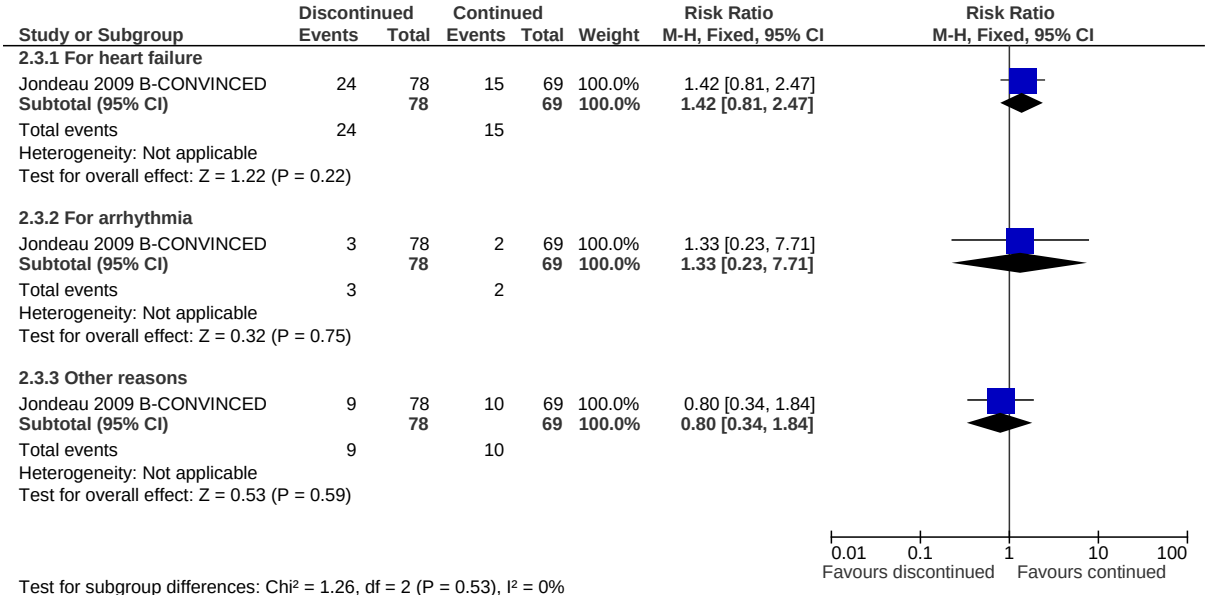
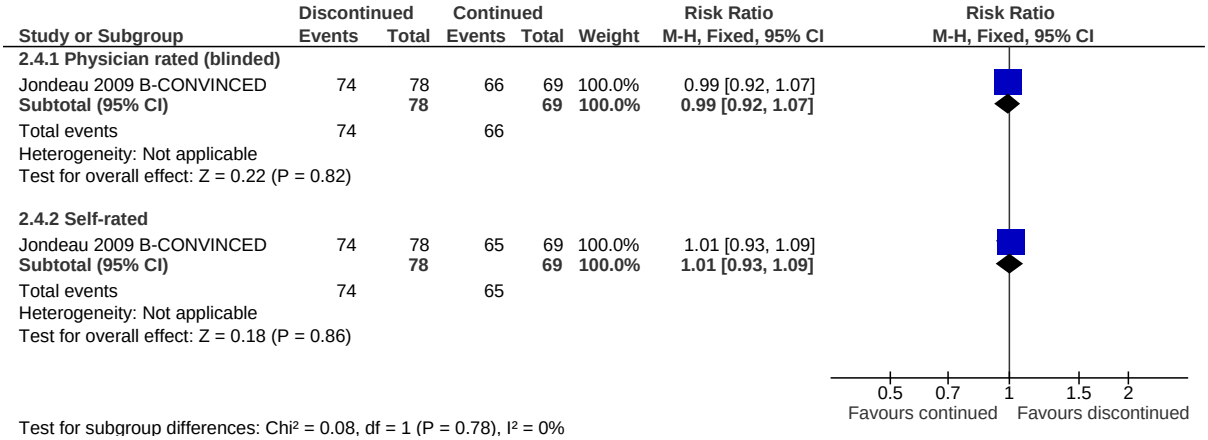


Figure 133: Re-hospitalisation within 3 months



Test for subgroup differences: Chi² = 1.26, df = 2 (P = 0.53), I² = 0%

Figure 134: Improvement of dyspnoea and well-being (day 8)



Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.78), I² = 0%

Figure 135: Rate of beta-blocker treatment post discharge

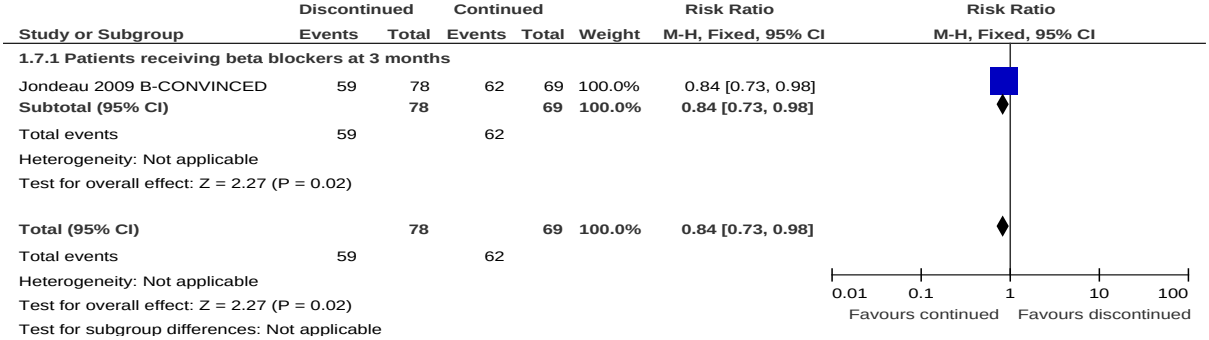
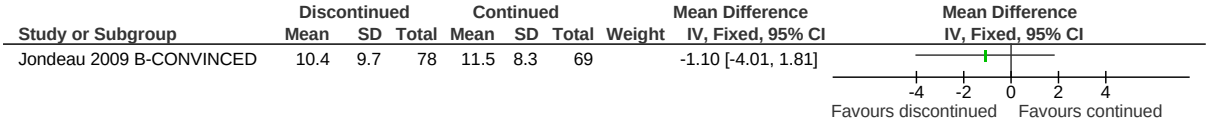


Figure 136: Length of hospital stay



I.4.1.2 Beta-blocker treatment started in hospital / discharge prescription vs. started after discharge (or possibly started after discharge)

Figure 137: Mortality from RCT evidence (60-day follow-up)

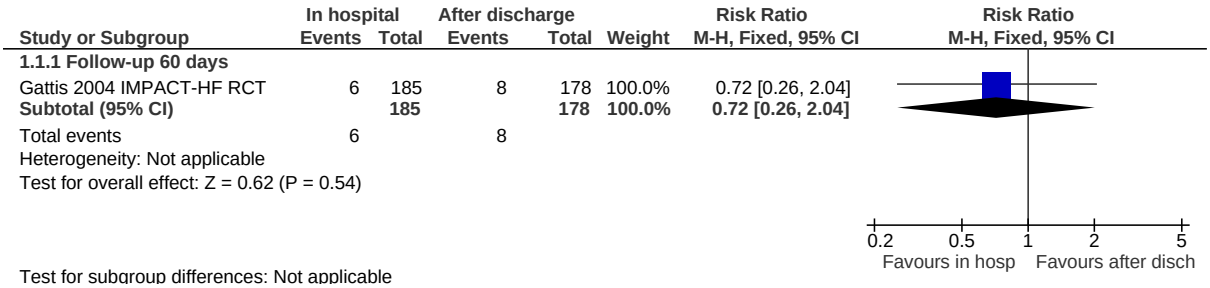
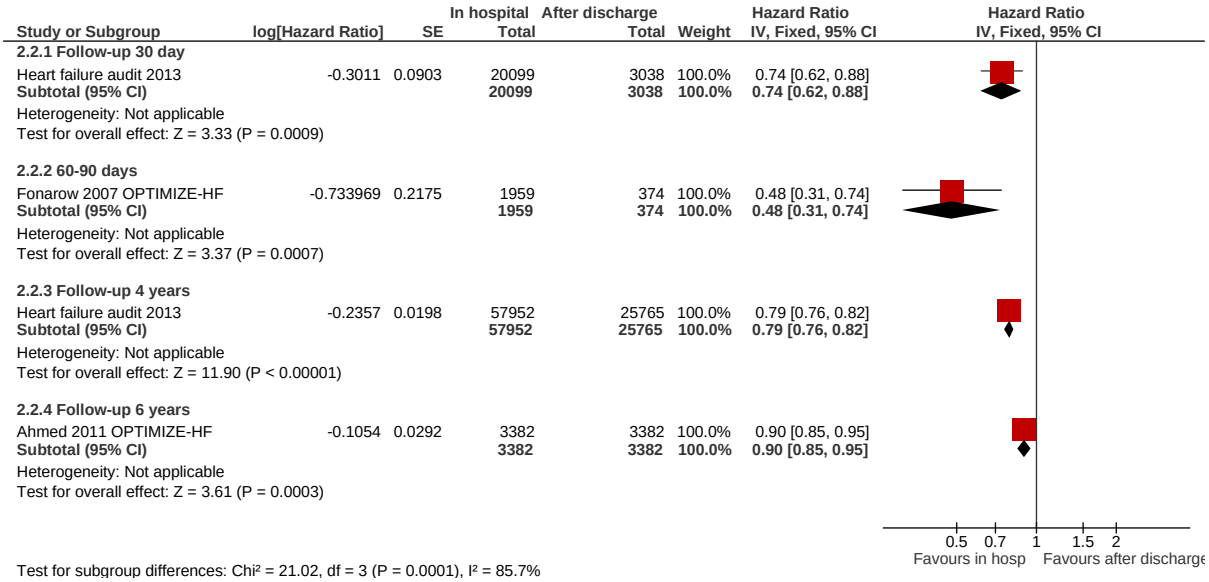


Figure 138: Mortality hazard ratios from observational studies (various follow-up times - see subgroup headings)



I.4.2 ACE inhibitors

I.4.2.1 Commencing ACE inhibitors in hospital

Figure 139: All cause mortality by length of follow-up

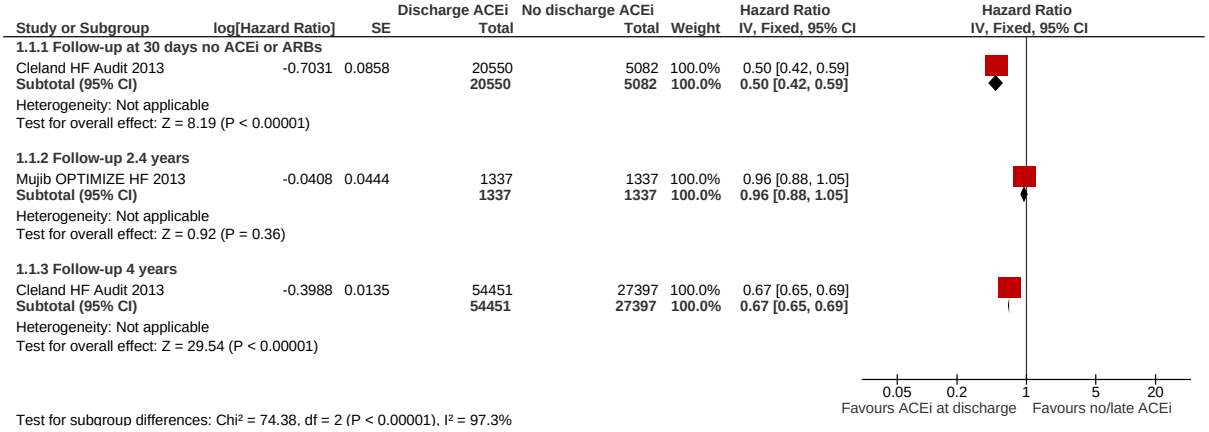


Figure 140: Mortality or heart failure hospitalisation

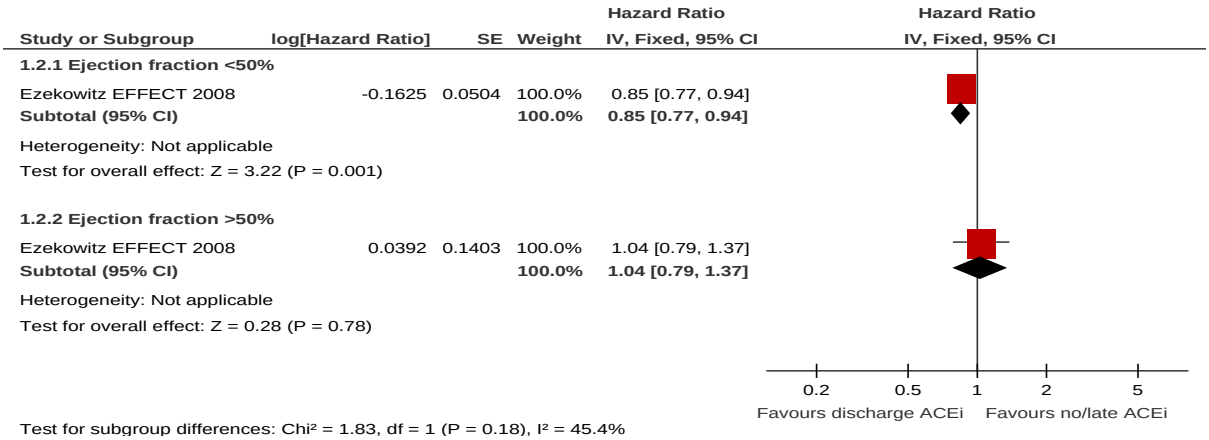


Figure 141: Rehospitalisation (for heart failure or all cause)

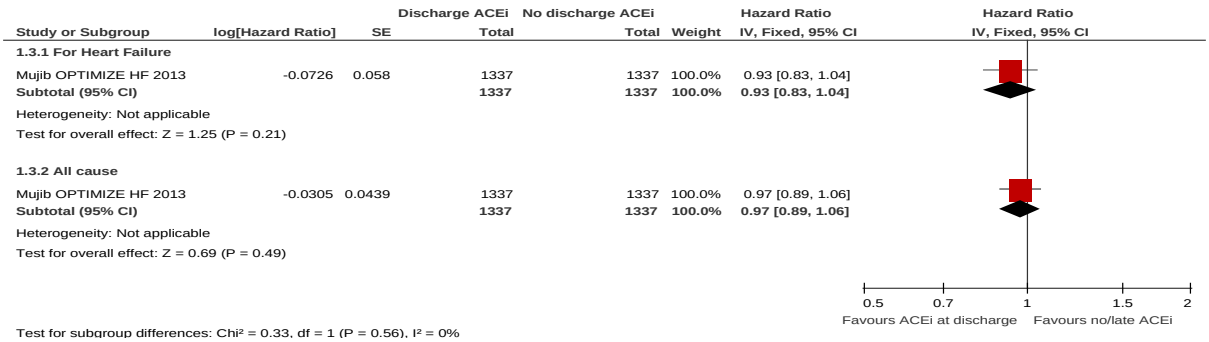


Figure 142: Mortality or heart failure hospitalisation subgrouped by ejection fraction <50% or >50%

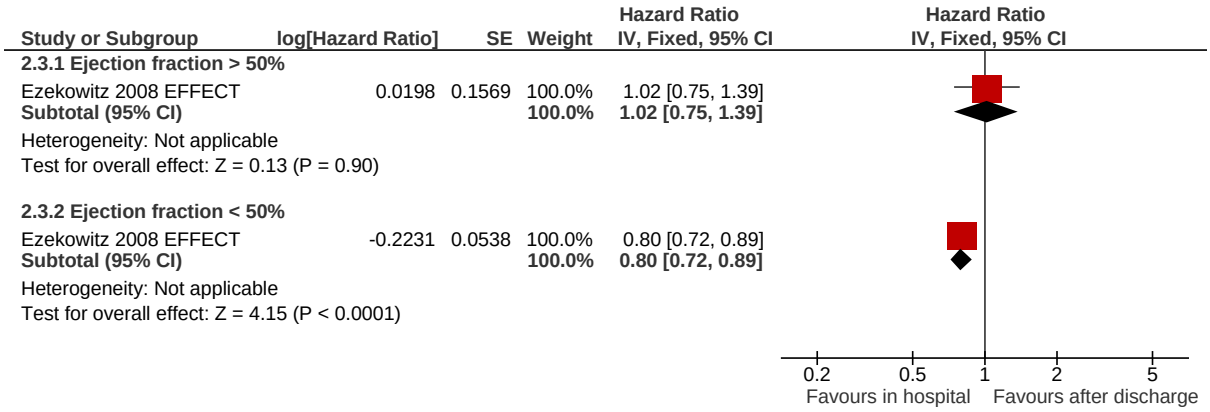


Figure 143: Withdrawal due to serious adverse events (60 days)

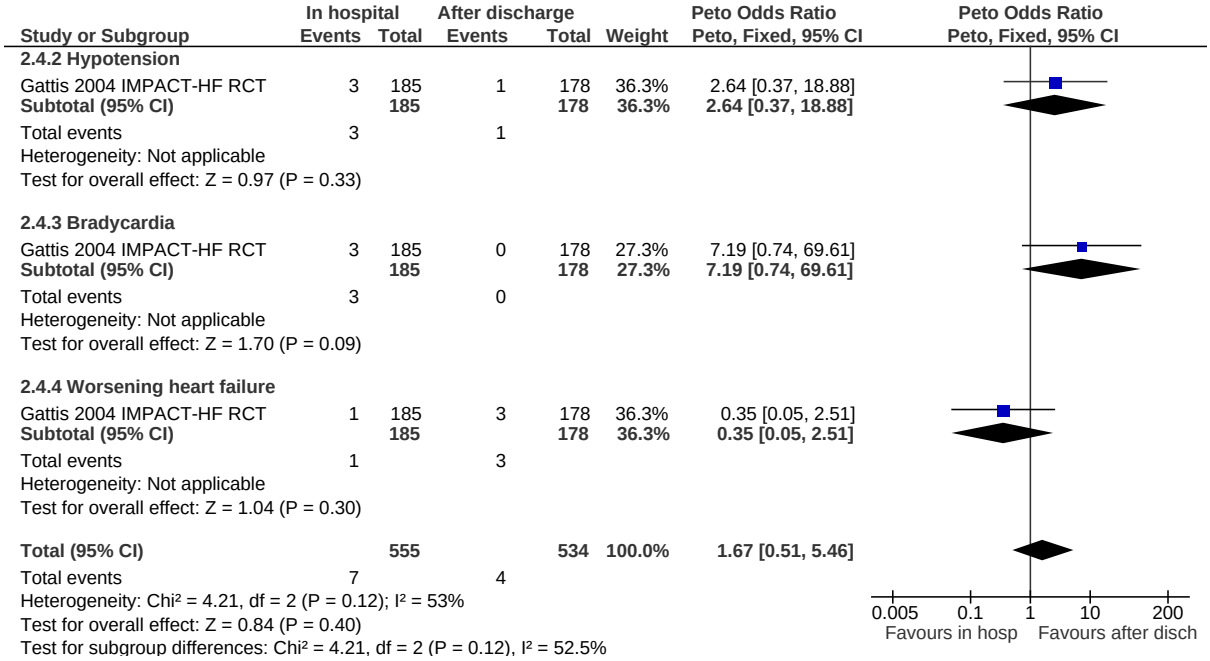


Figure 144: Rate of beta-blocker treatment post discharge

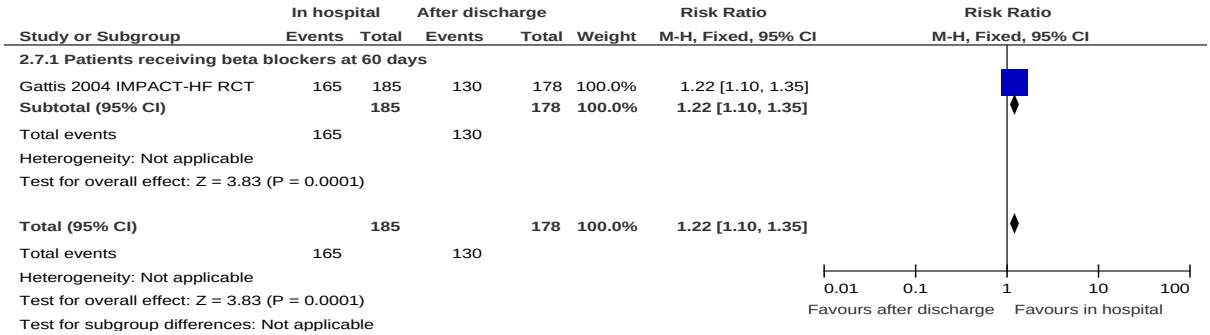
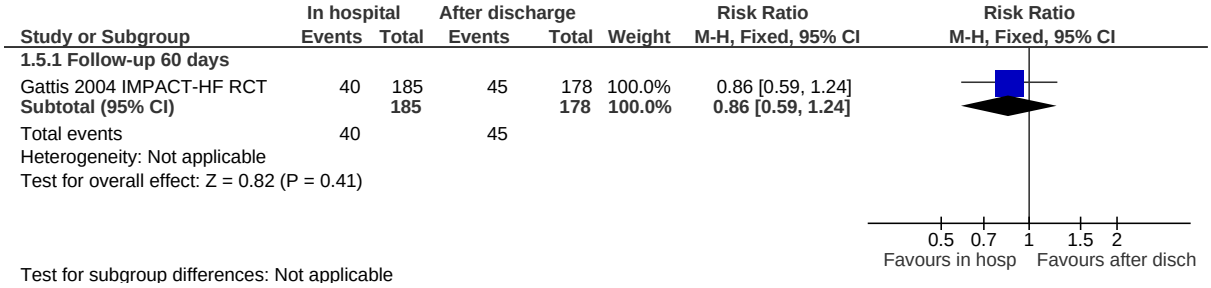


Figure 145: Rehospitalisation at 60 days



I.4.3 MRAs

I.4.3.1 Commencing MRAs in hospital

Figure 146: All-cause and sudden cardiac mortality by length of follow-up

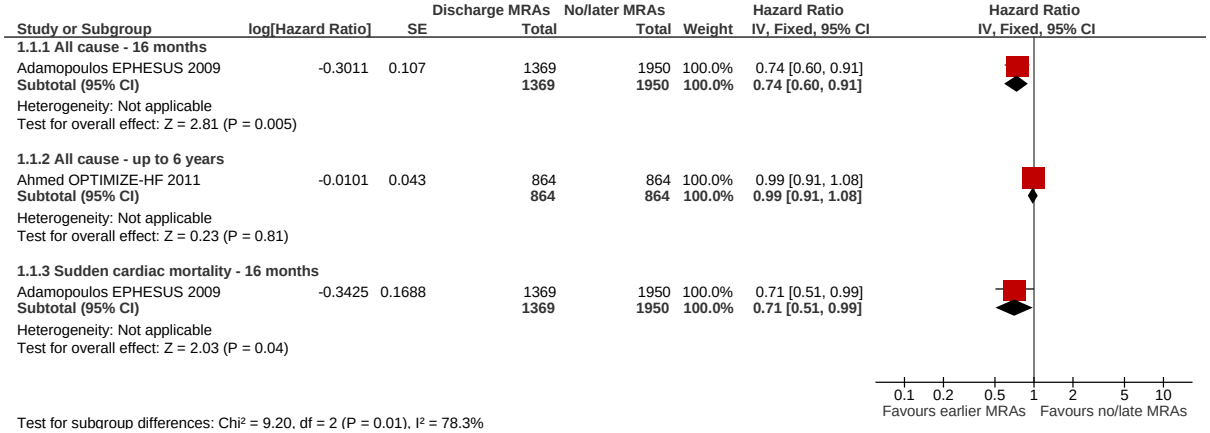
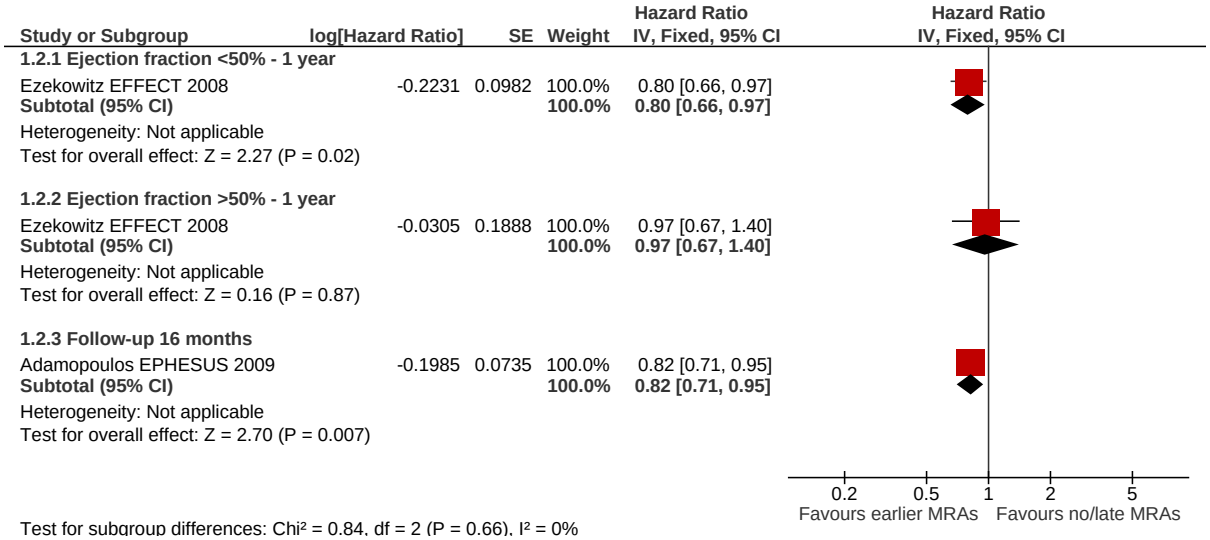


Figure 147: Mortality or heart failure hospitalisation



I.5 Surgical and percutaneous interventions

I.5.1 Aortic stenosis

I.5.1.1 Percutaneous vs. medical management of aortic stenosis

Figure 148: All cause mortality – hazard ratio (2 years follow-up)

Study or Subgroup	log[Hazard Ratio]	SE	TAVI Total	Medical Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Makkar PARTNER B 2012	-0.5798	0.1348	179	179	100.0%	0.56 [0.43, 0.73]
Total (95% CI)			**179**	**179**	**100.0%**	**0.56 [0.43, 0.73]**

Heterogeneity: Not applicable
Test for overall effect: Z = 4.30 (P < 0.0001)

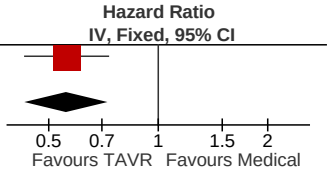


Figure 149: Mortality from cardiac causes (2 year follow-up)

Study or Subgroup	log[Hazard Ratio]	SE	TAVI Total	Medical Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Makkar PARTNER B 2012	-0.821	0.1625	179	179	100.0%	0.44 [0.32, 0.61]
Total (95% CI)			**179**	**179**	**100.0%**	**0.44 [0.32, 0.61]**

Heterogeneity: Not applicable
Test for overall effect: Z = 5.05 (P < 0.00001)

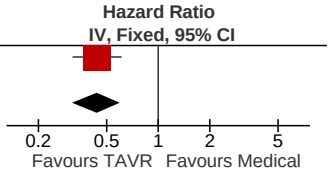


Figure 150: Stroke (2 year follow-up)

Study or Subgroup	TAVI Events	TAVI Total	Medical Events	Medical Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
1.4.1 Minor stroke 30 days							
Leon PARTNER B 2010	3	179	1	179	100.0%	3.00 [0.32, 28.57]	2010
Subtotal (95% CI)		**179**		**179**	**100.0%**	**3.00 [0.32, 28.57]**	
Total events	3		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.96 (P = 0.34)							
1.4.2 Minor stroke 12 mths							
Leon PARTNER B 2010	4	179	1	179	100.0%	4.00 [0.45, 35.44]	2010
Subtotal (95% CI)		**179**		**179**	**100.0%**	**4.00 [0.45, 35.44]**	
Total events	4		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.25 (P = 0.21)							
1.4.3 Major stroke 30 days							
Leon PARTNER B 2010	9	179	2	179	100.0%	4.50 [0.99, 20.54]	2010
Subtotal (95% CI)		**179**		**179**	**100.0%**	**4.50 [0.99, 20.54]**	
Total events	9		2				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.94 (P = 0.05)							
1.4.4 Major stroke 12 mths							
Leon PARTNER B 2010	14	179	7	179	100.0%	2.00 [0.83, 4.84]	2010
Subtotal (95% CI)		**179**		**179**	**100.0%**	**2.00 [0.83, 4.84]**	
Total events	14		7				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.54 (P = 0.12)							
1.4.5 Stroke 24 mths							
Makkar PARTNER B 2012	22	179	8	179	100.0%	2.75 [1.26, 6.01]	2012
Subtotal (95% CI)		**179**		**179**	**100.0%**	**2.75 [1.26, 6.01]**	
Total events	22		8				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.53 (P = 0.01)							

Test for subgroup differences: Chi² = 1.01, df = 4 (P = 0.91), I² = 0%

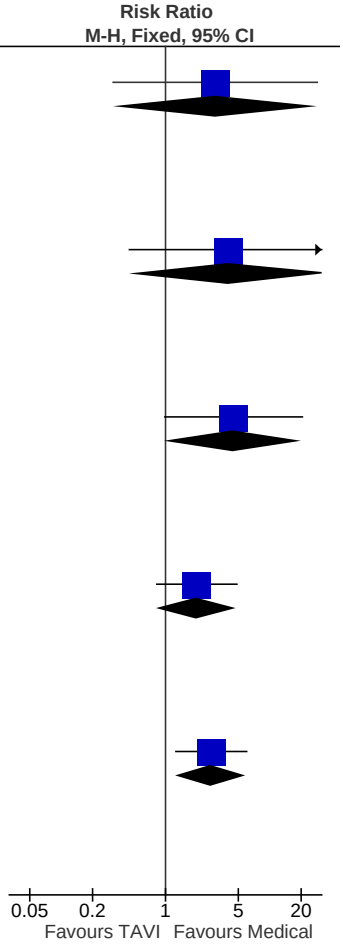
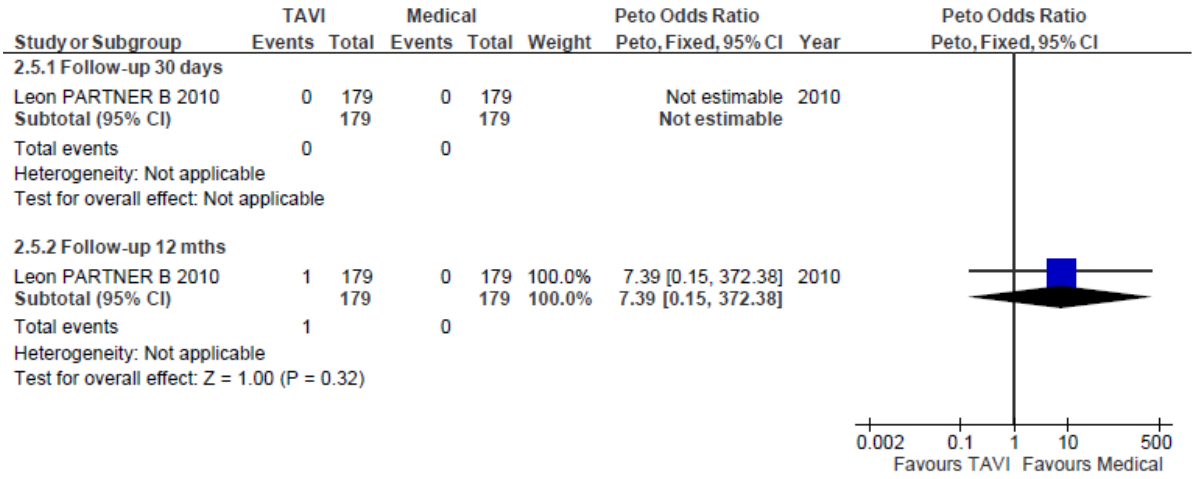
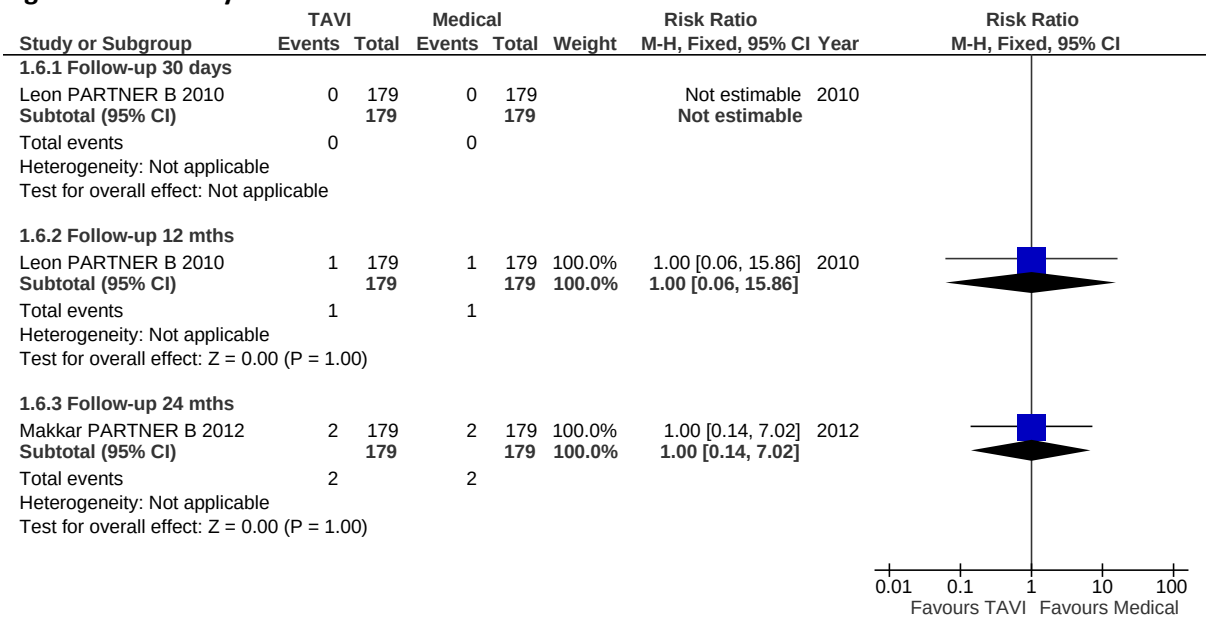


Figure 151: Transient ischemic attack



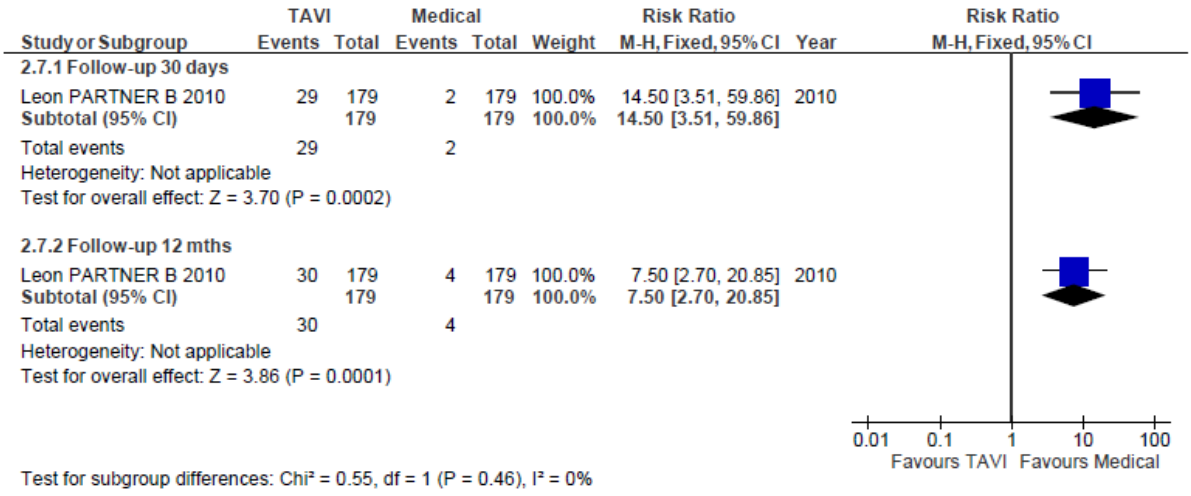
1

Figure 152: Myocardial infarction



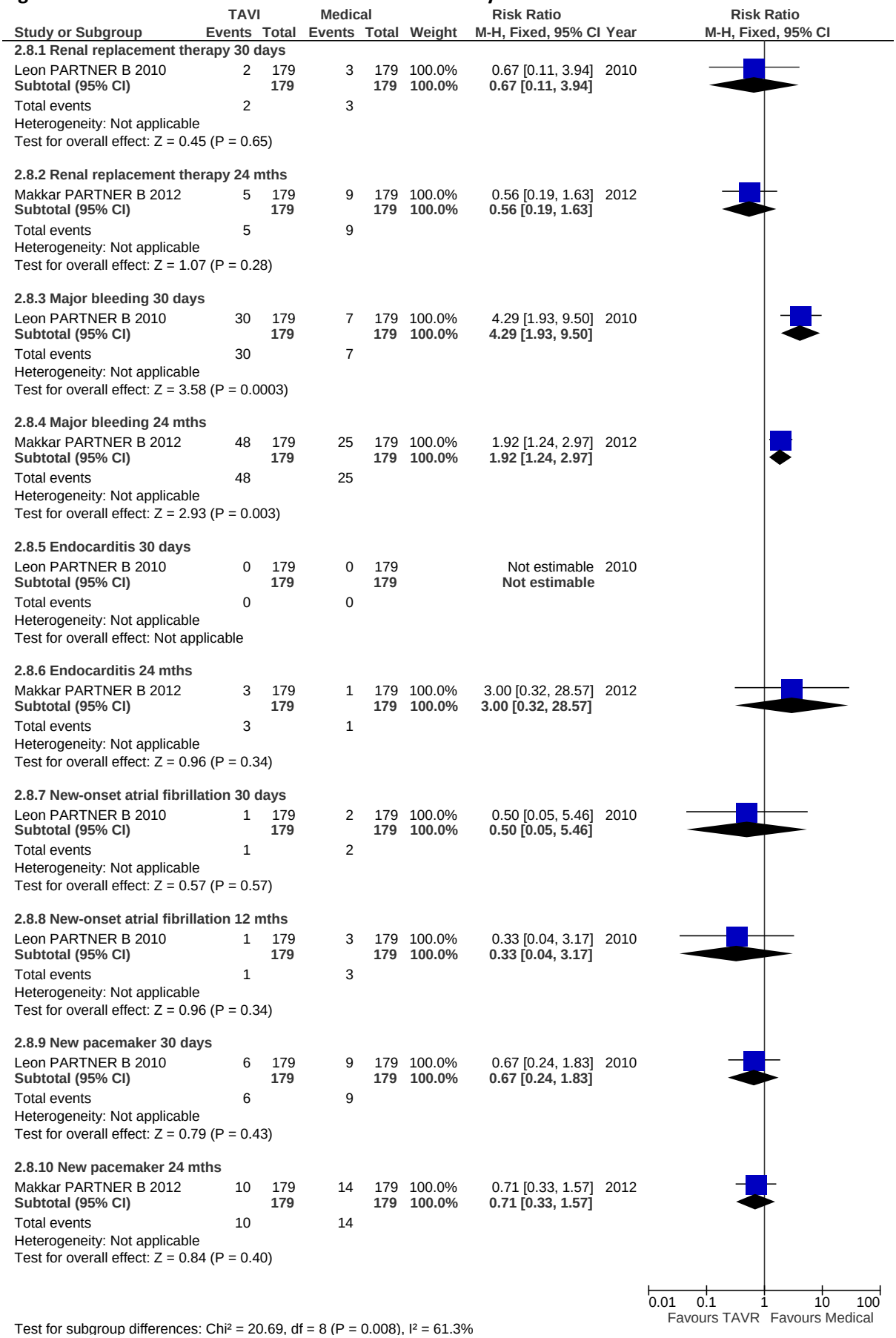
2

Figure 153: Major vascular complications



1

Figure 154: Other serious adverse events at 30 days and 24 months



Test for subgroup differences: Chi² = 20.69, df = 8 (P = 0.008), I² = 61.3%

1

2

Figure 155: Rehospitalisation (2 year follow-up)

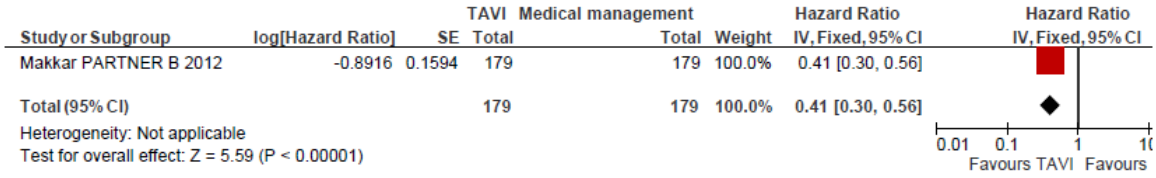
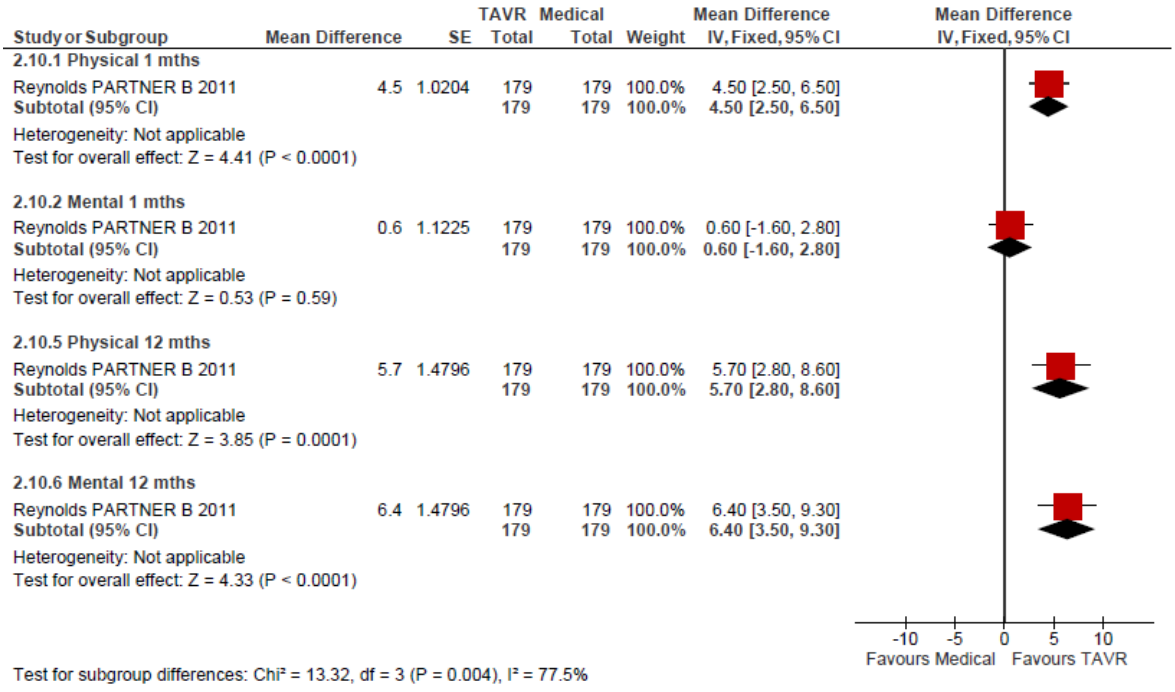
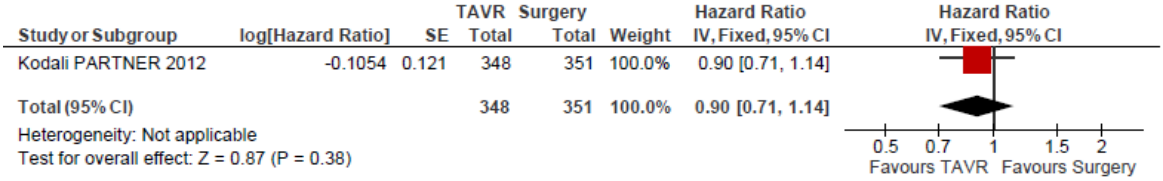


Figure 156: Quality of life (SF-12)



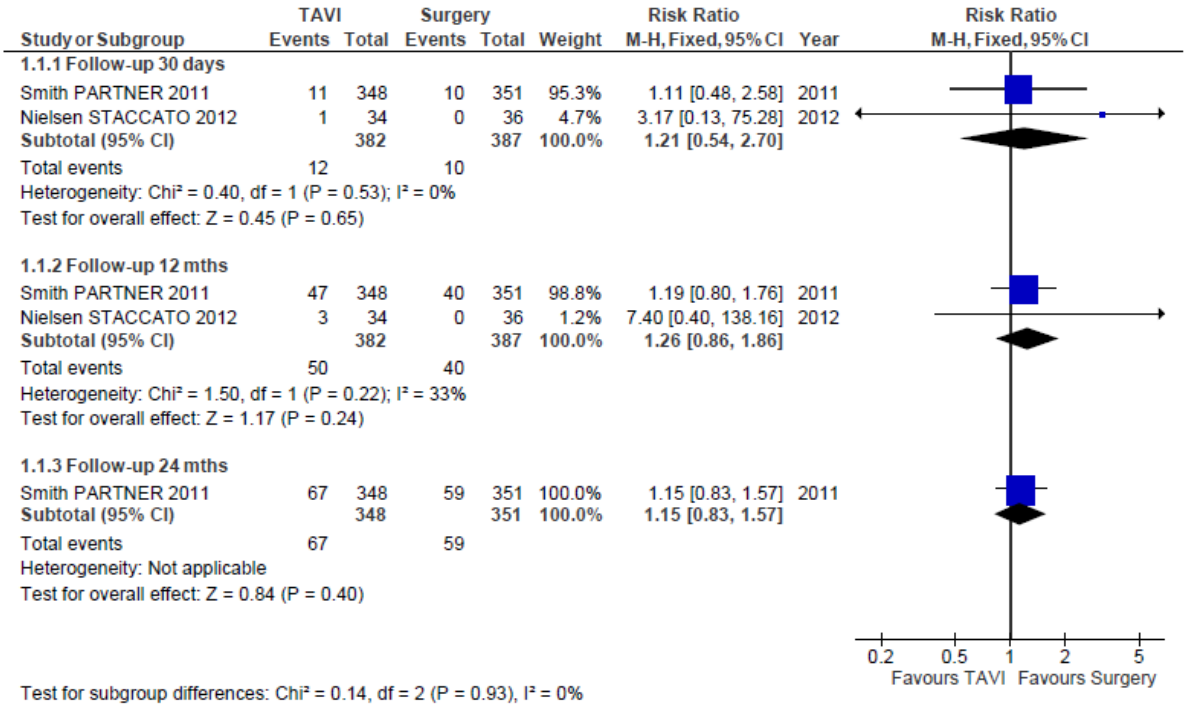
3 **I.5.1.2 Percutaneous vs. surgery**

Figure 157: All-cause mortality (3-year follow-up)



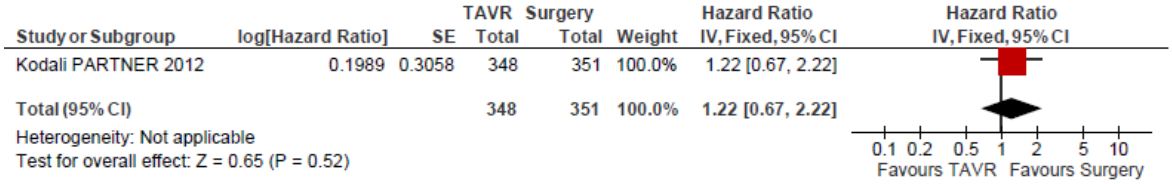
4

Figure 158: Mortality from cardiac causes (2-year follow-up)



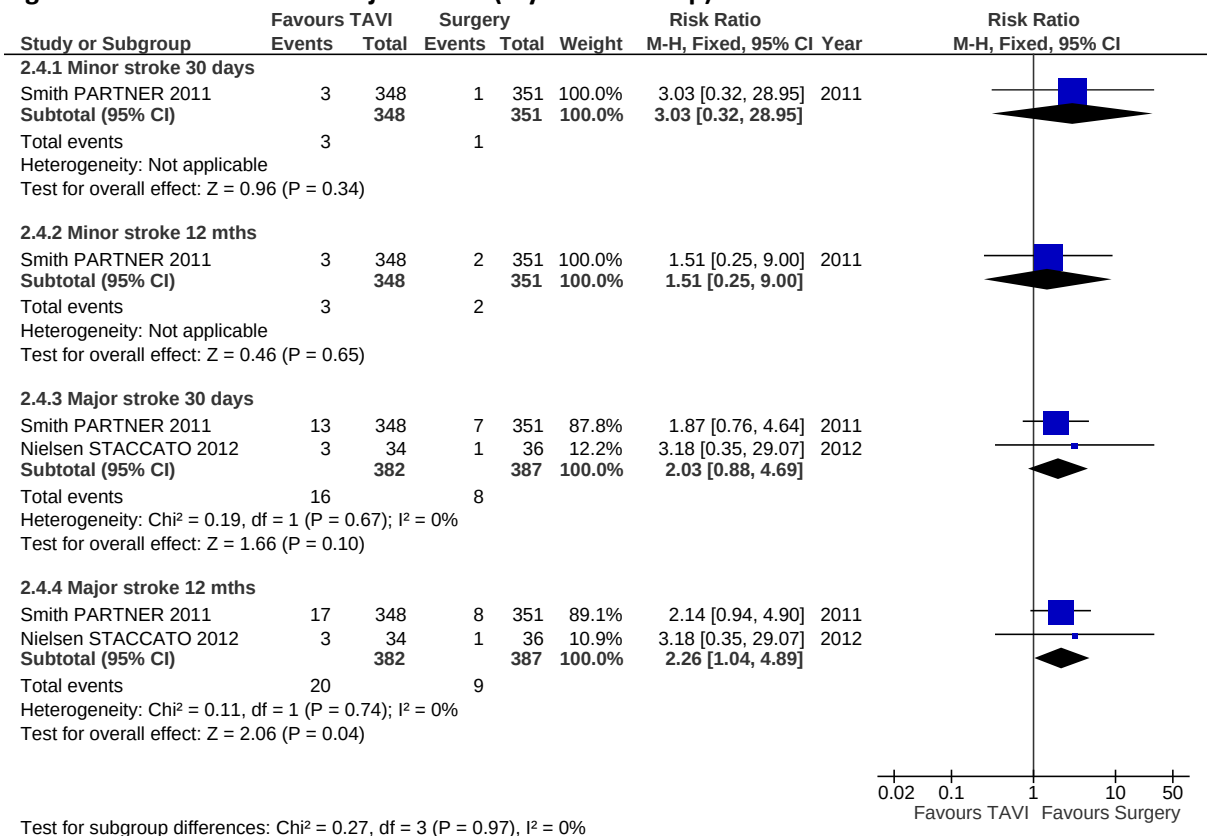
1

Figure 159: Stroke (3-year follow-up)



2

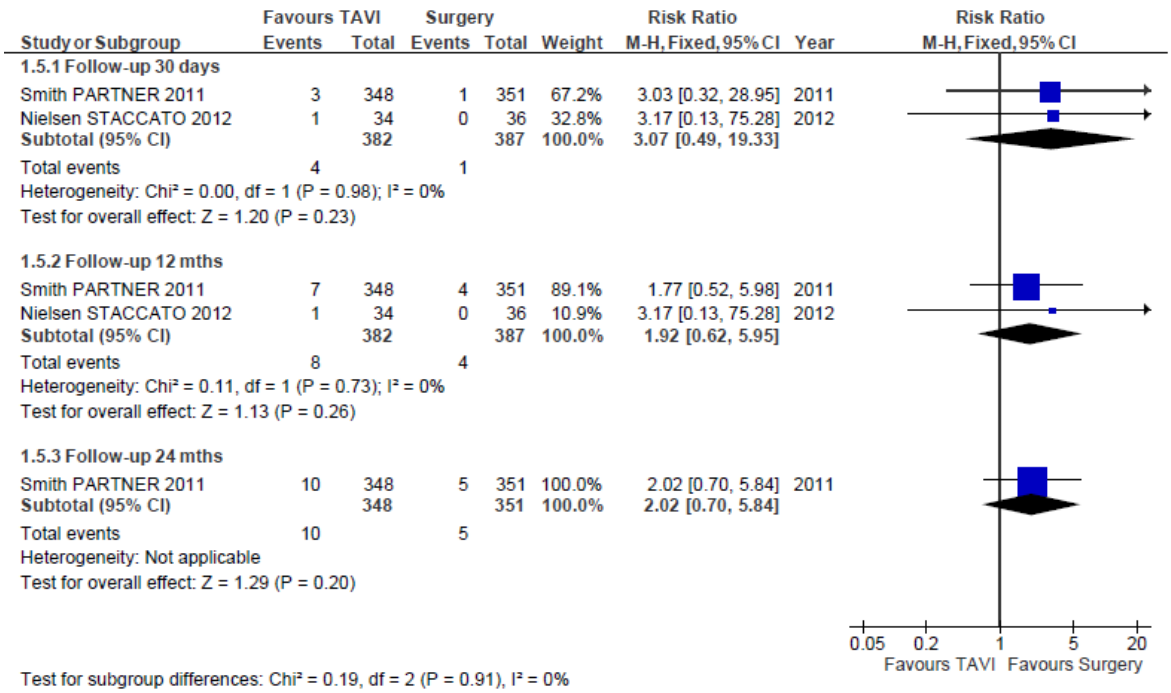
Figure 160: Minor and major stroke (2-year follow-up)



1

2

Figure 161: Transient ischemic attack (2-year follow-up)



3

Figure 162: Myocardial infarction (2-year follow-up)

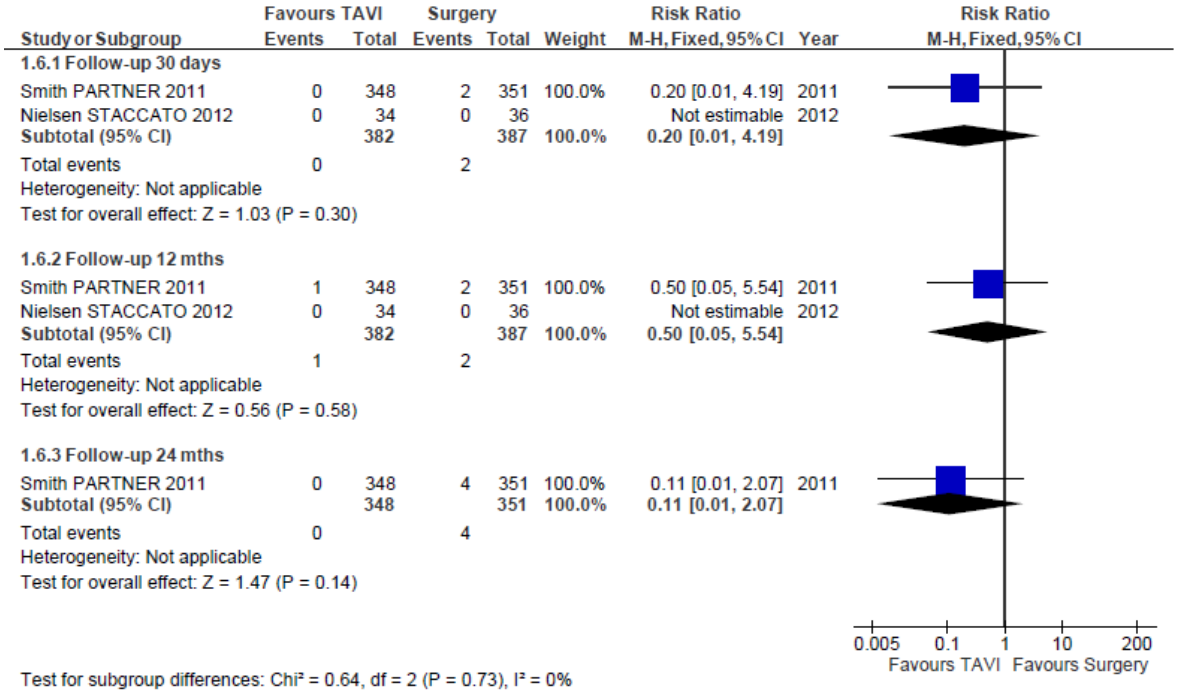
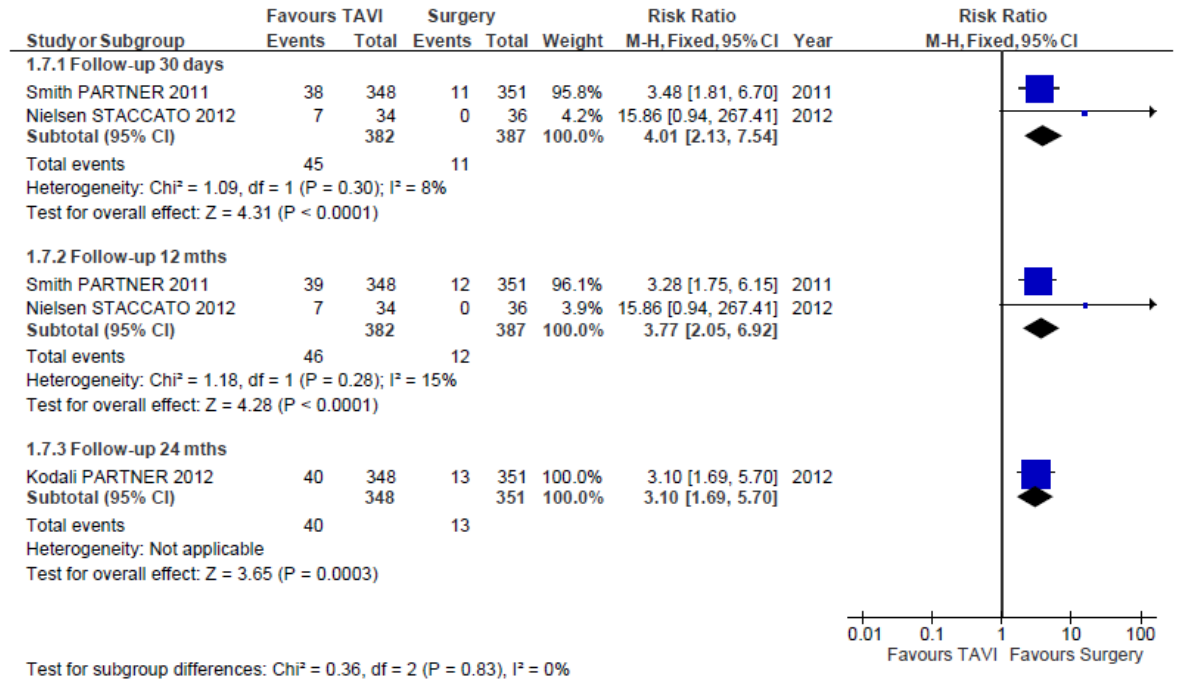


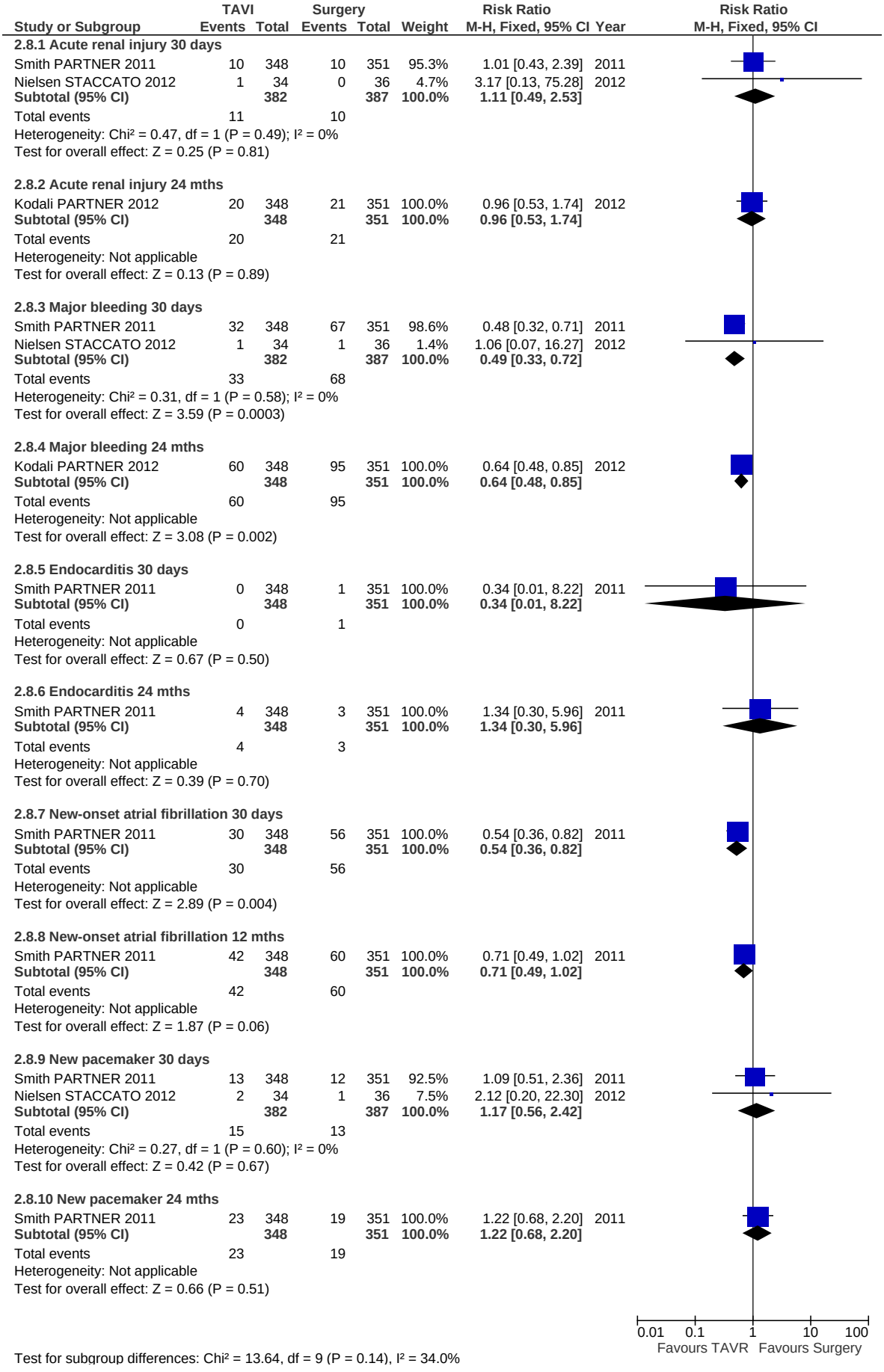
Figure 163: Major vascular complications (2-year follow-up)



1

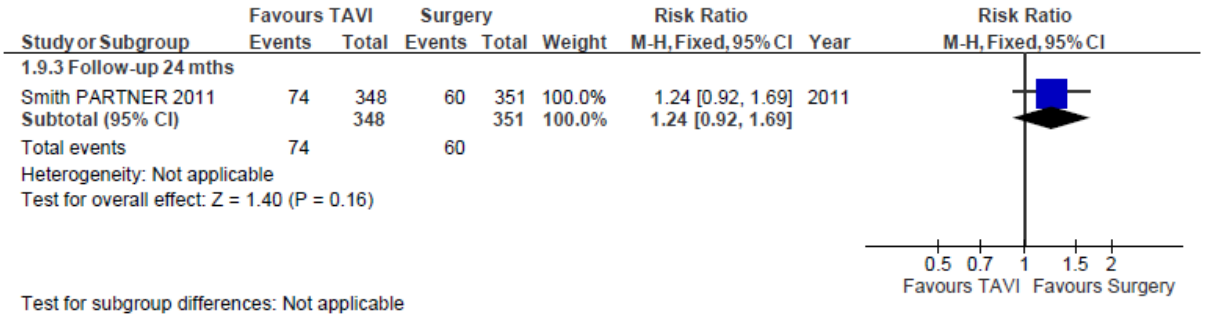
2

Figure 164: Other severe adverse events (30-day and 2-year follow-up)



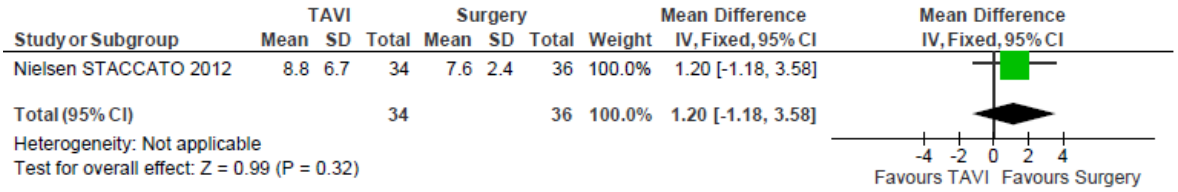
1

Figure 165: Rehospitalisation (2-year follow-up)



2

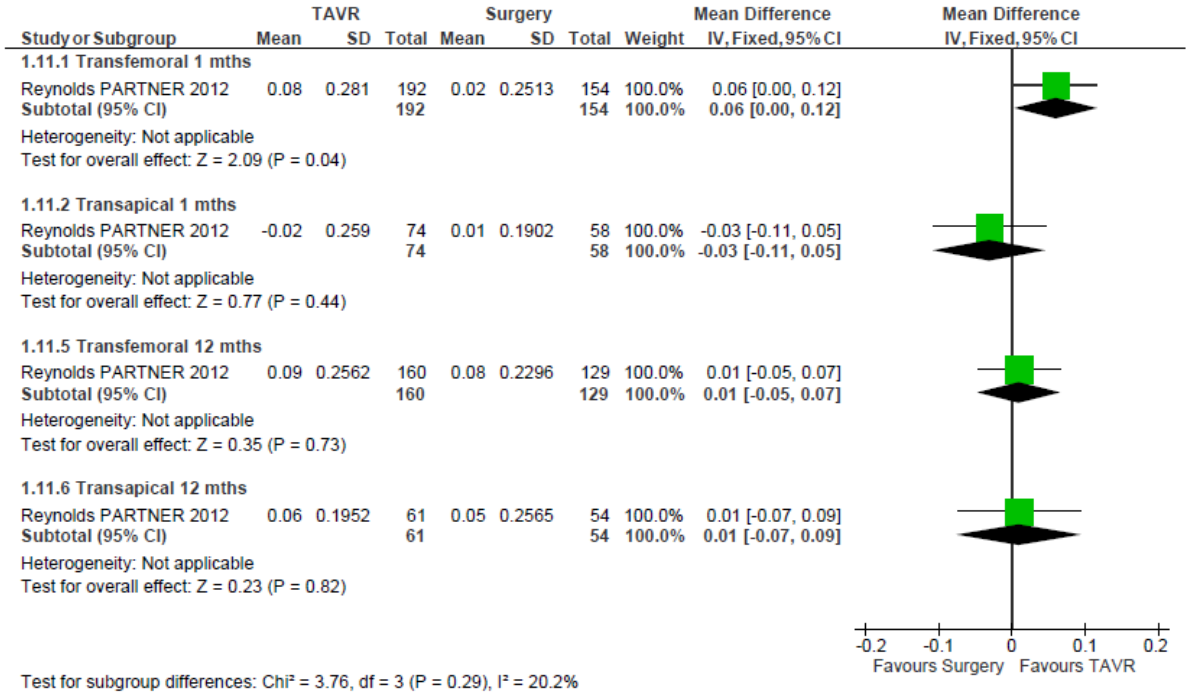
Figure 166: Length of index hospital stay



3

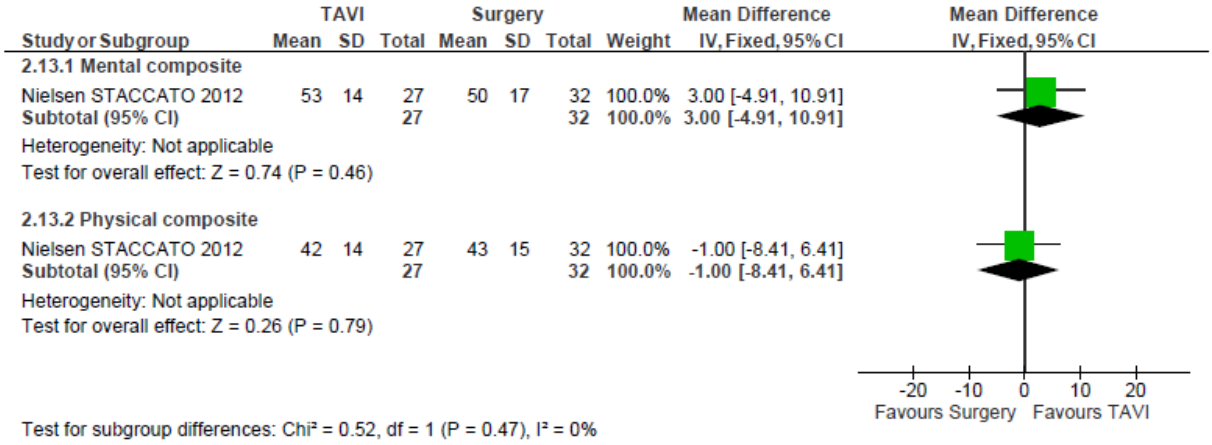
4

Figure 167: Health related quality of life – EQ5-D (1 year follow-up)



5

Figure 168: Quality of life –SF-36 (3 months)



I.5.2 Mitral regurgitation

I.5.2.1 Percutaneous vs. surgical treatment

Figure 169: Mortality

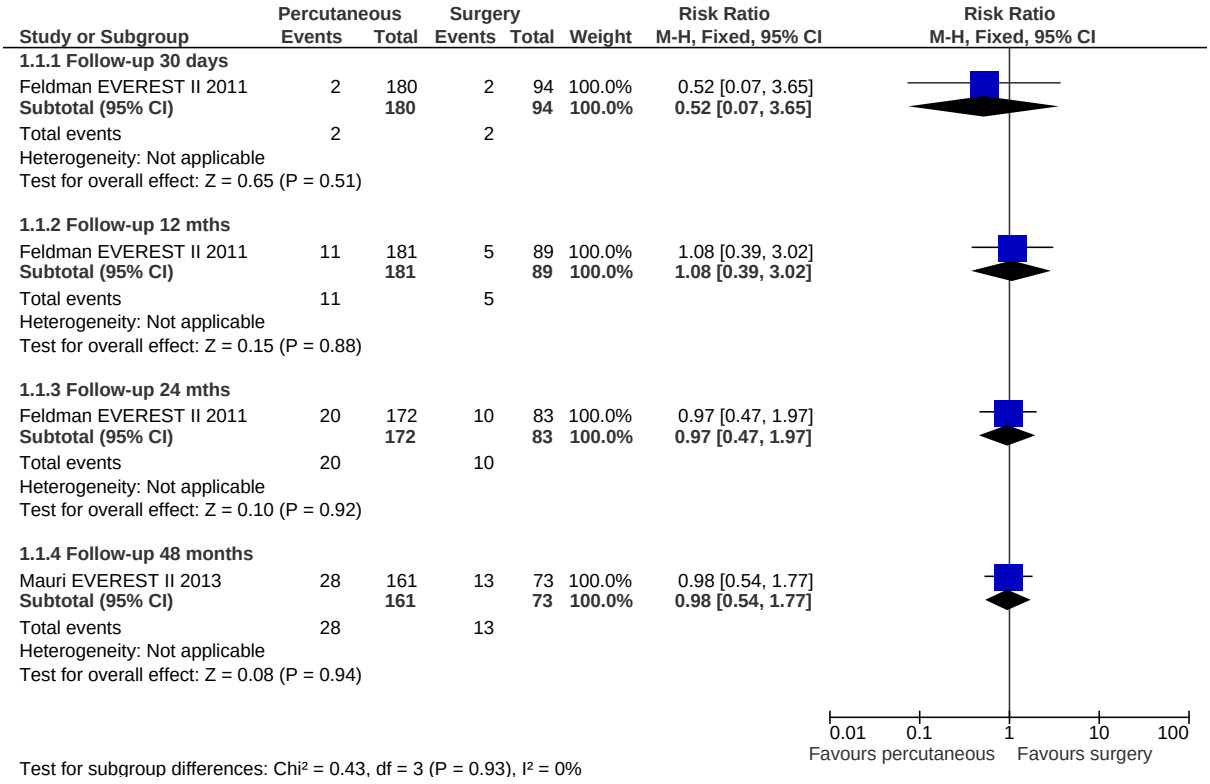
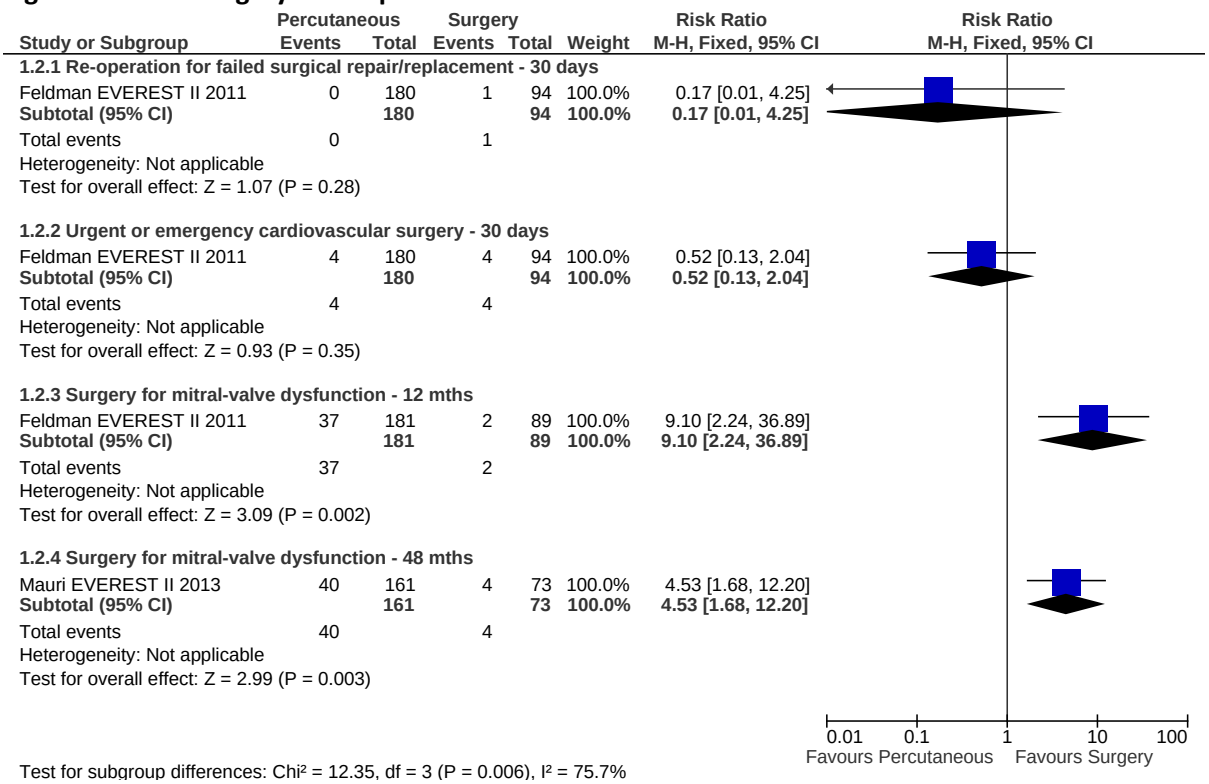
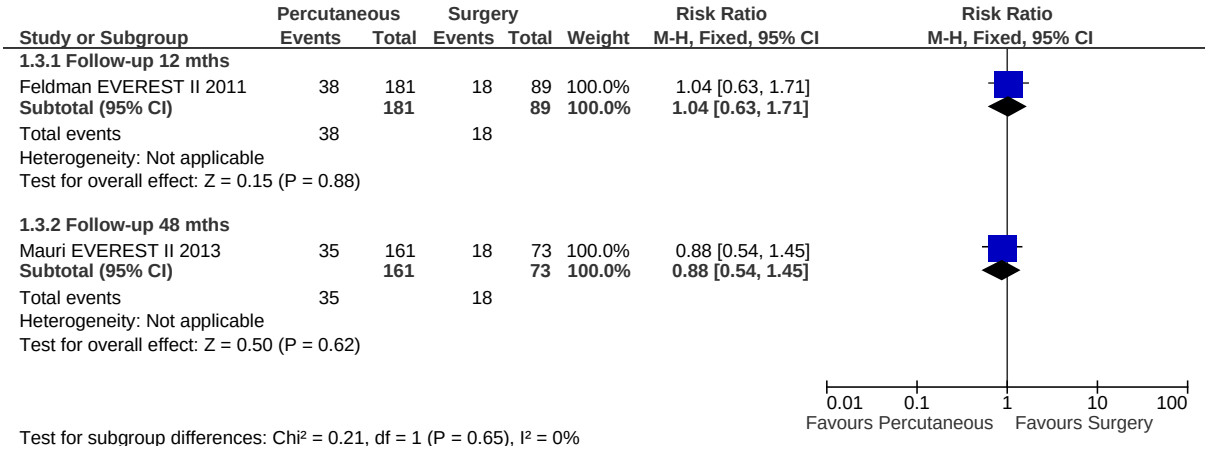


Figure 170: Surgery or re-operation



1

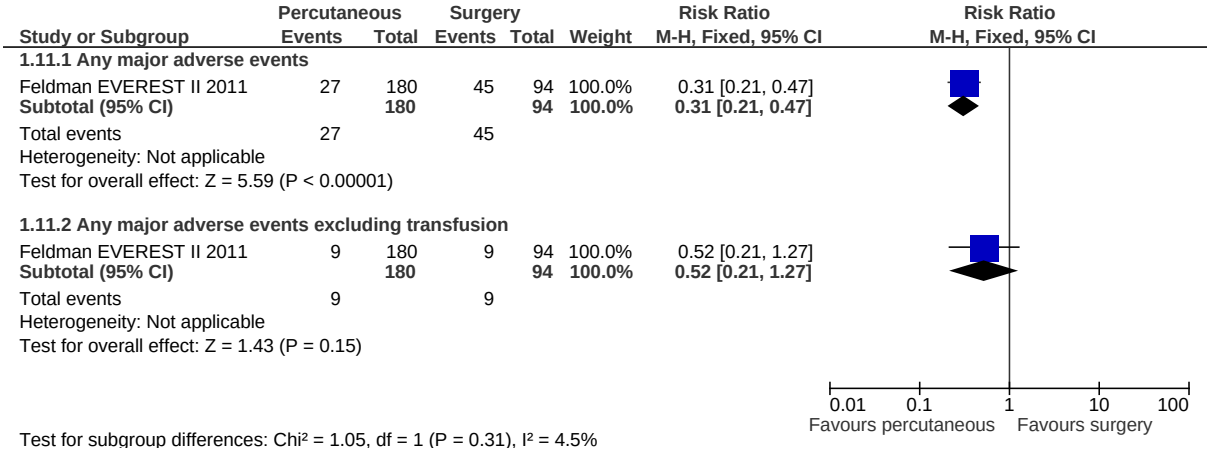
Figure 171: Grade 3+ or 4+ mitral regurgitation



2

3

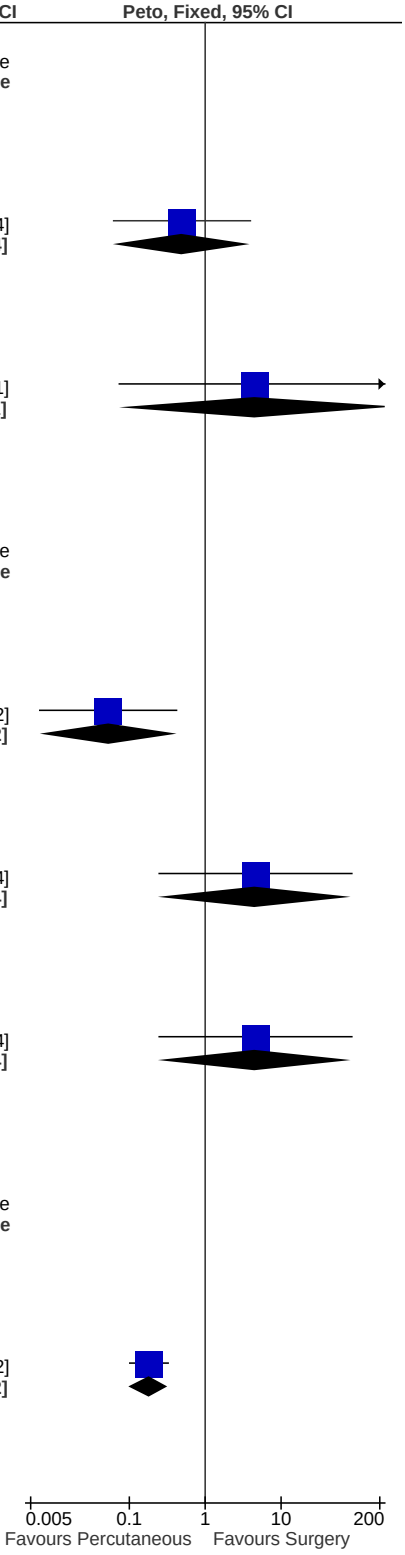
Figure 172: Rate of people experiencing major adverse events (overall) at 30 days



Test for subgroup differences: $Chi^2 = 1.05$, df = 1 (P = 0.31), $I^2 = 4.5\%$

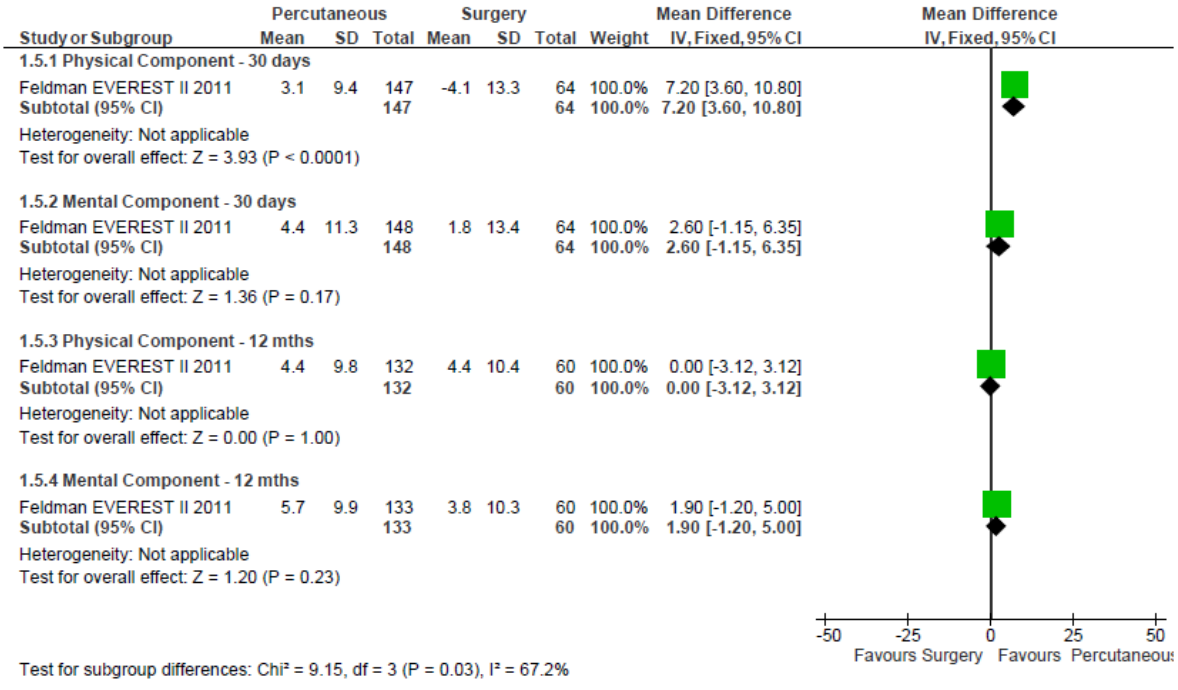
Figure 173: Adverse events (at 30 days)

Study or Subgroup	Percutaneous Events	Total	Surgery Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.4.1 Myorcardial Infarction						
Feldman EVEREST II 2011	0	180	0	94		Not estimable
Subtotal (95% CI)		**180**		**94**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.4.2 Major stroke						
Feldman EVEREST II 2011	2	180	2	94	100.0%	0.49 [0.06, 3.94]
Subtotal (95% CI)		**180**		**94**	**100.0%**	**0.49 [0.06, 3.94]**
Total events	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.66 (P = 0.51)						
1.4.3 Renal failure						
Feldman EVEREST II 2011	1	180	0	94	100.0%	4.58 [0.07, 284.51]
Subtotal (95% CI)		**180**		**94**	**100.0%**	**4.58 [0.07, 284.51]**
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.72 (P = 0.47)						
1.4.4 Deep wound infection						
Feldman EVEREST II 2011	0	180	0	94		Not estimable
Subtotal (95% CI)		**180**		**94**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.4.5 Mechanical ventilation >48hrs						
Feldman EVEREST II 2011	0	180	4	94	100.0%	0.05 [0.01, 0.42]
Subtotal (95% CI)		**180**		**94**	**100.0%**	**0.05 [0.01, 0.42]**
Total events	0		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.78 (P = 0.005)						
1.4.6 Gastrointestinal complications requiring surgery						
Feldman EVEREST II 2011	2	180	0	94	100.0%	4.61 [0.25, 85.84]
Subtotal (95% CI)		**180**		**94**	**100.0%**	**4.61 [0.25, 85.84]**
Total events	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.02 (P = 0.31)						
1.4.7 New onset permanent atrial fibrillation						
Feldman EVEREST II 2011	2	180	0	94	100.0%	4.61 [0.25, 85.84]
Subtotal (95% CI)		**180**		**94**	**100.0%**	**4.61 [0.25, 85.84]**
Total events	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.02 (P = 0.31)						
1.4.8 Septicemia						
Feldman EVEREST II 2011	0	180	0	94		Not estimable
Subtotal (95% CI)		**180**		**94**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.4.9 Transfusion of >=2 units of blood						
Feldman EVEREST II 2011	24	180	42	94	100.0%	0.18 [0.10, 0.32]
Subtotal (95% CI)		**180**		**94**	**100.0%**	**0.18 [0.10, 0.32]**
Total events	24		42			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.75 (P < 0.00001)						



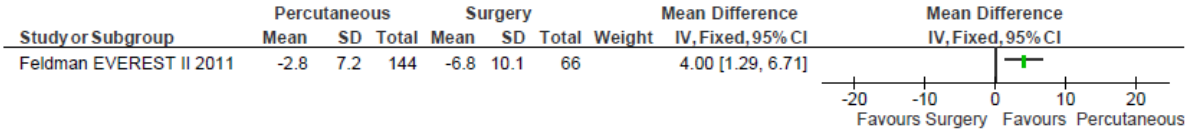
1

Figure 174: Quality of life – SF-36



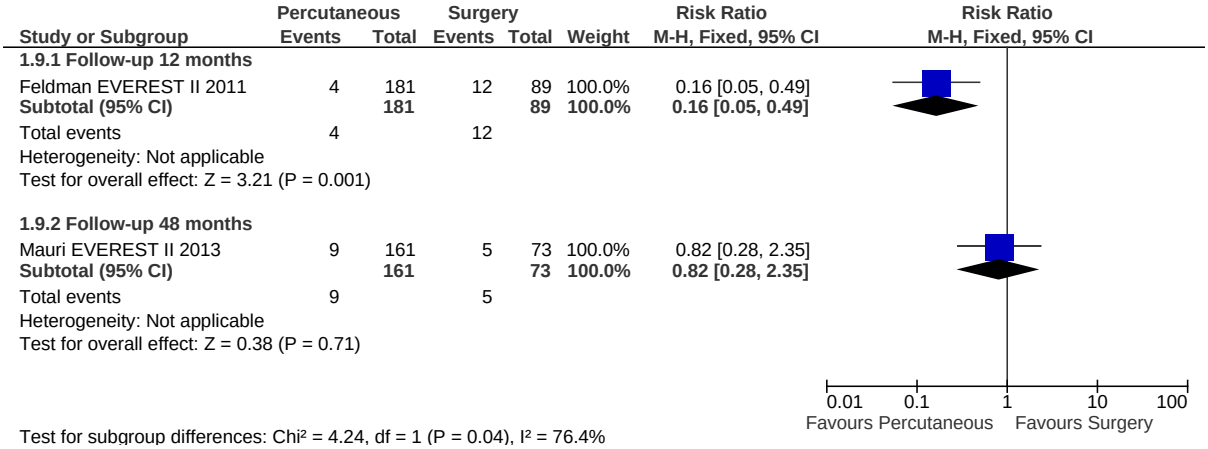
1

Figure 175: Change in Ejection Fraction % at 12 mths



2

Figure 176: Breathlessness – NYHA functional class III or IV



I.6 Mechanical assist devices

I.6.1 Intra-aortic balloon pump versus medical care

Figure 4: All-cause mortality distributions at 6 months and 12 months

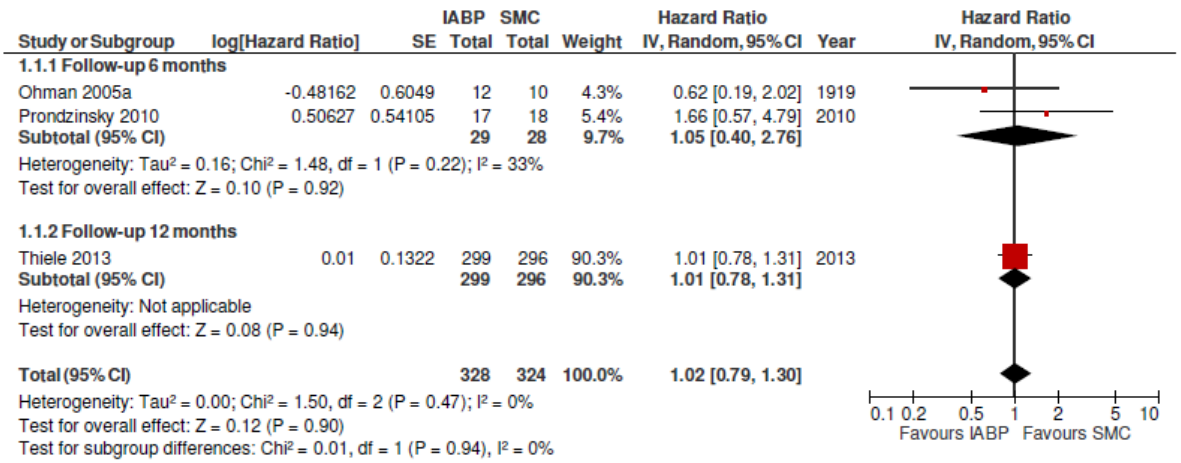


Figure 5: All-cause in-hospital mortality

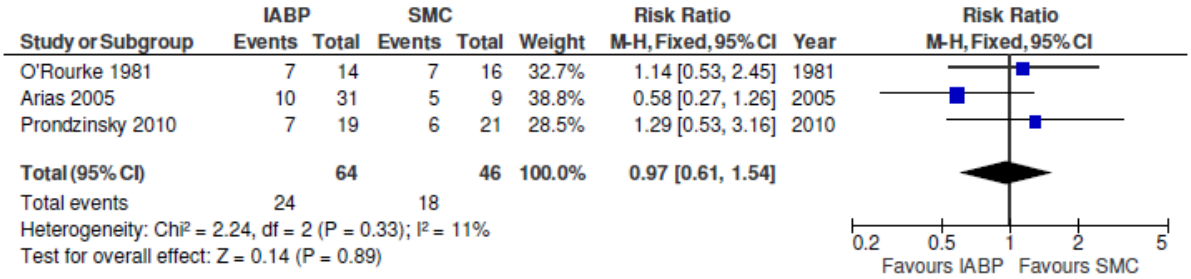


Figure 6: All-cause long-term mortality

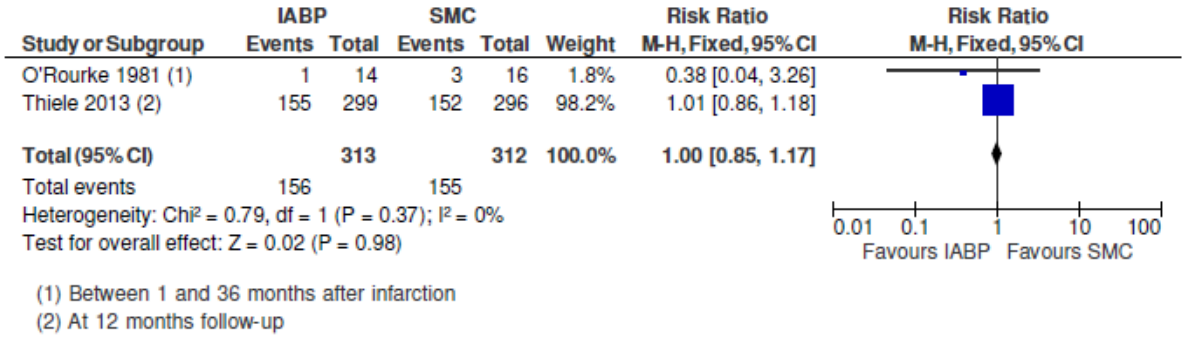


Figure 7: Cardiac mortality at 12 months

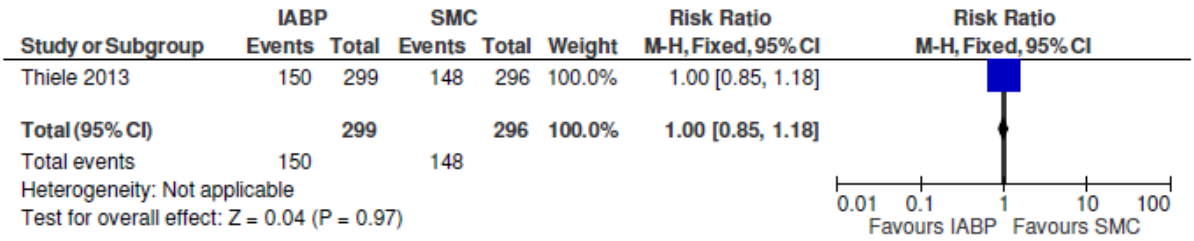


Figure 8: Serious adverse events – cardiovascular (myocardial infarction)

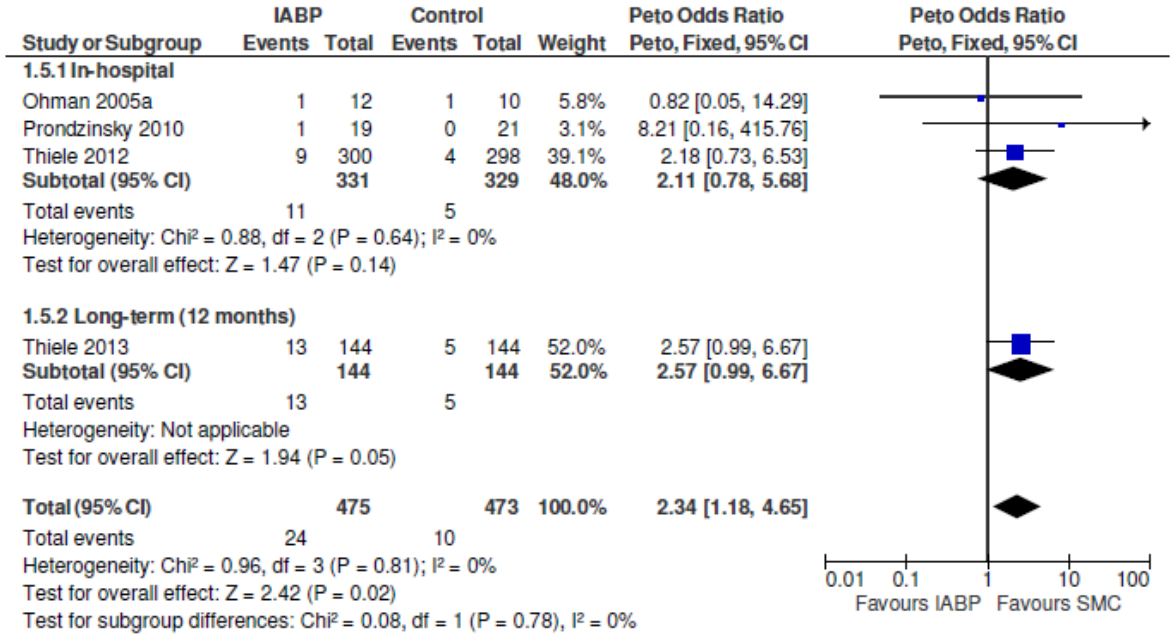


Figure 9: Serious adverse events – cardiovascular (stroke)

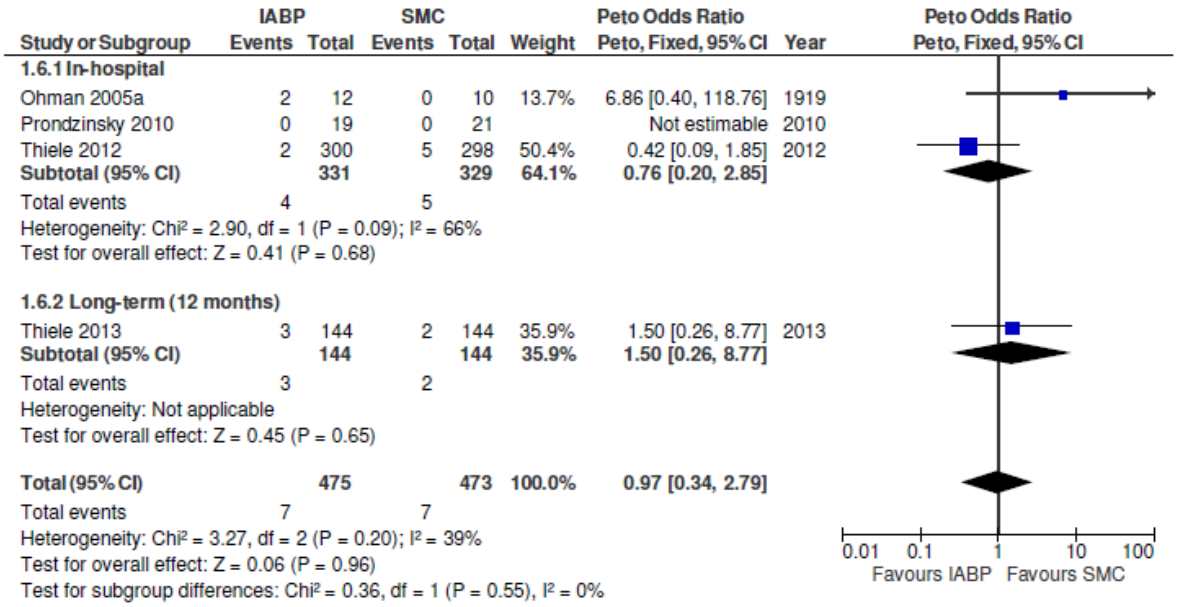
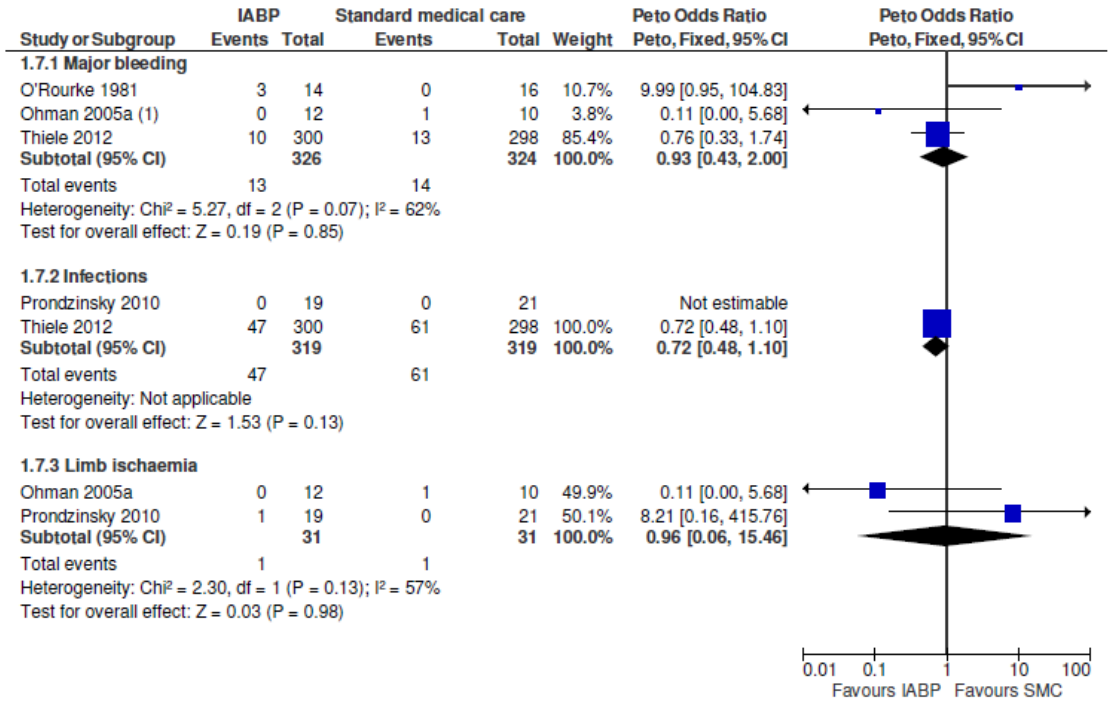
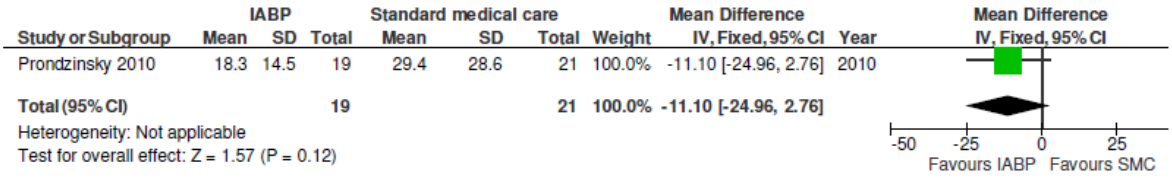


Figure 10: Serious adverse events – other



(1) One case in the control group was added after my inspection of the original study. It is recorded as zero in the Cochrane systematic review.

Figure 11: Length of hospital stay



I.6.2 Intra-aortic balloon pump versus left ventricular assist devices

- The comparator device used in Thiele 2005 and Burkhoff 2006 was TandemHeart percutaneous VAD.
- The comparator device in Seyfarth 2008 was Impella LP 2.5 LVAD.

Figure 12: All-cause mortality distribution at 30 days and 6 months

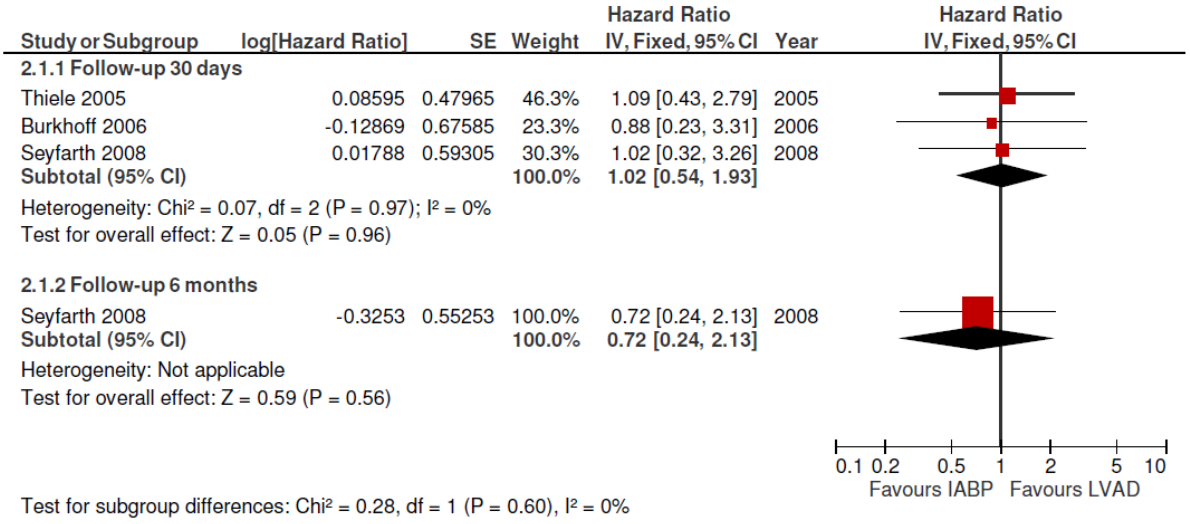


Figure 13: All-cause in-hospital and long-term (1 to 36 months) mortality rates

Figure 14: Serious adverse events – cardiovascular

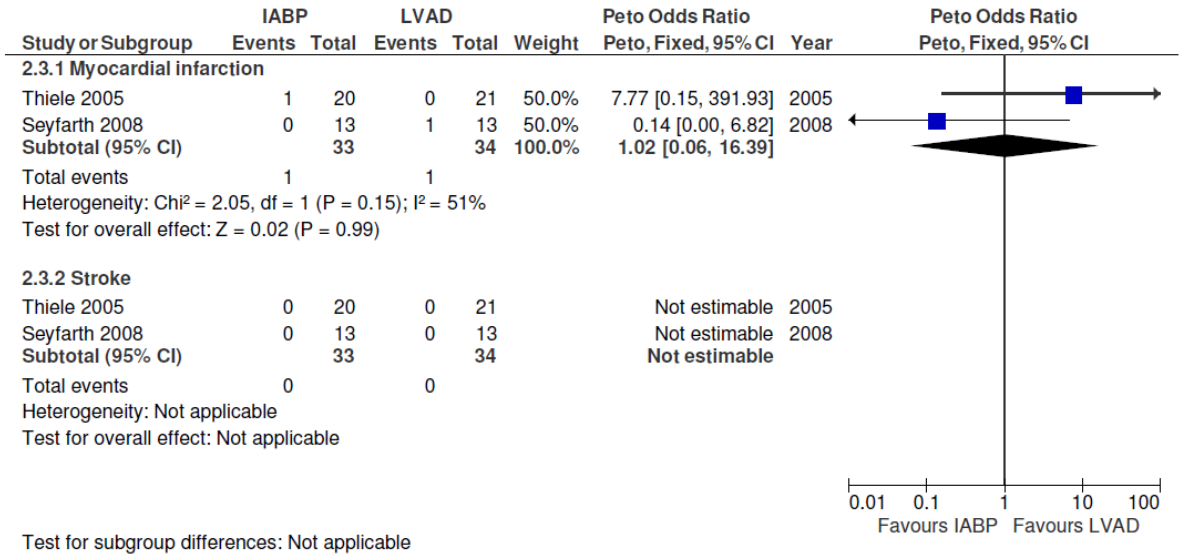


Figure 15: Serious adverse events – other

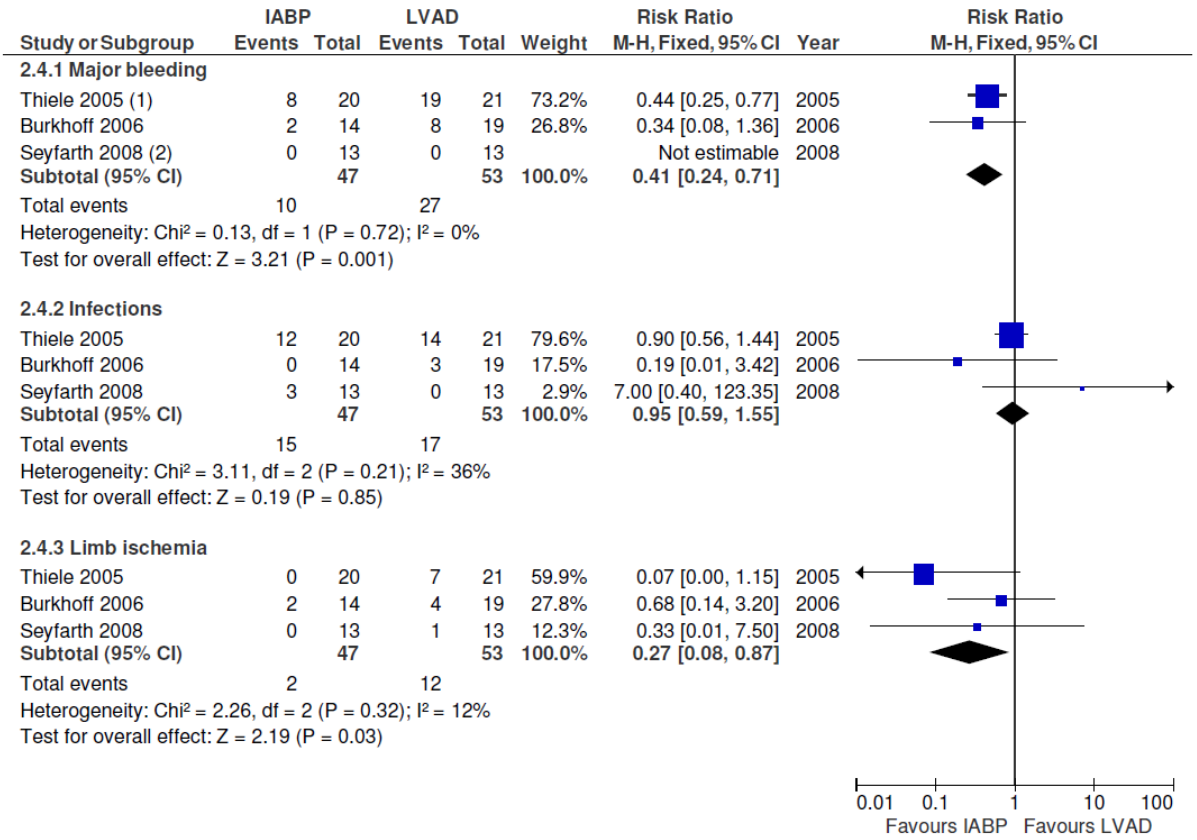
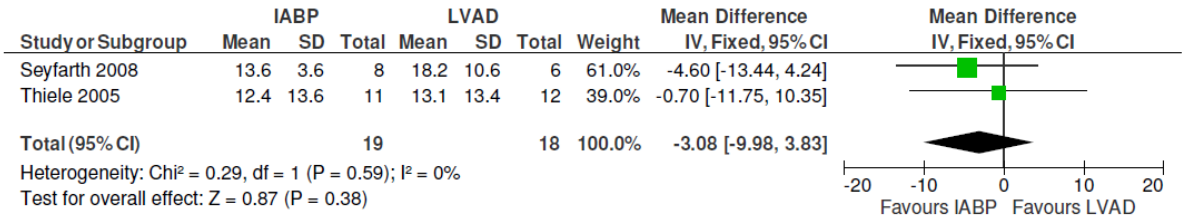


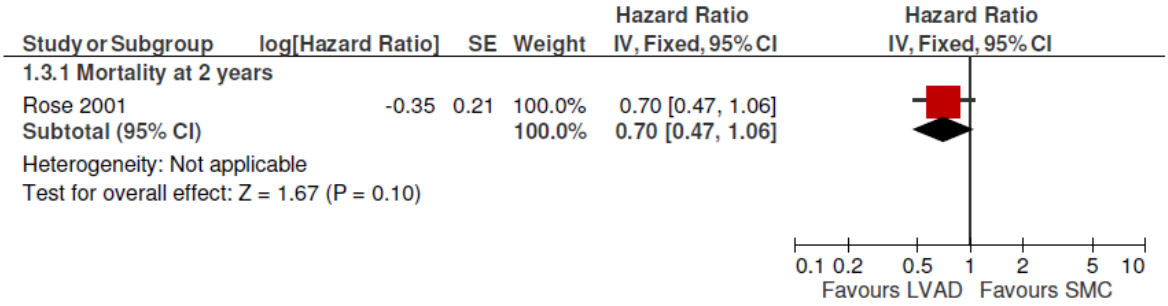
Figure 16: Length of hospital stay (days)



1 **I.6.3 Left ventricular assist devices vs. medical care**

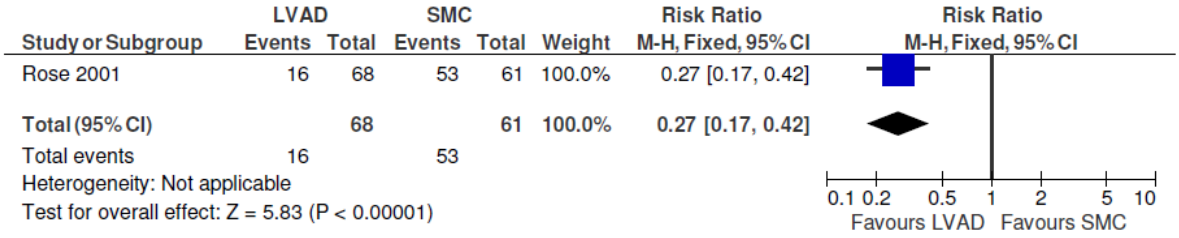
2

Figure 17: All-cause mortality at 2 years



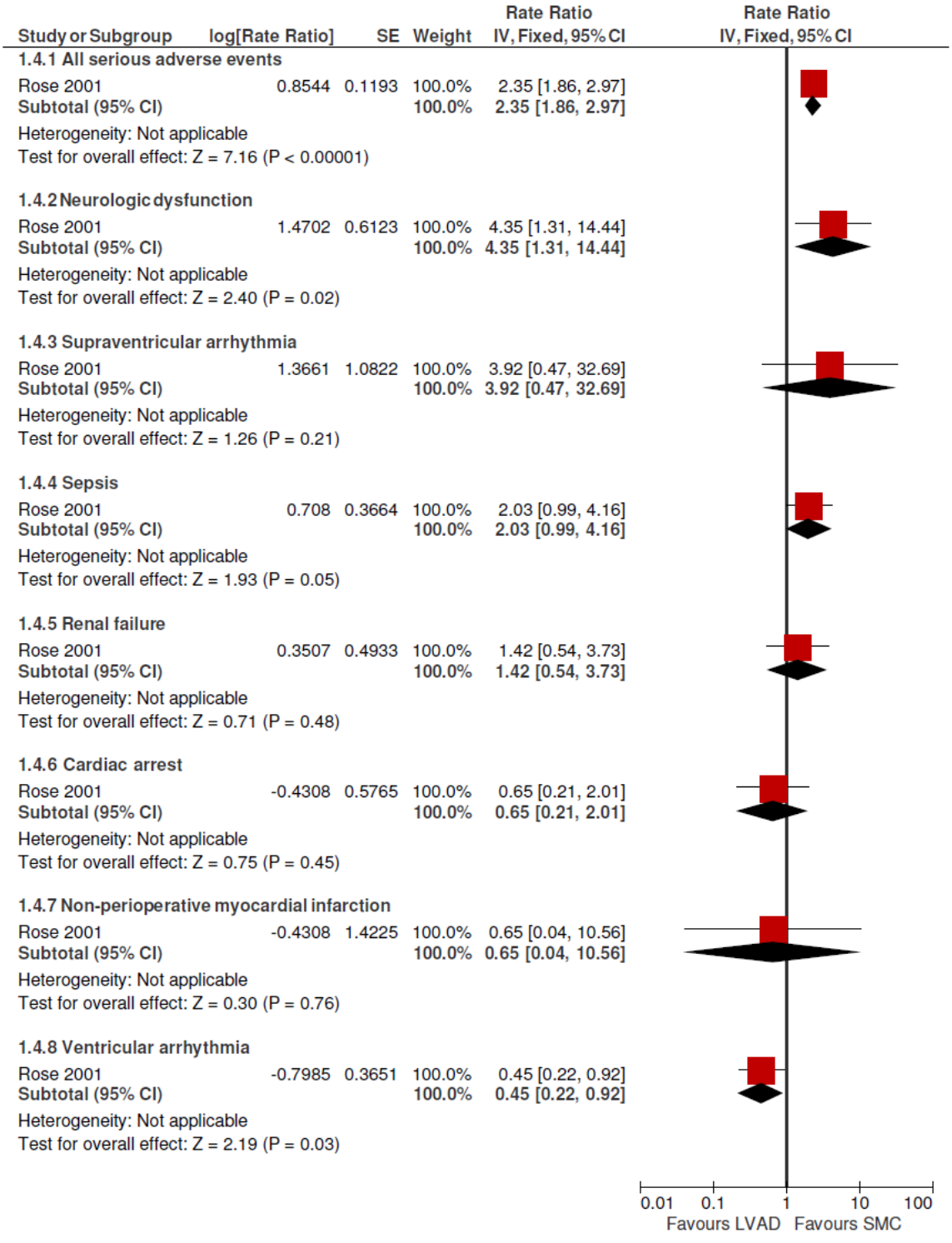
3

Figure 18: Cardiovascular deaths



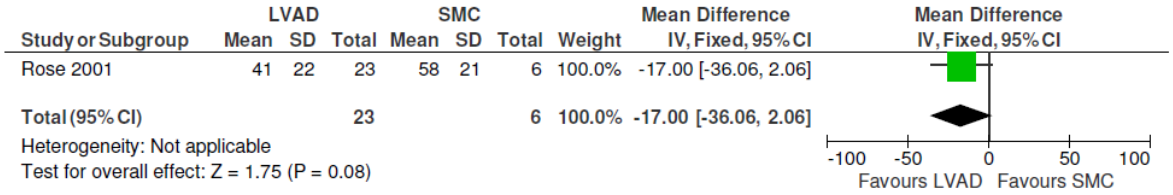
4

Figure 19: Serious adverse events



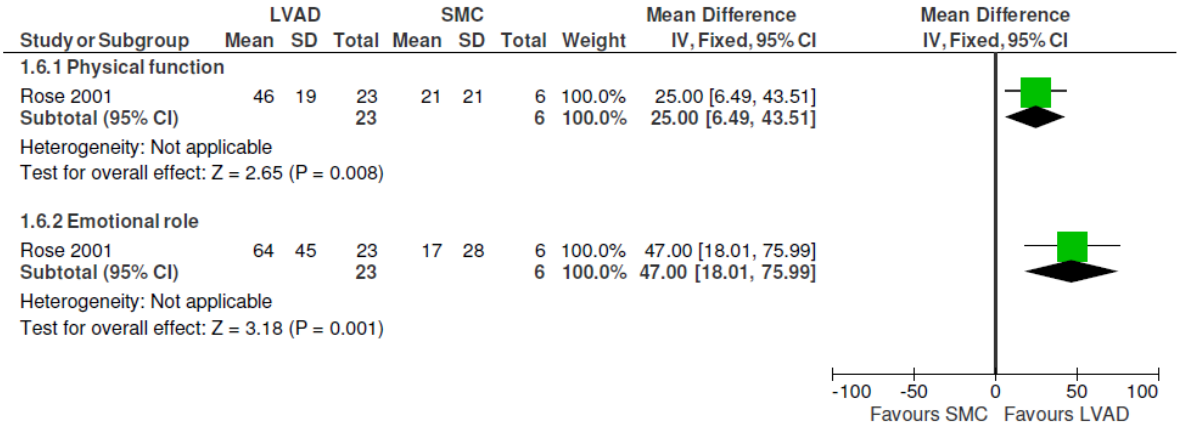
1

Figure 20: Quality of life (Minnesota Living with Heart Failure)



1

Figure 21: Quality of life (SF-36)

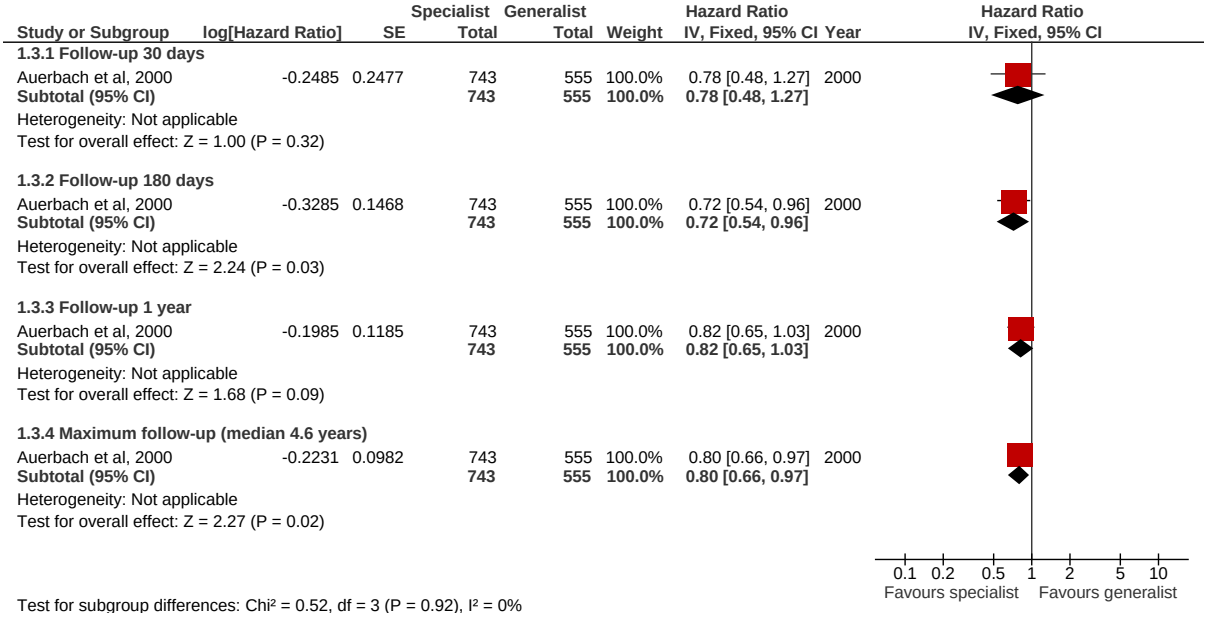


2 # I.7 Specialist management units

3 ## I.7.1 Specialist vs. generalist (including internists) management for suspected or confirmed
4 acute heart failure

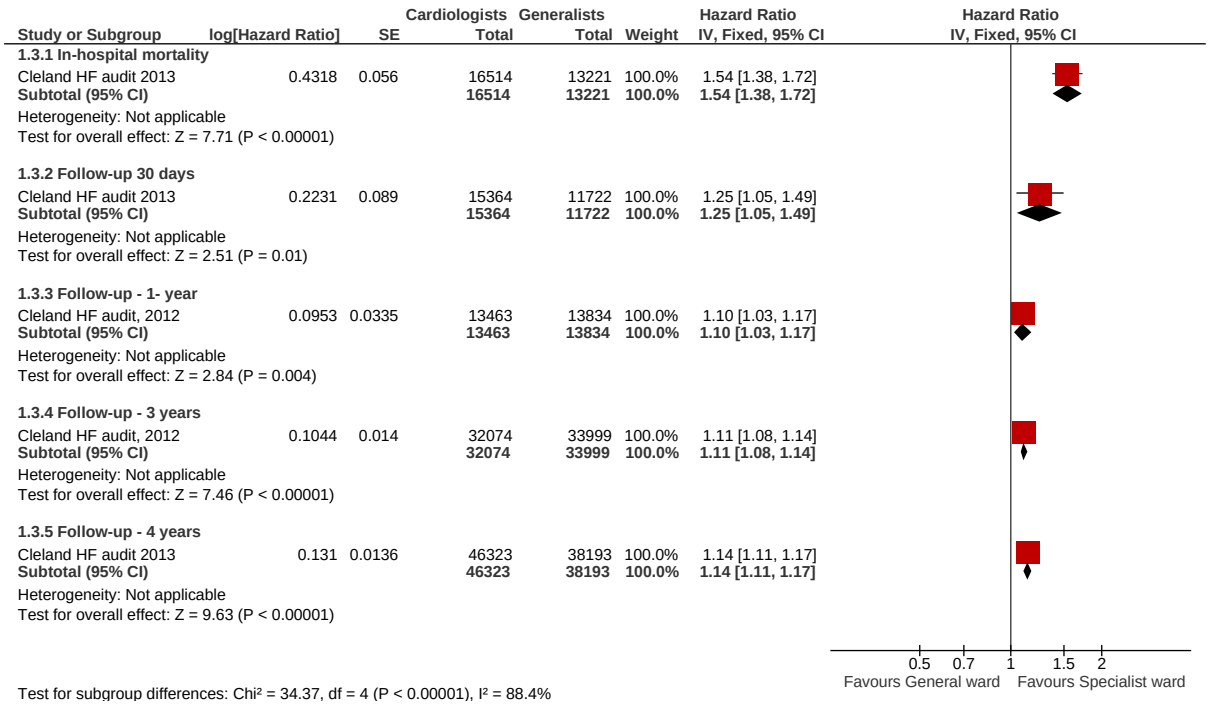
5

Figure 177: Mortality Hazard Ratios – Auerbach et al, 2000[12]



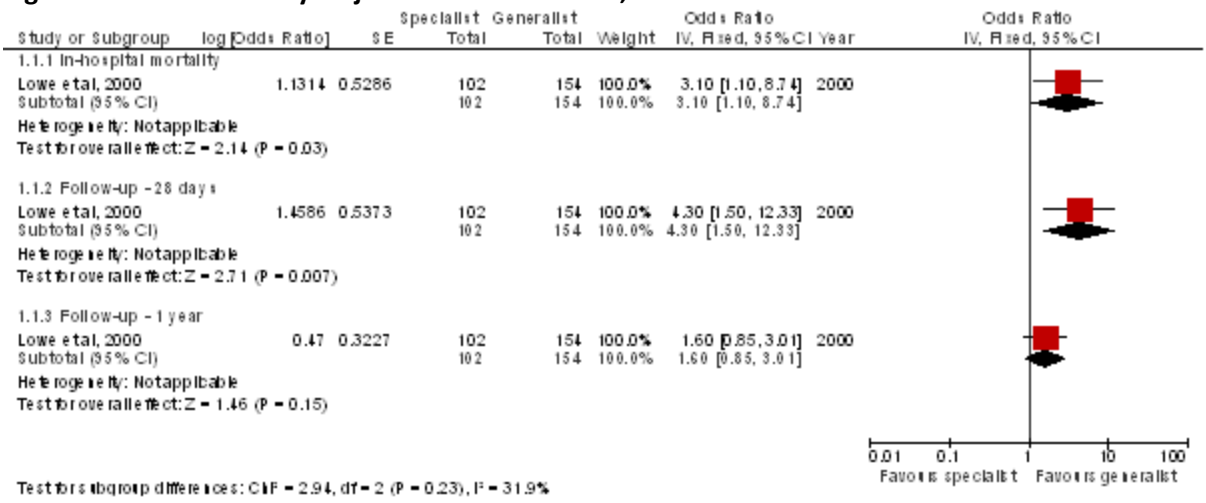
1

Figure 178: Mortality Hazard Ratios – Cleland et al., 2012 and 2013 National Heart Failure Audit[30,31]



2

Figure 179: Mortality adjusted OR - Lowe et al, 2000[97]



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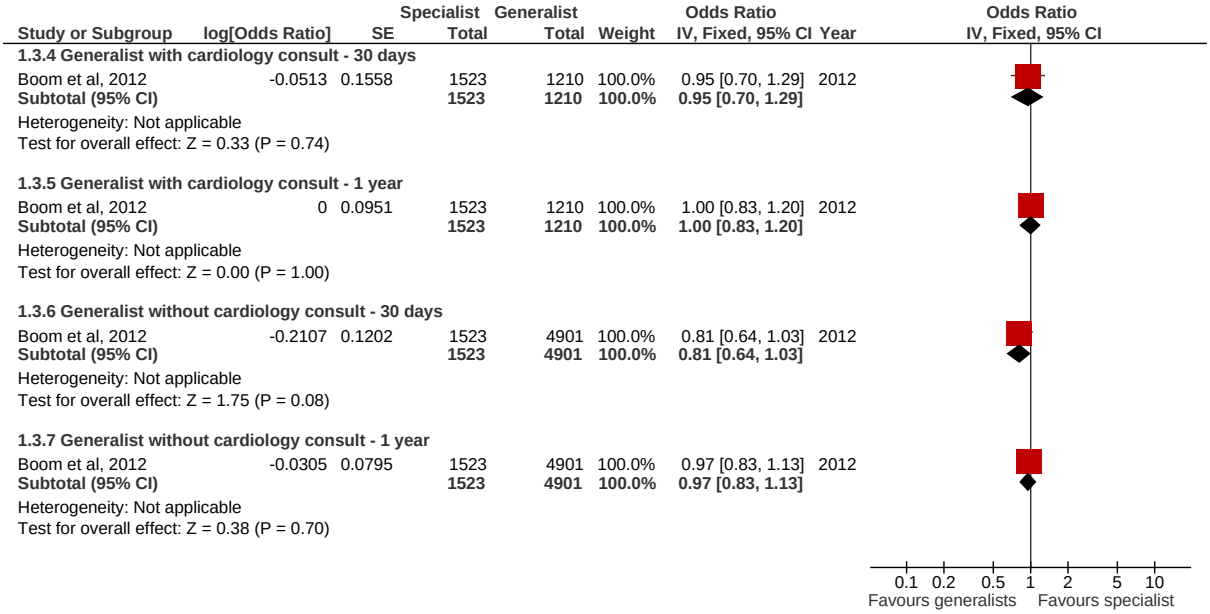
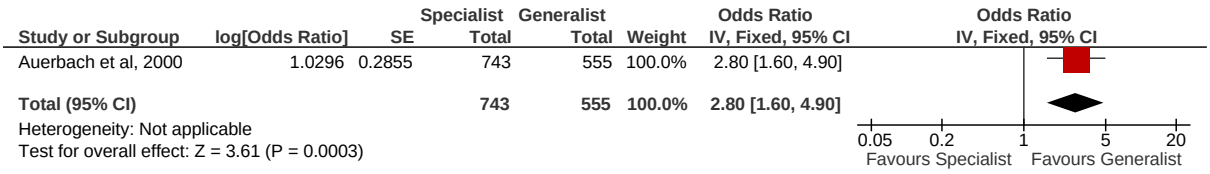
2

Figure 180: Readmission rates – Boom et al, 2012[23]



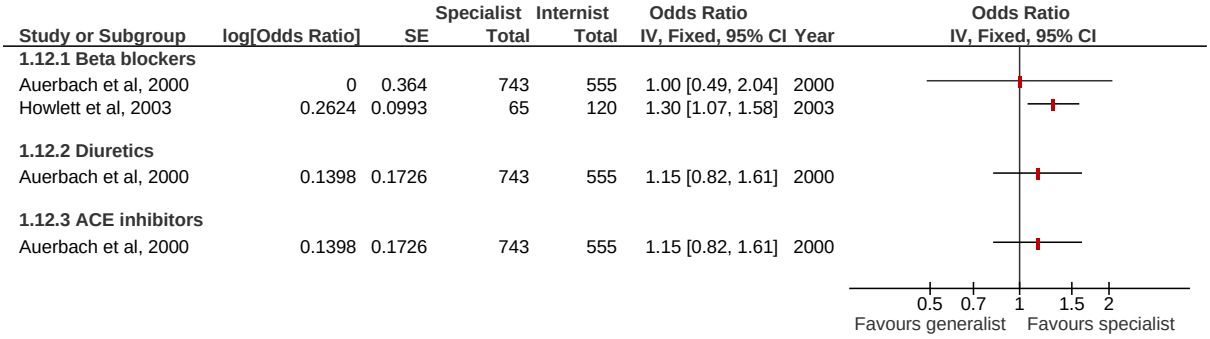
3

Figure 181: Transfer to the intensive care unit - Auerbach et al, 2000[12]



4

Figure 182: Discharge medication - Auerbach et al, 2000[12] and Howlett et al, 2003[76]



I.7.2 Generalists with or without cardiology consult vs. specialists

Figure 183: Mortality (patients without 'do not resuscitate' order) – Boom et al, 2012[23]

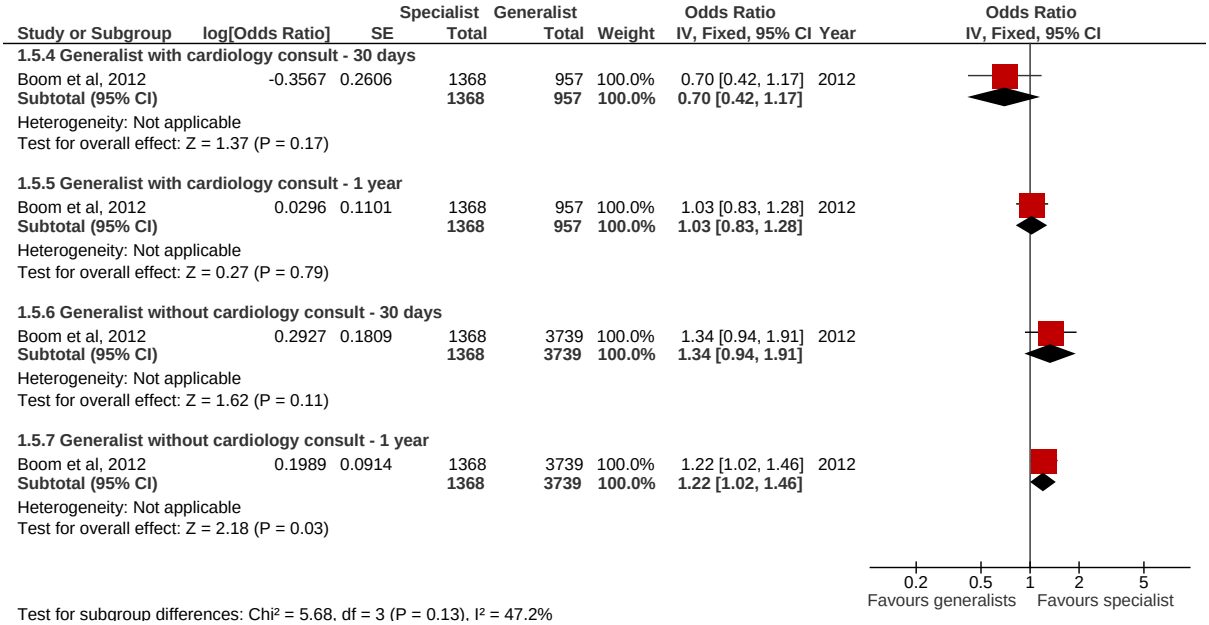
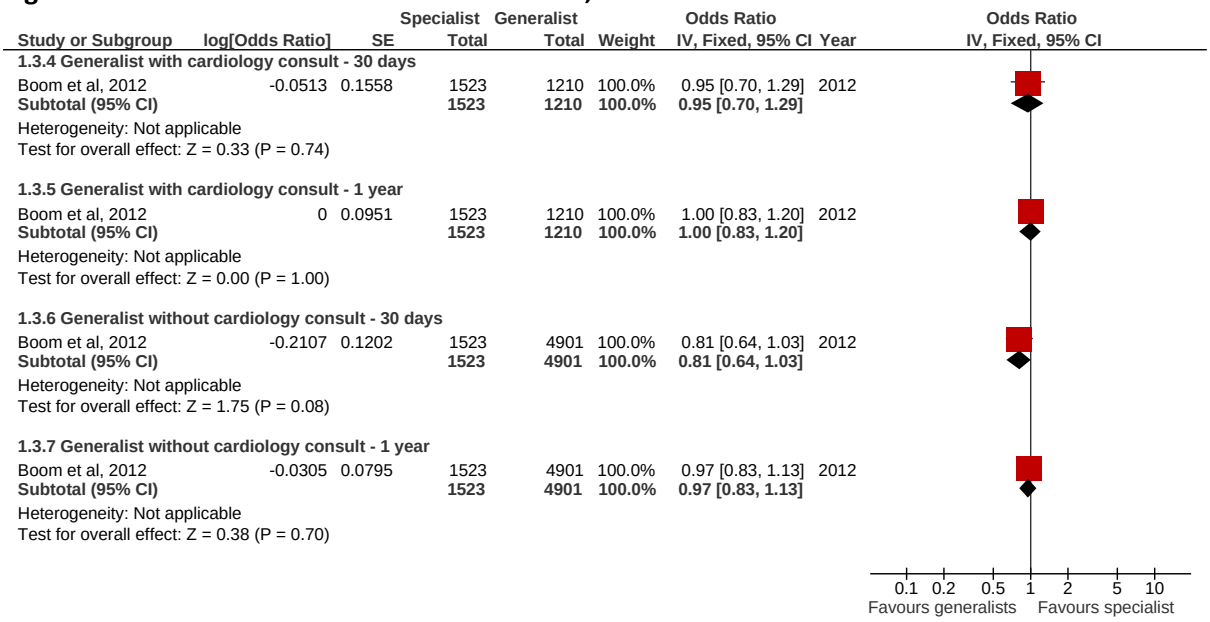


Figure 184: Readmission rates – Boom et al, 2012[23]



I.7.3 Type of specialist (cardiologists or internists) vs. generalists

Figure 185: 30 day mortality (medium physician volume)

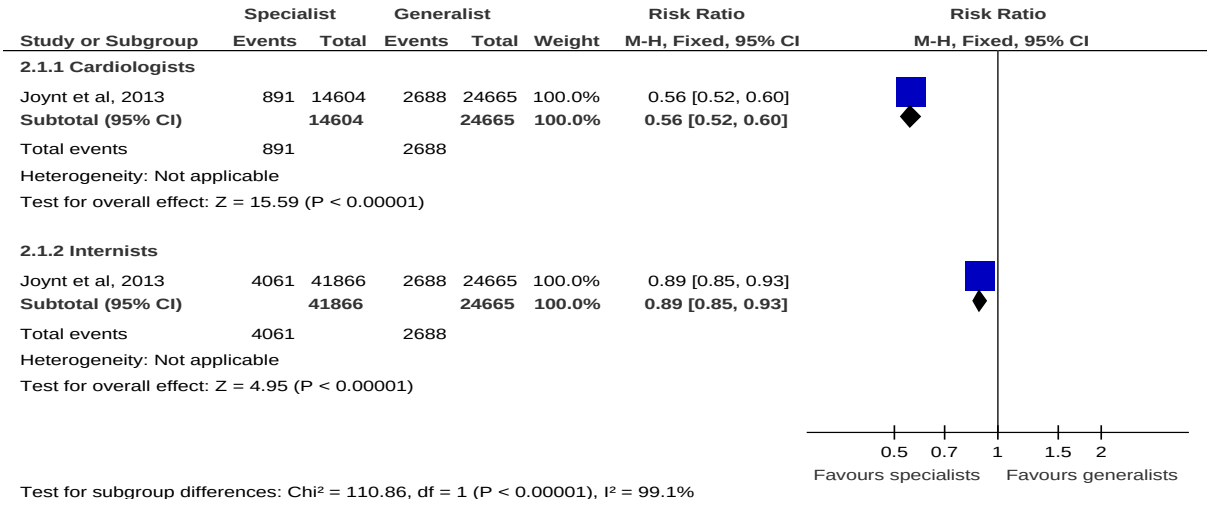
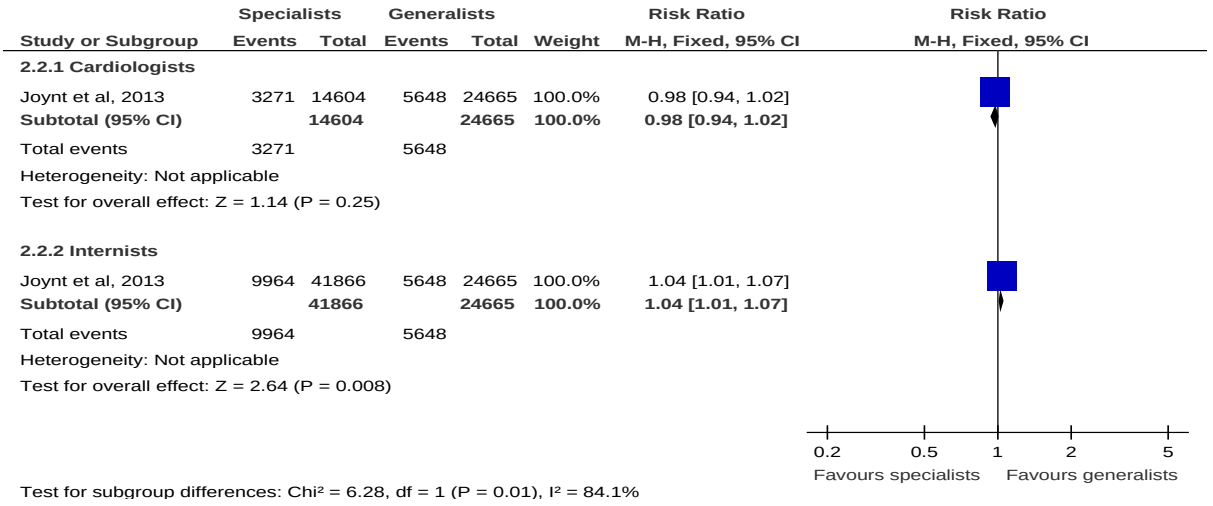


Figure 186: 30 day readmission rates (medium physician volume)



Appendix J: Natriuretic peptides: diagnostic meta-analysis methods

Diagnostic meta-analysis was conducted where 5 or more similar studies were identified that compared the index test to the reference standard. The test accuracy for the studies was pooled using the bivariate method modelled in Winbugs® by; the advantage of this approach is that it produces summary estimates of sensitivity and specificity that account for the correlation between the two. Other advantages of this method have been described elsewhere.[144,176,177]

J.1 Results

The results of each diagnostic meta-analysis are presented in chapter 5. The Winbugs® programming code is described in section J.3. Summary ROC curves, and paired sensitivity / specificity forest plots with summary statistics are presented in sections J.4 to J.7 below.

J.2 Analysis

The bivariate method utilises a logistic regression on the true positives, true negatives, false positives and false negatives reported in the studies and is parameterised as follows[144,176,177]:

$$TP_i \sim Binomial(\pi_{Ai}, (TP_i + FN_{i)})$$

$$TN_i \sim Binomial(\pi_{Bi}, (FP_i + TN_i))$$

$$\theta_{Ai} = ln\left(\frac{\pi_{Ai}}{1-\pi_{Ai}}\right)$$

$$\theta_{Bi} = ln\left(\frac{\pi_{Bi}}{1-\pi_{Bi}}\right)$$

$$\begin{pmatrix}\theta_{Ai}\\ \theta_{Bi}\end{pmatrix} \sim N\left(\begin{pmatrix}\theta_A\\ \theta_B\end{pmatrix}, \Sigma\right)$$

$$\Sigma = \begin{pmatrix}\sigma_A^2 & \sigma_{AB}\\ \sigma_{AB} & \sigma_B^2\end{pmatrix}$$

$$\alpha = \frac{e^{\theta_A}}{1+e^{\theta_A}}$$

$$\beta = \frac{e^{\theta_B}}{1+e^{\theta_B}}$$

Where:

TP_i, TN_i, FP_i and FN_i represent the true positives, true negatives, false positives and false negatives, respectively, reported in study i.

$\theta_{Ai}$and θ_{Bi}represent the sensitivity and specificity calculated from the results of study i on the log odds scale.

$\theta_A$and $\theta_B$represent the mean pooled sensitivity and specificity on the log odds scale, i.e. the results of the meta analysis.

Σ represents the variance-covariance matrix of the pooled sensitivity and specificity on the log odds scale.

α and β represent the pooled sensitivity and specificity on the natural scale; these are the final summary estimates of interest.

The model above was fitted in WinBUGS®. Using the output from WinBUGS®, we constructed and plotted confidence regions and, where appropriate ROC curves, using methods outlined by Novielli et al., 2010[122] in Microsoft Excel®.

As it was a Bayesian analysis, the evidence distribution is weighted by a distribution of prior beliefs. Vague non-informative priors were used for all parameters. For each analysis, a series of 50,000 burn-in simulations were run to allow convergence and then a further 50,000 simulations were run to produce the outputs. Convergence was assessed by investigating density plots, auto correlation plots and history plots for parameters of interest.

J.3 WinBUGS code

Model

```
{

for (i in 1:NS)

        {

        TotP[i]<-TP[i] + FN[i]
        TotN[i]<-FP[i] + TN[i]
        TP[i] ~ dbin(p[i , 1] , TotP[i])
        TN[i] ~ dbin(p[i , 2]  , TotN[i])

                for (j in 1:2)

                {
                logit(p[i , j]) <- MeanS[i , j]
                }
        MeanS[i , 1:2] ~ dmnorm(md[] , sigma[,])

        }
        sigma[1:2,1:2]~dwish(R[,] , 2)
        Sigma.sq[1:2,1:2] <- inverse(sigma[,])

                for (i in 1:2)
                        {
                        parms[i] <- exp(md[i])/(1+exp(md[i]))
                        }

        sens <- parms[1]
        spec<- parms[2]


                for (i in 1:2)
                        {
                        md[i] ~ dnorm(0 , 0.001)
                        }
```

```
                    sensitivity.bar <- exp(md[1])/(1+ exp(md[1]))
          specificity.bar <- exp(md[2])/(1+exp(md[2]))


    }



}
```

Data

```
list(NS= Number of studies)

list(R = structure(
        .Data = c(1, 0,
              0, 1), .
        Dim = c(2, 2))
```

Cell Counts for each study are entered below, in place of the ni values – for data see forest plots below

```
TP=True positives
FP=False positives
FN=False negatives
TN=True negatives

TP[]      FP[]      FN[]      TN[]
n1        n2        n3        n4
END
```

Initial conditions

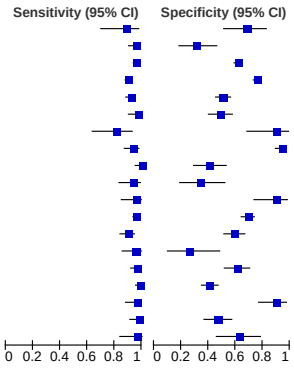
```
list(md=c(0,0))
```

J.4 BNP

Figure 187: Paired sensitivity and specificity for BNP with 95% confidence intervals

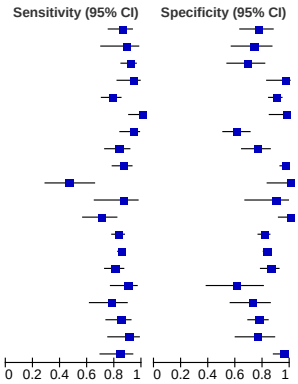
BNP ≤100 pg/mL

Study	TP	FP	FN	TN	Setting	Threshold	Assay	Sensitivity (95% CI)	Specificity (95% CI)
Blonde-Cynober 2011	23	12	3	26	Inpatient	100.0	Triage (Biosite)	0.88 [0.70, 0.98]	0.68 [0.51, 0.82]
Logeart 2002	110	33	5	15	ICU	100.0	Triage (Biosite)	0.96 [0.90, 0.99]	0.31 [0.19, 0.46]
Maisel 2010	543	409	25	664	ED	100.0	Triage (Biosite)	0.96 [0.94, 0.97]	0.62 [0.59, 0.65]
Maisel 2002	670	202	74	640	ED	100.0	Triage (Biosite)	0.90 [0.88, 0.92]	0.76 [0.73, 0.79]
Lokuge 2010	252	166	22	172	ED	101.0	Abbott	0.92 [0.88, 0.95]	0.51 [0.45, 0.56]
Lainchbury 2003	68	69	2	66	ED	104.0	Triage (Biosite)	0.97 [0.90, 1.00]	0.49 [0.40, 0.58]
Davis 1994	26	2	6	18	ED	100.0	In house	0.81 [0.64, 0.93]	0.90 [0.68, 0.99]
Dao 2001	91	9	6	144	ED	100.0	Triage (Biosite)	0.94 [0.87, 0.98]	0.94 [0.89, 0.97]
Chung 2006	72	42	0	29	ED	100.0	Triage (Biosite)	1.00 [0.95, 1.00]	0.41 [0.29, 0.53]
Wang 2010	46	23	3	12	ED	100.0	Abbott	0.94 [0.83, 0.99]	0.34 [0.19, 0.52]
Sanz 2006	43	3	2	27	ED	100.0	Access	0.96 [0.85, 0.99]	0.90 [0.73, 0.98]
Rogers 2009	353	115	15	257	ED	100.0	Triage (Biosite)	0.96 [0.93, 0.98]	0.69 [0.64, 0.74]
Ray 2004	127	68	14	99	ED	100.0	Triage (Biosite)	0.90 [0.84, 0.94]	0.59 [0.51, 0.67]
Parab 2005	45	17	2	6	ED	100.0	Triage (Biosite)	0.96 [0.85, 0.99]	0.26 [0.10, 0.48]
Mueller 2005	132	44	5	70	ED	100.0	Abbott	0.96 [0.92, 0.99]	0.61 [0.52, 0.70]
Chenevier-Gobeaux 2010	114	155	1	108	ED	100.0	Triage (Biosite)	0.99 [0.95, 1.00]	0.41 [0.35, 0.47]
Barcase 2004	55	4	2	37	ED	100.0	Triage (Biosite)	0.96 [0.88, 1.00]	0.90 [0.77, 0.97]
Alibay 2005	59	53	1	47	ED	100.0	Triage (Biosite)	0.98 [0.91, 1.00]	0.47 [0.37, 0.57]
Arques 2005	31	14	1	24	Acute Referral	100.0	Triage (Biosite)	0.97 [0.84, 1.00]	0.63 [0.46, 0.78]



BNP 100-500 pg/mL

Study	TP	FP	FN	TN	Setting	Threshold	Assay	Sensitivity (95% CI)	Specificity (95% CI)
Dokainish 2004	60	12	10	40	Inpatient	250.0	Triage (Biosite)	0.86 [0.75, 0.93]	0.77 [0.63, 0.87]
Blonde-Cynober 2011	23	10	3	28	Inpatient	129.0	Triage (Biosite)	0.88 [0.70, 0.98]	0.74 [0.57, 0.87]
Logeart 2002	105	15	10	33	ICU	250.0	Triage (Biosite)	0.91 [0.85, 0.96]	0.69 [0.54, 0.81]
Sanz 2006	42	1	3	29	ED	116.0	Access	0.93 [0.82, 0.99]	0.97 [0.83, 1.00]
Ray 2004	110	17	31	150	ED	250.0	Triage (Biosite)	0.78 [0.70, 0.85]	0.90 [0.84, 0.94]
Villacorta 2002	36	1	0	33	ED	200.0	Triage (Biosite)	1.00 [0.90, 1.00]	0.97 [0.85, 1.00]
Alibay 2005	56	39	4	61	ED	150.0	Triage (Biosite)	0.93 [0.84, 0.98]	0.61 [0.51, 0.71]
Chung 2006	60	17	12	54	ED	400.0	Triage (Biosite)	0.83 [0.73, 0.91]	0.76 [0.64, 0.85]
Dao 2001	84	5	13	148	ED	150.0	Triage (Biosite)	0.87 [0.78, 0.93]	0.97 [0.93, 0.99]
Davis 1994	15	0	17	20	ED	195.0	In house	0.47 [0.29, 0.65]	1.00 [0.83, 1.00]
Arques 2007	19	2	3	17	ED	253.0	Triage (Biosite)	0.86 [0.65, 0.97]	0.89 [0.67, 0.99]
Barcase 2004	40	0	17	41	ED	300.0	Triage (Biosite)	0.70 [0.57, 0.82]	1.00 [0.91, 1.00]
Lokuge 2010	227	64	47	274	ED	265.0	Abbott	0.83 [0.78, 0.87]	0.81 [0.76, 0.85]
Maisel 2002	632	143	112	699	ED	150.0	Triage (Biosite)	0.85 [0.82, 0.87]	0.83 [0.80, 0.85]
Mueller 2005	110	16	27	98	ED	295.0	Abbott	0.80 [0.73, 0.87]	0.86 [0.78, 0.92]
Parab 2005	42	9	5	14	ED	300.0	Triage (Biosite)	0.89 [0.77, 0.96]	0.61 [0.39, 0.80]
Gorissen 2007	31	11	9	29	ED	225.0	Triage (Biosite)	0.78 [0.62, 0.89]	0.72 [0.56, 0.85]
Lainchbury 2003	59	31	11	104	ED	347.0	Triage (Biosite)	0.84 [0.74, 0.92]	0.77 [0.69, 0.84]
Arques 2005	29	9	3	29	Acute Referral	146.0	Triage (Biosite)	0.91 [0.75, 0.98]	0.76 [0.60, 0.89]
Fleischer 1997	36	4	7	76	Acute Referral	173.0	In house	0.84 [0.69, 0.93]	0.95 [0.88, 0.99]



BNP ≥ 500 pg/mL

Study	TP	FP	FN	TN	Setting	Threshold	Assay	Sensitivity (95% CI)	Specificity (95% CI)
Blonde-Cynober 2011	9	0	17	38	Inpatient	635.0	Triage (Biosite)	0.35 [0.17, 0.56]	1.00 [0.91, 1.00]
Karmpaliotis 2007	13	8	10	43	ICU	1000.0	Triage (Biosite)	0.57 [0.34, 0.77]	0.84 [0.71, 0.93]
Wang 2010	32	9	17	26	ED	500.0	Abbott	0.65 [0.50, 0.78]	0.74 [0.57, 0.88]
Parab 2005	39	5	8	18	ED	500.0	Triage (Biosite)	0.83 [0.69, 0.92]	0.78 [0.56, 0.93]

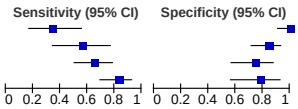
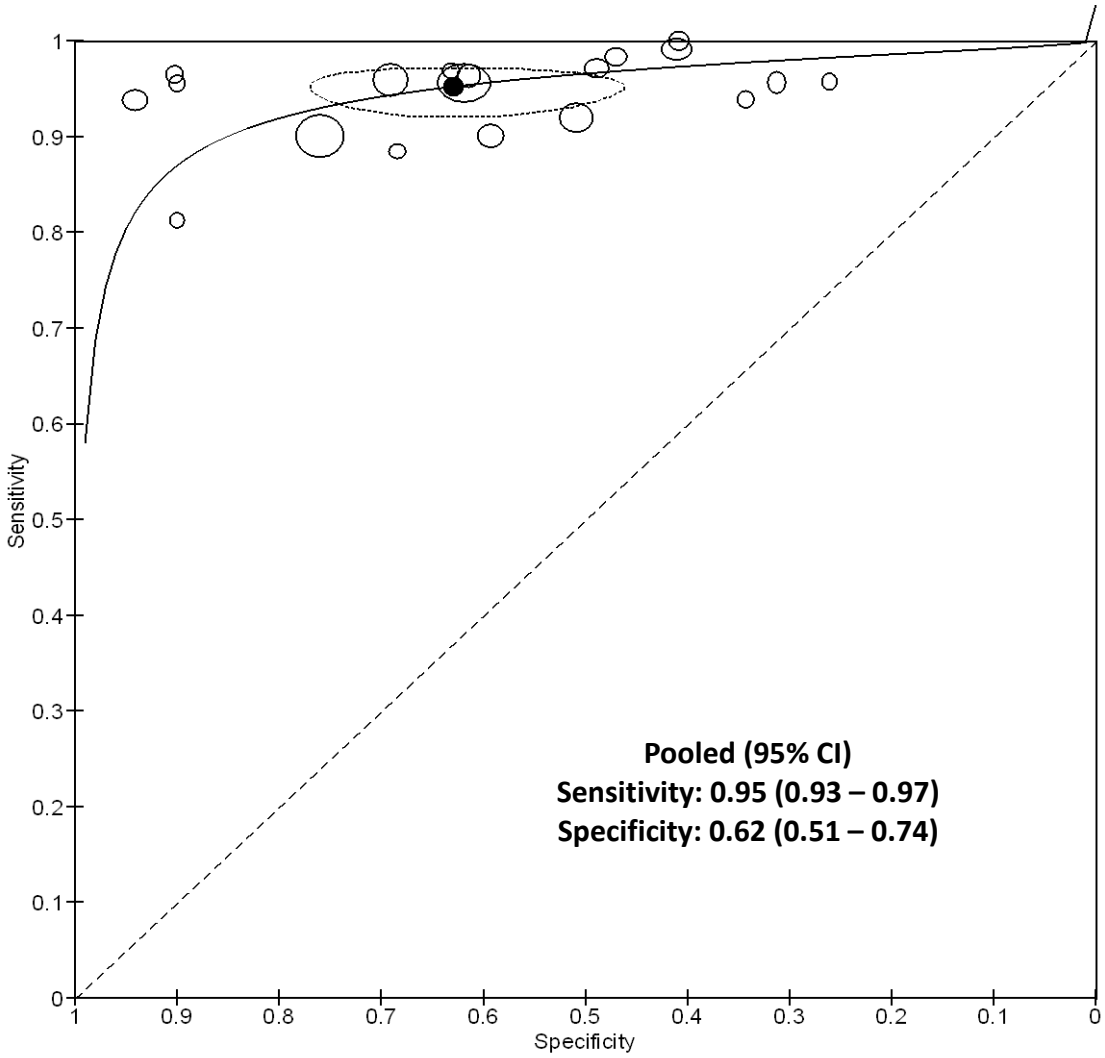
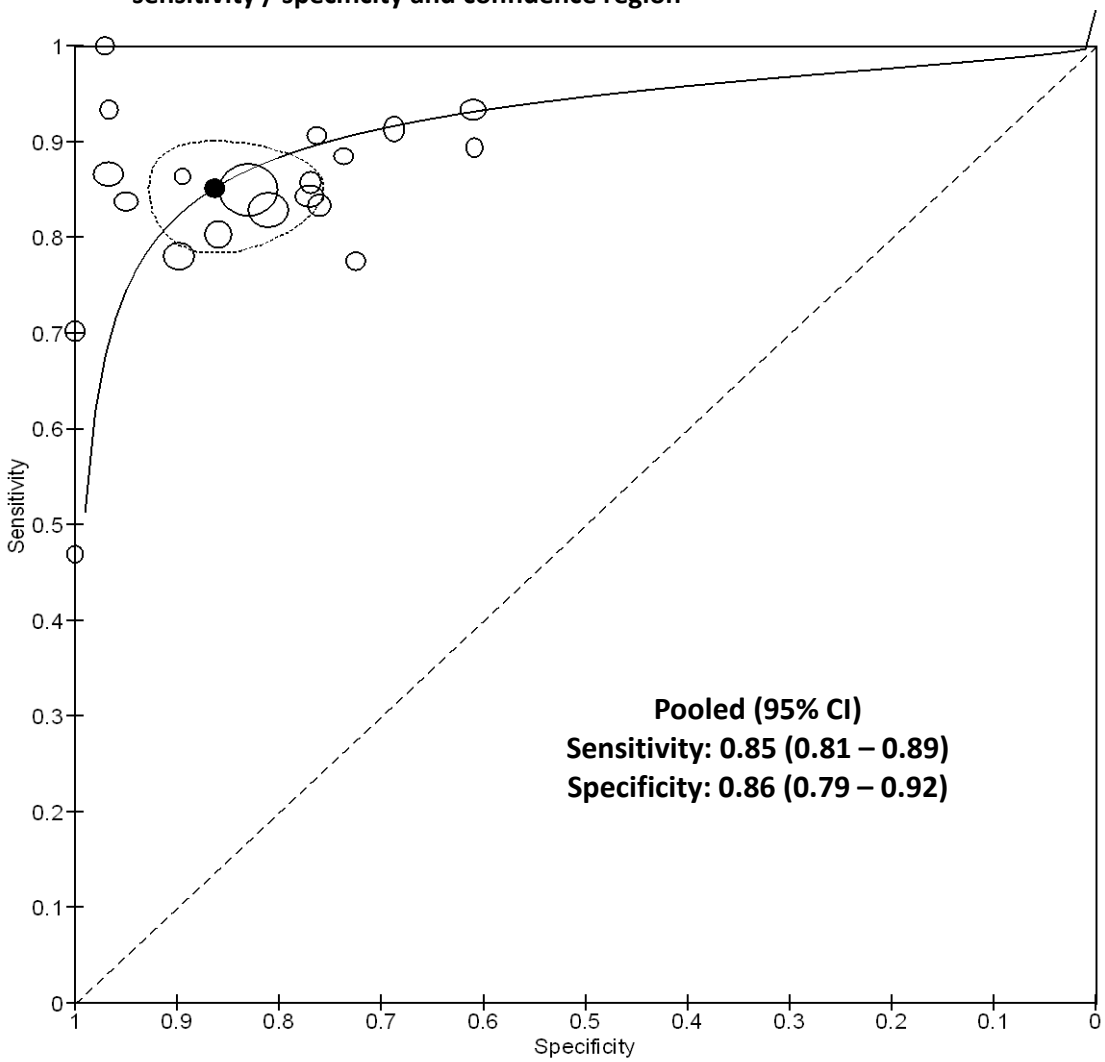


Figure 188: Summary ROC curve (sROC curve) for BNP ≤ 100pg/mL with summary sensitivity / specificity and confidence region


Sensitivity
Specificity
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Pooled (95% CI)
Sensitivity: 0.95 (0.93 – 0.97)
Specificity: 0.62 (0.51 – 0.74)

1

Figure 189: Summary ROC curve (sROC curve) for BNP 100-500 pg/mL with summary sensitivity / specificity and confidence region



2

3

Figure 190: sROC curves for BNP at all thresholds (size of shapes indicates study size)

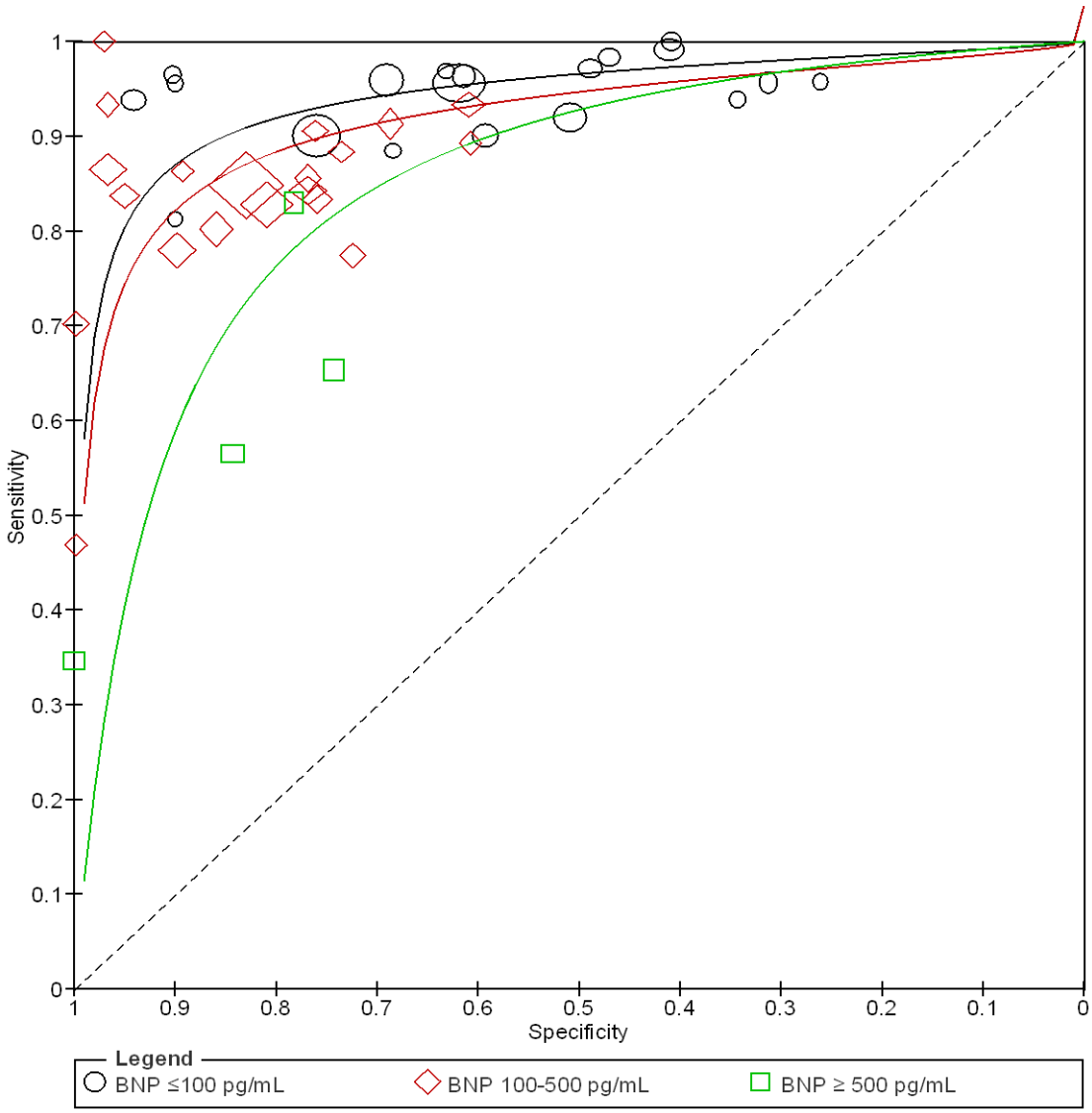
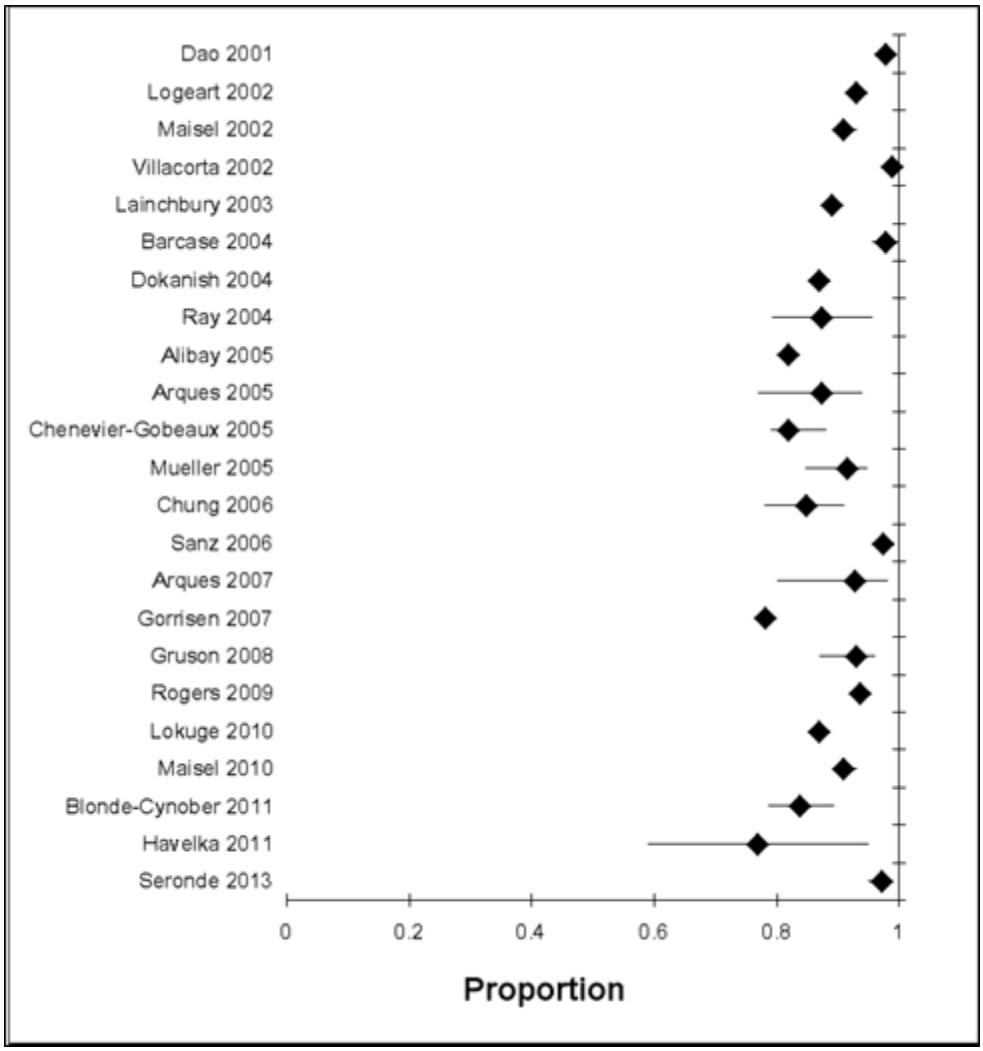


Figure 191: BNP - Area under the curve (AUC) by study plot


Dao 2001
Logeart 2002
Maisel 2002
Villacorta 2002
Lainchbury 2003
Barcase 2004
Dokanish 2004
Ray 2004
Alibay 2005
Arques 2005
Chenevier-Gobeaux 2005
Mueller 2005
Chung 2006
Sanz 2006
Arques 2007
Gorrisen 2007
Gruson 2008
Rogers 2009
Lokuge 2010
Maisel 2010
Blonde-Cynober 2011
Havelka 2011
Seronde 2013
0
0.2
0.4
0.6
0.8
1
Proportion

J.5 NTproBNP

Figure 192: Paired sensitivity and specificity for NTproBNP with 95% confidence intervals

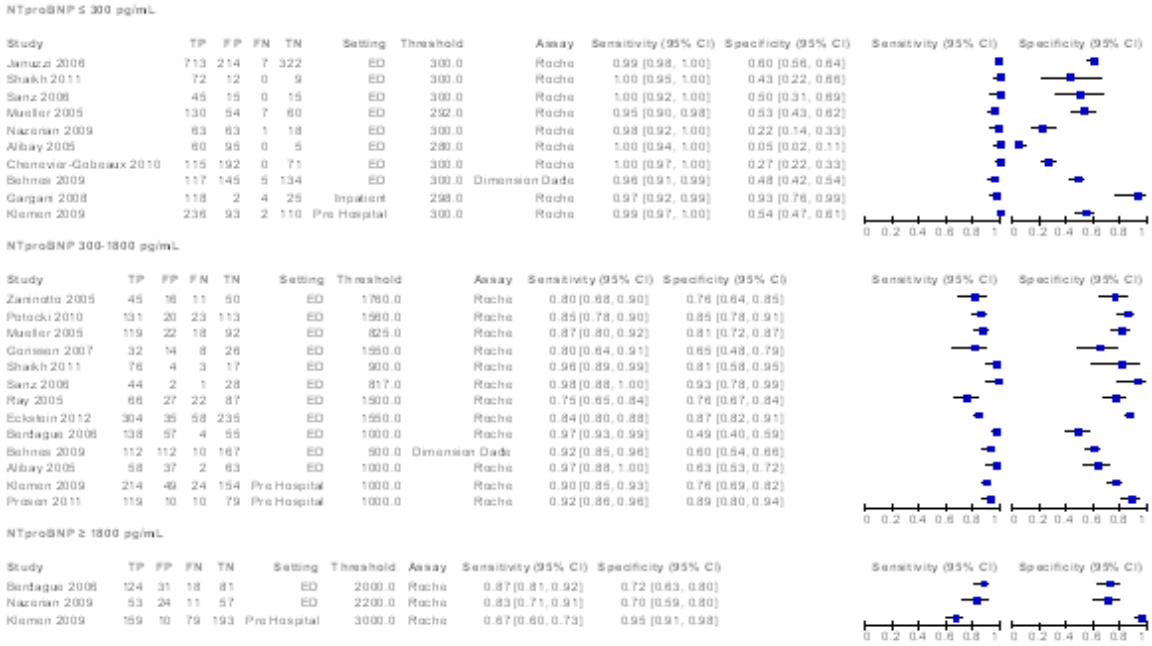


Figure 193: Paired sensitivity and specificity for NTproBNP with 95% confidence intervals

Figure 194: Summary ROC curve (sROC curve) for NTproBNP ≤ 300 pg/mL with summary sensitivity /specificity and confidence region

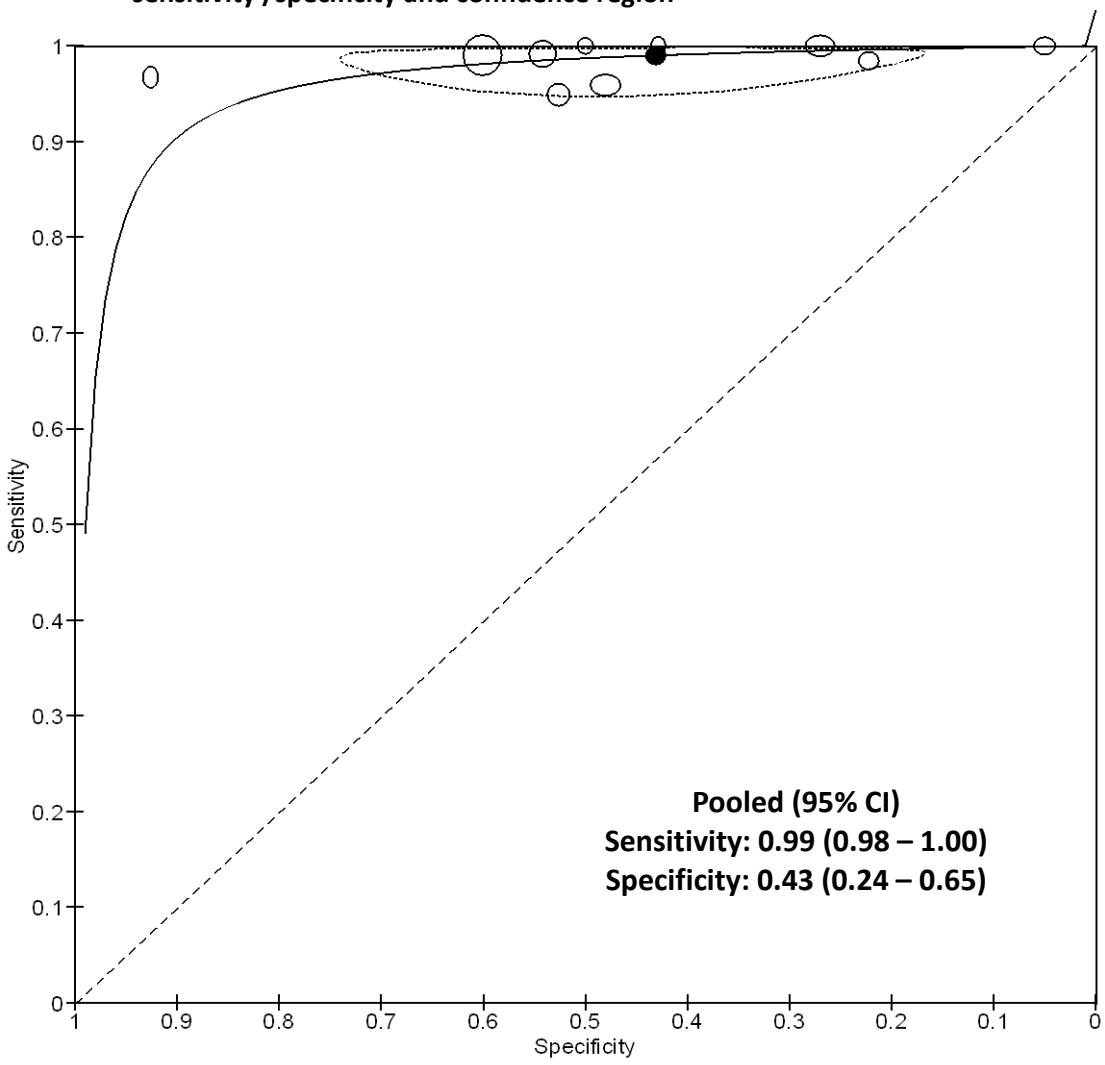
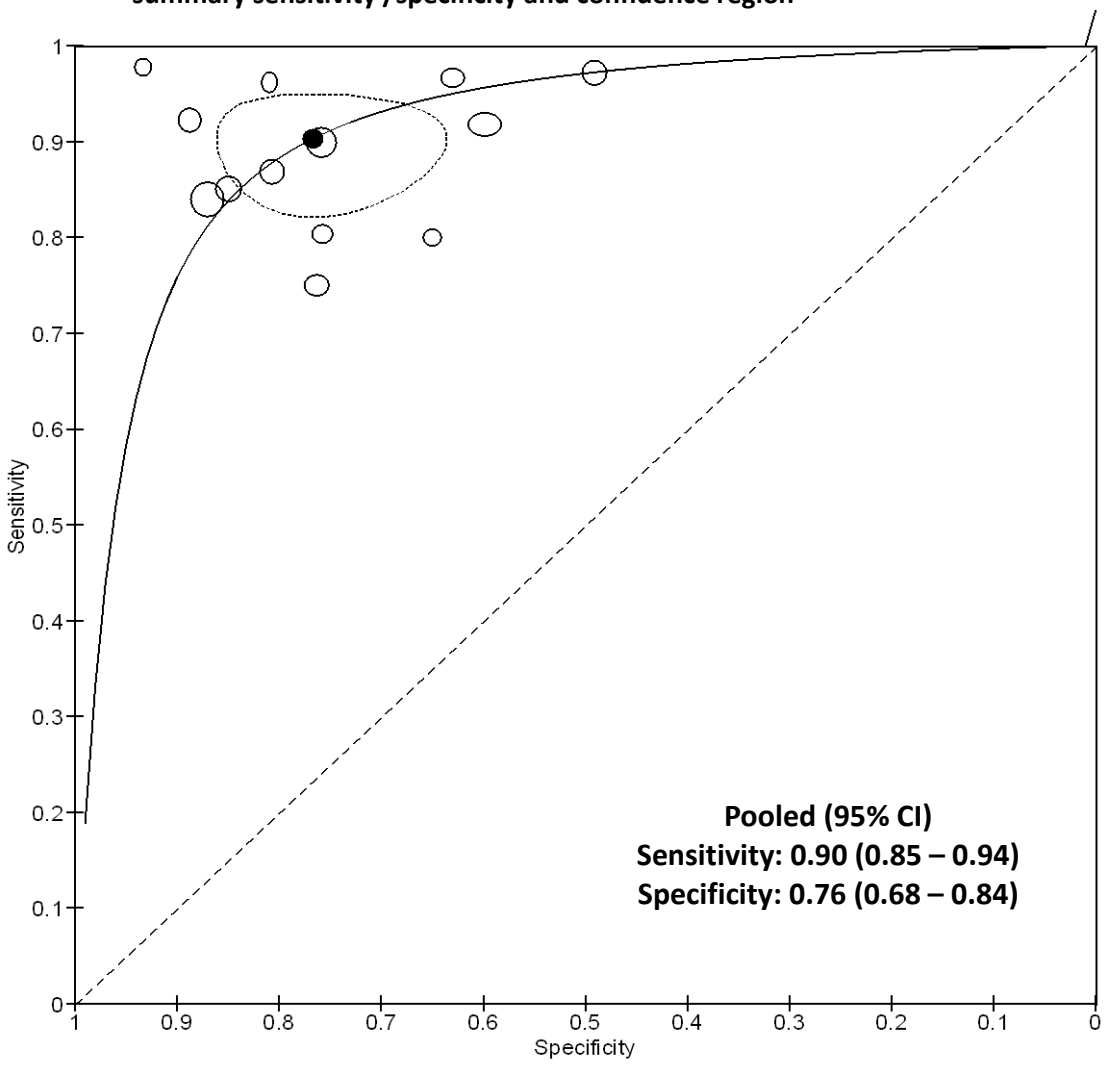


Figure 195: Summary ROC curve (sROC curve) for NTproBNP 300 - 1800 pg/mL with summary sensitivity /specificity and confidence region



1

Figure 196: sROC curves for NTproBNP at all thresholds (size of shapes indicate study size)

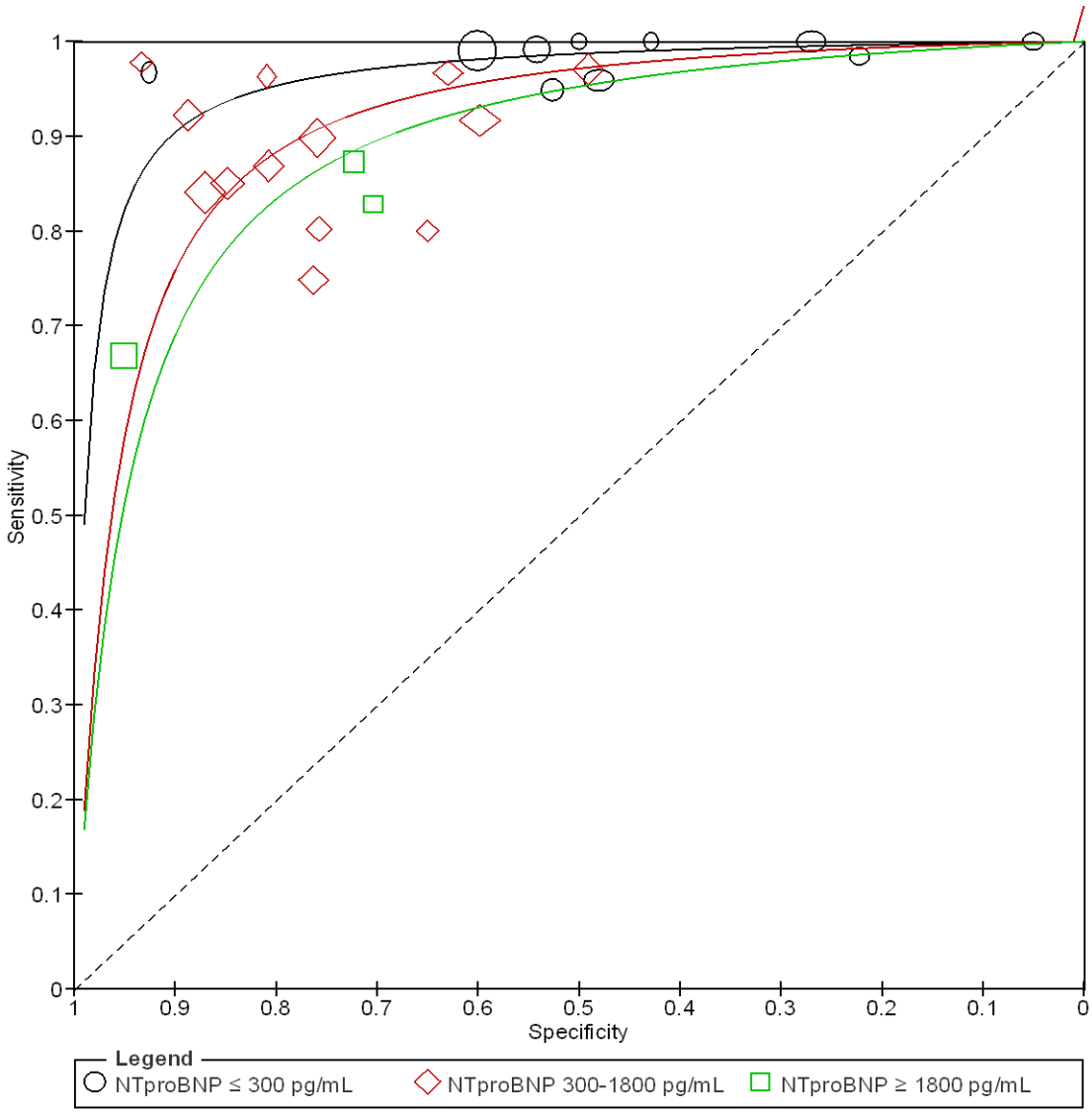
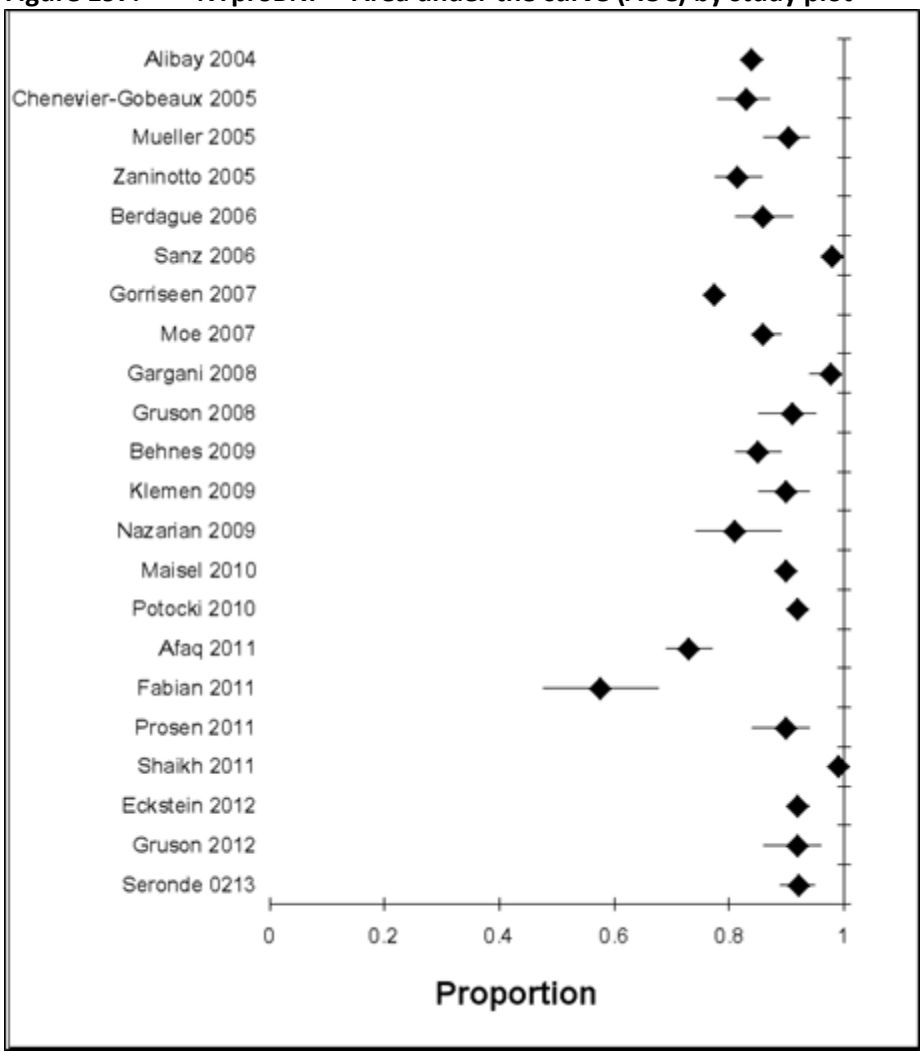
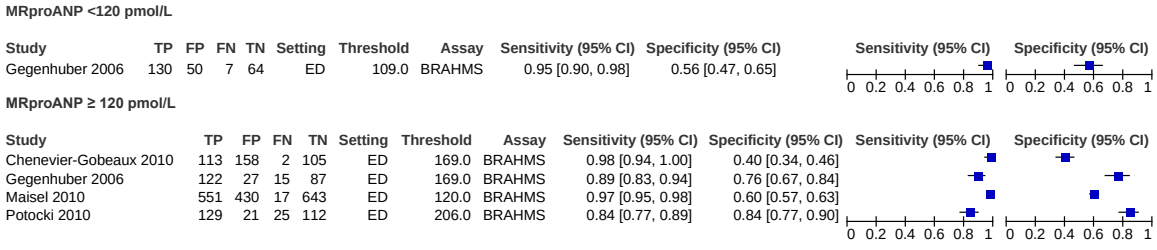


Figure 197: NTproBNP – Area under the curve (AUC) by study plot



J.6 MRproANP

Figure 198: Paired sensitivity and specificity for MRproANP with 95% confidence intervals



MRproANP <120 pmol/L

Study	TP	FP	FN	TN	Setting	Threshold	Assay	Sensitivity (95% CI)	Specificity (95% CI)
Gegenhuber 2006	130	50	7	64	ED	109.0	BRAHMS	0.95 [0.90, 0.98]	0.56 [0.47, 0.65]

MRproANP ≥ 120 pmol/L

Study	TP	FP	FN	TN	Setting	Threshold	Assay	Sensitivity (95% CI)	Specificity (95% CI)
Chenevier-Gobeaux 2010	113	158	2	105	ED	169.0	BRAHMS	0.98 [0.94, 1.00]	0.40 [0.34, 0.46]
Gegenhuber 2006	122	27	15	87	ED	169.0	BRAHMS	0.89 [0.83, 0.94]	0.76 [0.67, 0.84]
Maisel 2010	551	430	17	643	ED	120.0	BRAHMS	0.97 [0.95, 0.98]	0.60 [0.57, 0.63]
Potocki 2010	129	21	25	112	ED	206.0	BRAHMS	0.84 [0.77, 0.89]	0.84 [0.77, 0.90]

Figure 199: sROC curves for MRproANP at all thresholds (size of shapes indicates study size)

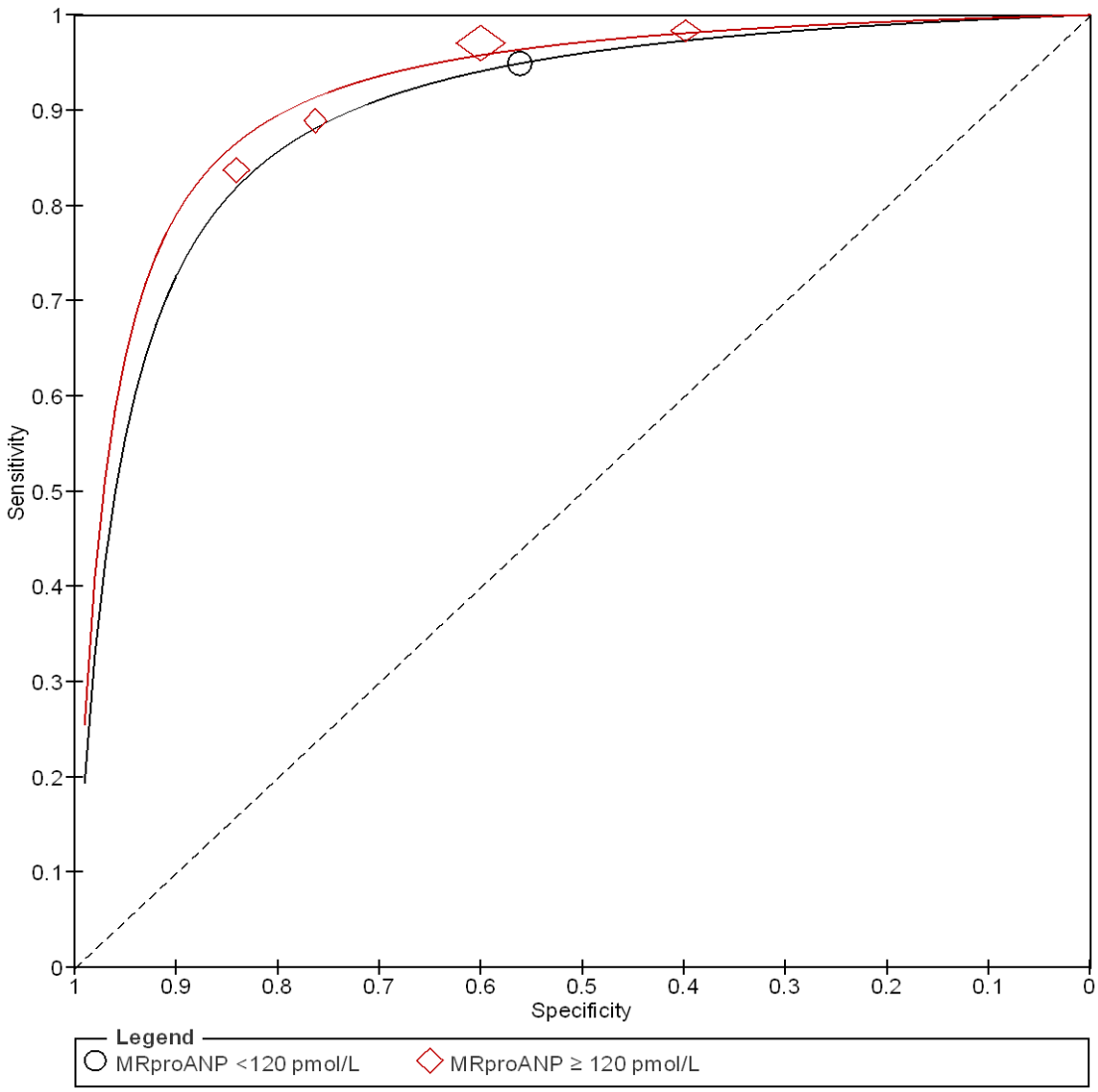
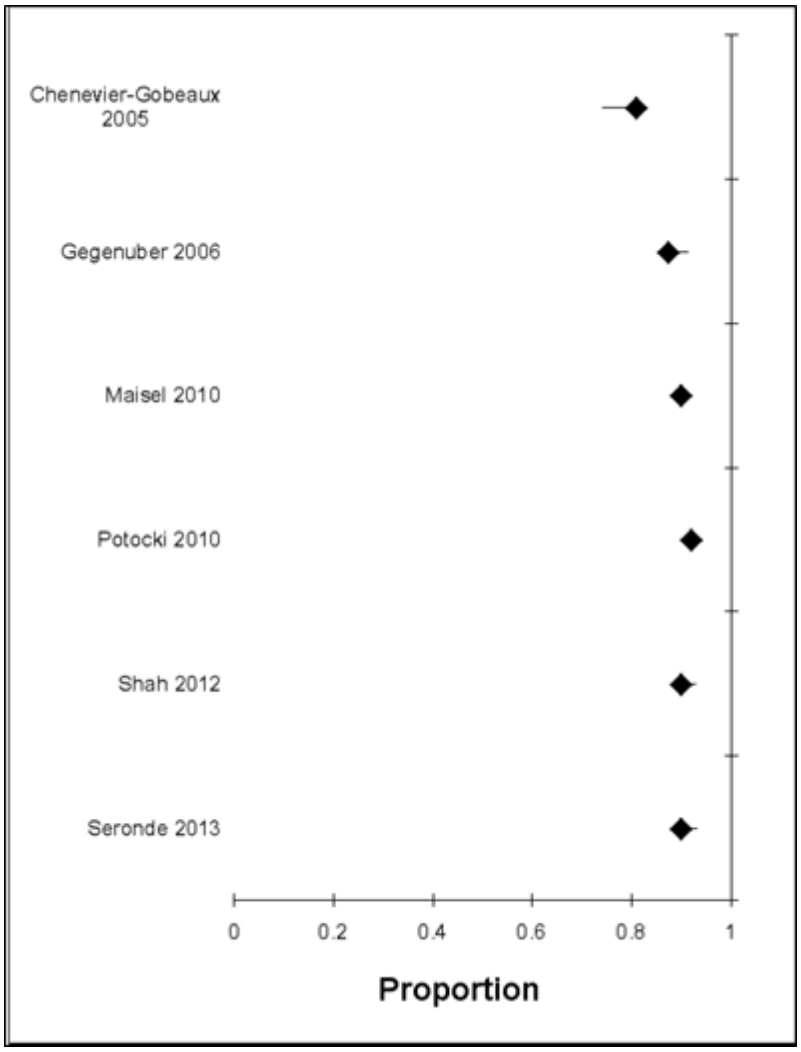


Figure 200: MRproANP - Area under the curve (AUC) by study plot



J.7 BNP vs NTproBNP vs MRproANP

Figure 201: sROC curves at 'rule-out' thresholds BNP ≤ 100pg/mL vs NTproBNP ≤ 300 pg/mL vs MRproANP ≥120pmol/L (size of shapes indicate study size)

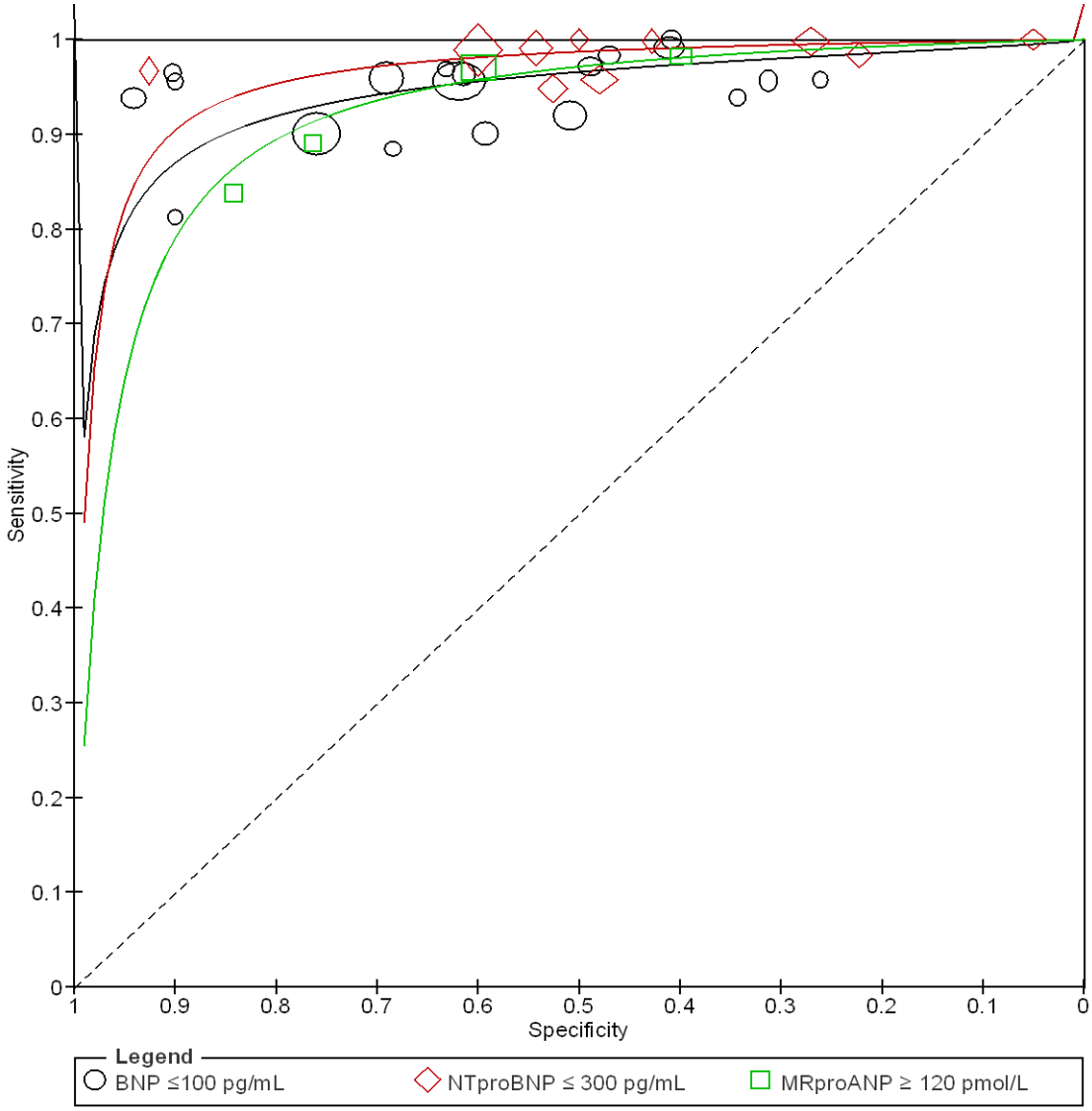


Figure 202: Graph of sROC curves comparing sensitivity/specificity summaries and confidence regions for BNP ≤ 100pg/mL versus NTproBNP ≤300 pg/mL

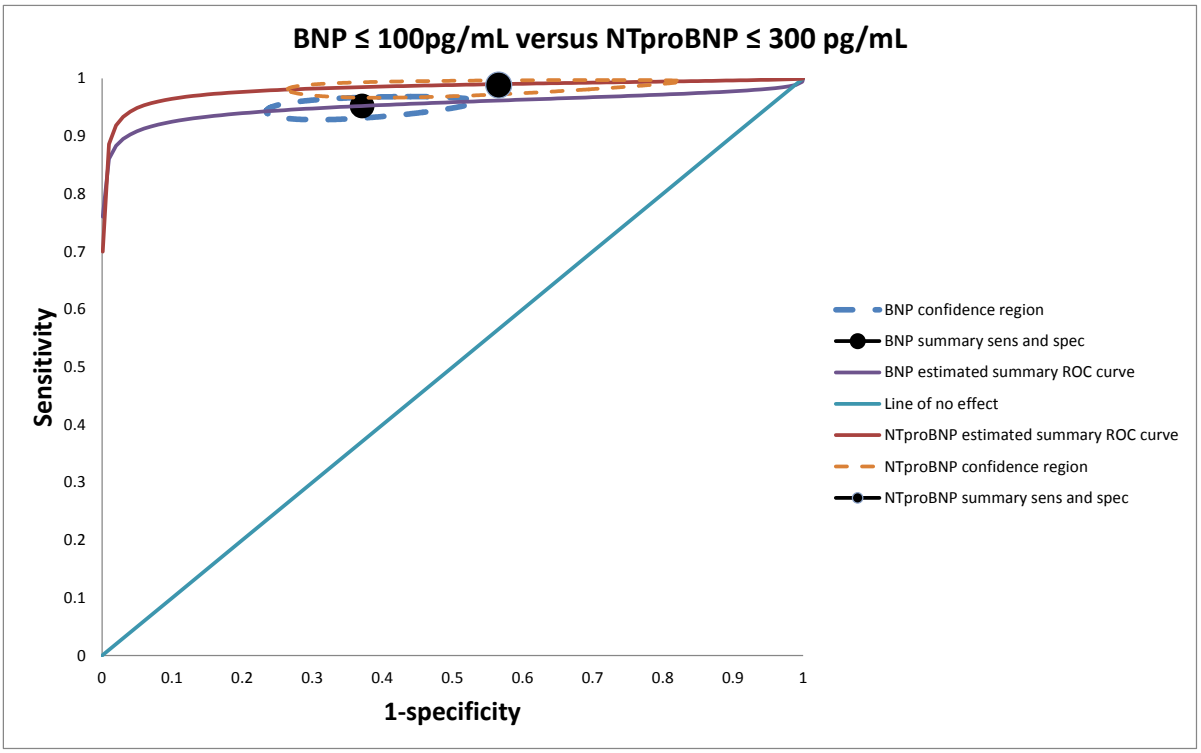


Figure 203: Graph of sROC curves comparing sensitivity/specificity summaries and confidence regions for BNP ≤ 100pg/mL versus NTproBNP ≤300 pg/mL

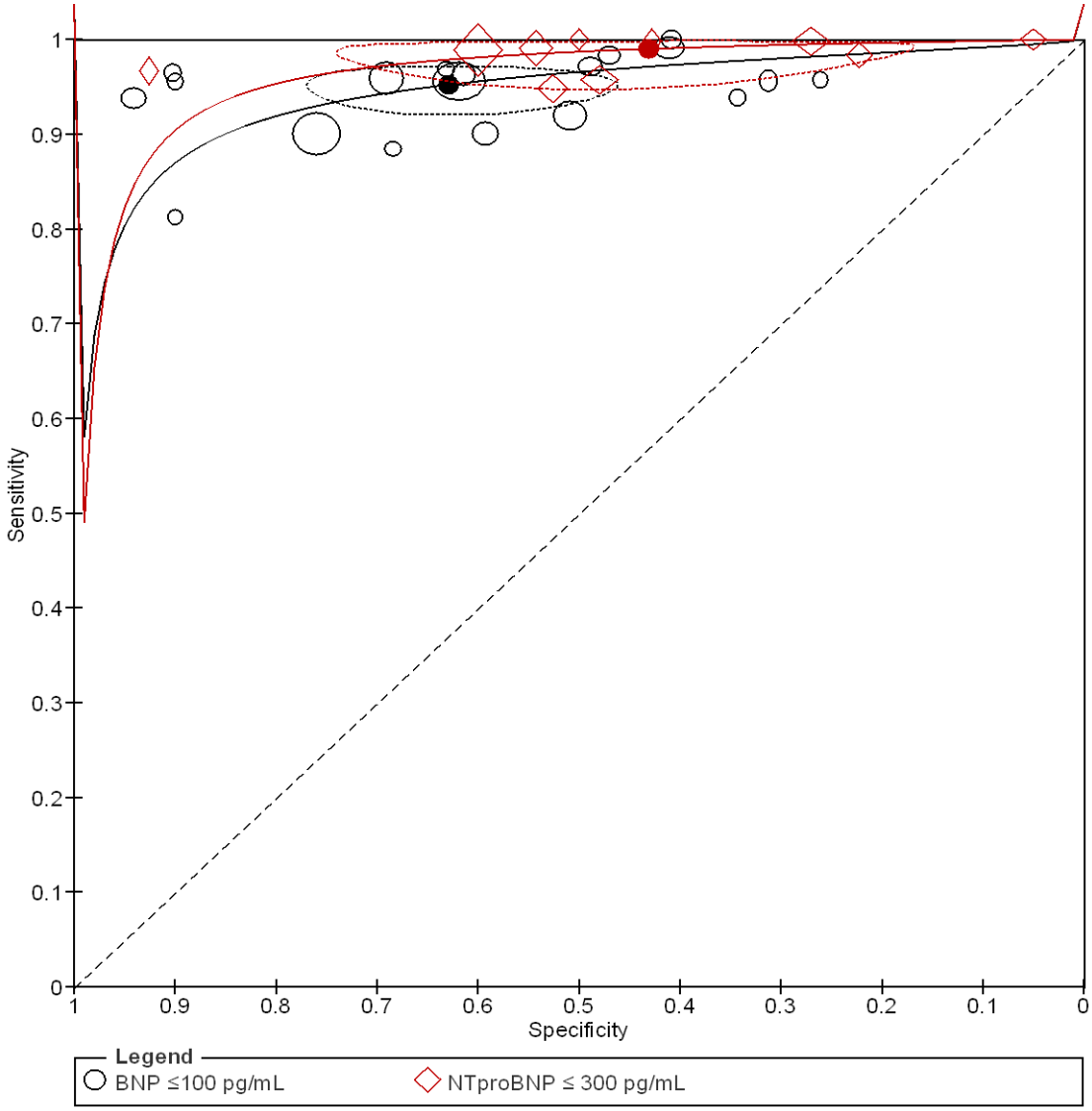
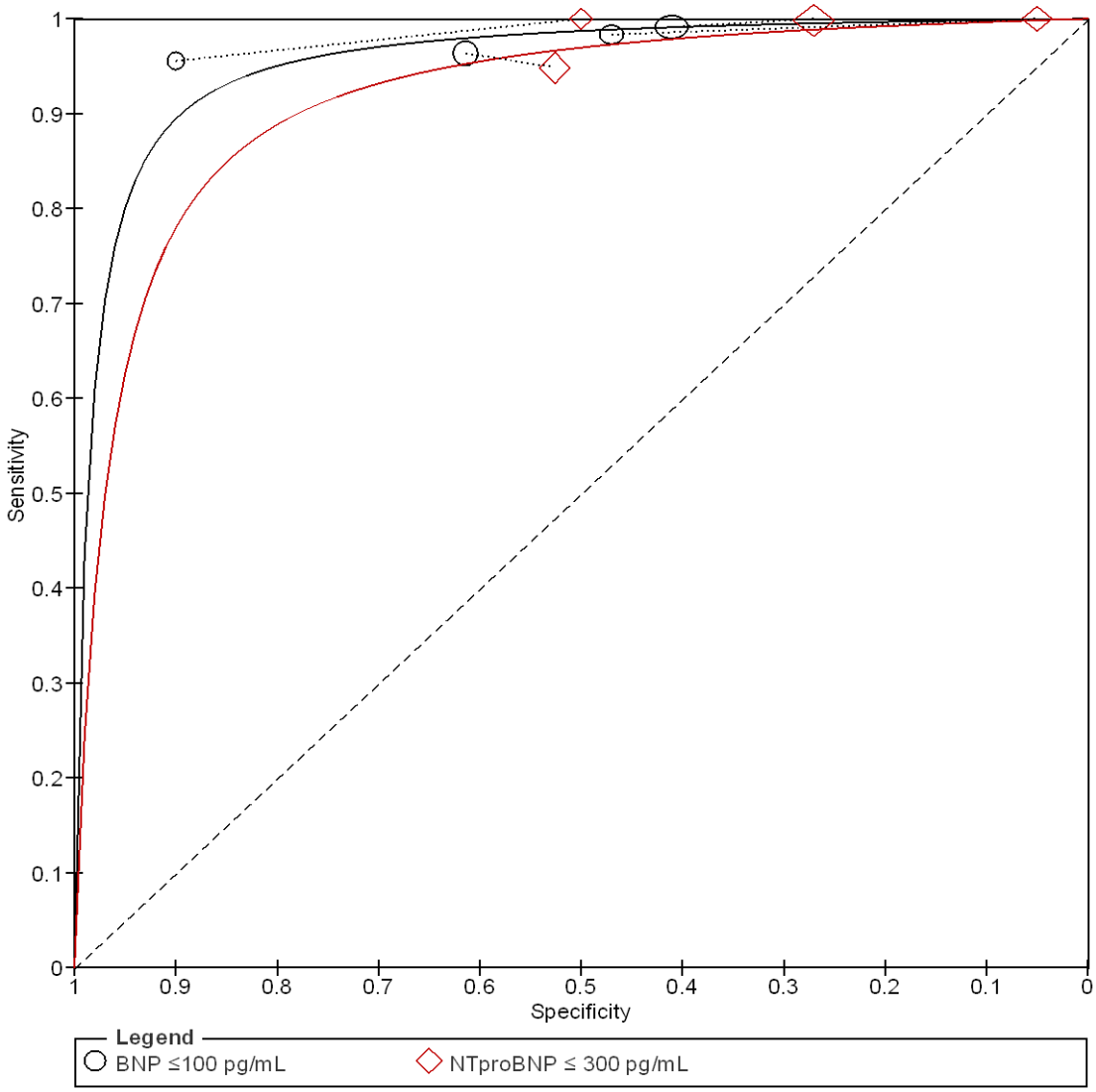


Figure 204: BNP (≤ 100 pg/mL) vs NTproBNP (≤ 300 pg/mL) in studies with both natriuretic peptides reporting at the rule out threshold


Sensitivity
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Specificity
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Legend
BNP ≤100 pg/mL
NTproBNP ≤ 300 pg/mL

1

Appendix K: Excluded clinical studies

K.1 Natriuretic peptides

Table 73: Studies excluded from the clinical review

Reference	Reason for exclusion
Ababsa R, Jourdain P, Funck F, Deschamps P, Sadeg N. [BNP and dyspnea: proposition of a diagnostic strategy based on two cut-off]. Annales De Biologie Clinique. 2005; 63(2):213-216	Not in English
Ajuluchukwu JNA, Ekure EN, Mbakwem AC, Okoromah CN, Oladipo OO. Reliability and accuracy of point-of-care amino-terminal probrain natriuretic peptide in congestive heart failure patients. International Journal of Cardiology. 2010; 9(2):2	Case-control study: Population consists of known CHF patients and healthy controls not suspected heart failure.
Anjan VY, Loftus TM, Burke MA, Akhter N, Fonarow GC, Gheorghiade M et al. Prevalence, clinical phenotype, and outcomes associated with normal B-type natriuretic Peptide levels in heart failure with preserved ejection fraction. American Journal of Cardiology. 2012; 110(6):870-876	Indirect population: Stable outpatients with HFpEF
Anwaruddin S, Lloyd-Jones DM, Baggish A, Chen A, Krauser D, Tung R et al. Renal function, congestive heart failure, and amino-terminal pro-brain natriuretic peptide measurement: results from the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) Study. Journal of the American College of Cardiology. 2006; 47(1):91-97	Post-hoc analysis of included (PRIDE) study in patients with renal insufficiency
Bal L, Thierry S, Brocas E, Van de Louw A, Pottecher J, Hours S et al. B-type natriuretic peptide (BNP) and N-terminal-proBNP for heart failure diagnosis in shock or acute respiratory distress. Acta Anaesthesiologica Scandinavica. 2006; 50(3):340-347	Indirect reference standard: Final diagnosis of heart failure was defined by echocardiography
Balion C, Santaguida PL, Hill S, Worster A, McQueen M, Oremus M et al. Testing for BNP and NT-proBNP in the diagnosis and prognosis of heart failure. Evidence Report/Technology Assessment. 2006;(142):1-147	HTA: Canada: Cross checked for references
Bay M, Kirk V, Parner J, Hassager C, Nielsen H, Krogsgaard K et al. NT-proBNP: a new diagnostic screening tool to differentiate between patients with normal and reduced left ventricular systolic function. Heart. 2003; 89(2):150-154	Indirect population: Screening for reduced LVEF in all patients admitted to hospital
Bayes-Genis A, Lloyd-Jones DM, van Kimmenade RRJ, Lainchbury JG, Richards AM, Ordonez-Llanos J et al. Effect of body mass index on diagnostic and prognostic usefulness of amino-terminal pro-brain natriuretic peptide in patients with acute dyspnea. Archives of Internal Medicine. 2007; 167(4):400-407	Post-hoc analysis of included (ICON) study in overweight and obese patients
Belagavi AC, Rao M, Pillai AY, Srihari US. Correlation between NT proBNP and left ventricular ejection fraction in elderly patients presenting to emergency department with dyspnoea. Indian Heart Journal. 2012; 64(3):302-304	Non diagnostic accuracy study, looks at correlation of NTproBNP and echo findings
Belovicova M, Kinova S, Hrusovsky S. Brain natriuretic peptide (BNP) in differential diagnosis of dyspnea. Bratislavske Lekarske Listy. 2005; 106(6-7):203-206	Non diagnostic accuracy study, examine correlation of BNP levels with NYHA class of patients presenting to clinic.
Boldanova T, Noveanu M, Breidthardt T, Potocki M, Reichlin T, Taegtmeyer A et al. Impact of history of heart failure on diagnostic and prognostic value of BNP: results from the B-type Natriuretic Peptide for Acute Shortness of Breath Evaluation (BASEL) study. International Journal of Cardiology. 2010; 142(3):265-272	Post hoc analysis of included (BASEL) study comparing history of heart failure with no history of heart failure

Brenden CK, Hollander JE, Guss D, McCullough PA, Nowak R, Green G et al. Gray zone BNP levels in heart failure patients in the emergency department: results from the Rapid Emergency Department Heart Failure Outpatient Trial (REDHOT) multicenter study. American Heart Journal. 2006; 151(5):1006-1011	Non diagnostic accuracy study studies implications of BNP>100 pg/mL on outcomes in ED patients with dyspnoea
Carpenter CR, Keim SM, Worster A, Rosen P, BEEM (Best Evidence in Emergency Medicine). Brain natriuretic peptide in the evaluation of emergency department dyspnea: is there a role? Journal of Emergency Medicine. 2012; 42(2):197-205	Prognostic evidence review for BNP and NTproBNP on patient oriented outcomes
Cavallazzi R, Nair A, Vasu T, Marik PE. Natriuretic peptides in acute pulmonary embolism: a systematic review. Intensive Care Medicine. 2008; 34(12):2147-2156	Systematic review for RVD in patients with PE
Chen AA, Wood MJ, Krauser DG, Baggish AL, Tung R, Anwaruddin S et al. NT-proBNP levels, echocardiographic findings, and outcomes in breathless patients: results from the ProBNP Investigation of Dyspnoea in the Emergency Department (PRIDE) echocardiographic substudy. European Heart Journal. 2006; 27(7):839-845	Post-hoc analysis of included (PRIDE) study in prognostic outcomes
Chenevier-Gobeaux C, Delerme S, Allo JC, Arthaud M, Claessens YE, Ekindjian OG et al. B-type natriuretic peptides for the diagnosis of congestive heart failure in dyspneic oldest-old patients. Clinical Biochemistry. 2008; 41(13):1049-1054	Post-hoc analysis of included study Chenevier-Gobeaux 2005[12] in oldest old patients
Chien TI, Chen HH, Kao JT. Comparison of Abbott AxSYM and Roche Elecsys 2010 for measurement of BNP and NT-proBNP. Clinica Chimica Acta; International Journal of Clinical Chemistry. 2006; 369(1):95-99	Indirect reference standard: Final diagnosis of heart failure was defined by echocardiography
Choi S, Park D, Lee S, Hong Y, Kim S, Lee J. Cut-off values of B-type natriuretic peptide for the diagnosis of congestive heart failure in patients with dyspnoea visiting emergency departments: a study on Korean patients visiting emergency departments. Emergency Medicine Journal. 2007; 24(5):343-347	Indirect reference standard: Final diagnosis of heart failure was defined by transthoracic echocardiography
Cinar O, Cevik E, Acar A, Kaya C, Ardic S, Comert B et al. Evaluation of mid-regional pro-atrial natriuretic peptide, procalcitonin, and mid-regional pro-adrenomedullin for the diagnosis and risk stratification of dyspneic ED patients. American Journal of Emergency Medicine. 2012; 30(9):1915-1920	Comparison of initial diagnosis, marker aided diagnosis and final diagnosis as a process.
Clerico A, Fontana M, Zyw L, Passino C, Emdin M. Comparison of the diagnostic accuracy of brain natriuretic peptide (BNP) and the N-terminal part of the propeptide of BNP immunoassays in chronic and acute heart failure: a systematic review. Clinical Chemistry. 2007; 53(5):813-822	Systematic review of BNP and NTproBNP: cross checked for all references
Clerico A, Prontera C, Emdin M, Passino C, Storti S, Poletti R et al. Analytical performance and diagnostic accuracy of immunometric assays for the measurement of plasma B-type natriuretic peptide (BNP) and N-terminal proBNP. Clinical Chemistry. 2005; 51(2):445-447	Indirect population: Healthy subjects
Collin-Chavagnac D, Jacques D, Perrin M, Rabilloud M, Manchon M. [BNP/NT-proBNP: what is the best choice in an emergency laboratory?]. Annales De Biologie Clinique. 2006; 64(3):275-280	Not in English
Collins SP, Lindsell CJ, Peacock WF, Hedger VD, Askew J, Eckert DC et al. The combined utility of an S3 heart sound and B-type natriuretic peptide levels in emergency department patients with dyspnea. Journal of Cardiac Failure. 2006; 12(4):286-292	Diagnostic accuracy of S3 auscultation + BNP. No individually extractable data for BNP alone
Collins SP, Lindsell CJ, Yealy DM, Maron DJ, Naftilan AJ, McPherson JA et al. A comparison of criterion standard methods to diagnose acute heart failure. Congestive Heart Failure. 2012; 18(5):262-271	Non diagnostic accuracy study no reference standard; Comparison of diagnostic strategies in ED
Coquet I, Darmon M, Doise JM, Degres M, Blettery B, Schlemmer B et al. Performance of N-terminal-pro-B-type natriuretic peptide in critically ill patients: a prospective observational cohort study. Critical Care. 2008; 12(6):R137	Indirect population: Any patients admitted to ICU not patients with suspected heart failure
Coskun B, Kirkil G, Muz MH, Yildiz M, Ozbay Y. The diagnostic values of brain natriuretic peptide and cardiac troponin i for determining the right ventricle dysfunction in patients with submassive pulmonary thromboembolism. Turk Toraks Dergisi. 2012; 13(4):163-168	Not in English

Coste J, Jourdain P, Pouchot J. A gray zone assigned to inconclusive results of quantitative diagnostic tests: Application to the use of brain natriuretic peptide for diagnosis of heart failure in acute dyspneic patients. Clinical Chemistry. 2006; 52(12):2229-2235	No extractable diagnostic accuracy data; calculation of grey zone likelihood ratios on the basis of history of heart failure
Craig, J, Bradbury, I, Cummins, E, Downie, S, Foster, L, and Stout, A. The use of B-type natriuretic peptides in the investigation of patients with suspected heart failure; Understanding our Advice: The use of B-type natriuretic peptides in the investigation of patients with suspected heart failure. NHS Quality Improvement Scotland (NHS QIS), 2005 Available from: http://www.healthcareimprovementscotland.org/previous_resources/archived/use_of_bnp_in_the_investigatio.aspx	HTA: Scotland: Cross checked for references
Daniels LB, Clopton P, Bhalla V, Krishnaswamy P, Nowak RM, McCord J et al. How obesity affects the cut-points for B-type natriuretic peptide in the diagnosis of acute heart failure. Results from the Breathing Not Properly Multinational Study. American Heart Journal. 2006; 151(5):999-1005	Post-hoc analysis of included (Breathing Not Properly) study in obese patients
Dieplinger B, Gegenhuber A, Haltmayer M, Mueller T. Evaluation of novel biomarkers for the diagnosis of acute destabilised heart failure in patients with shortness of breath. Heart. 2009; 95(18):1508-1513	Duplicate data: Previously presented in included study Gegenuber 2006[23]
Diercks DB, Miller CD. Natriuretic peptide testing: a useful diagnostic test. Annals of Emergency Medicine. 2009; 53(3):386-387	Letter to editor
Doust JA, Glasziou PP, Pietrzak E, Dobson AJ. A systematic review of the diagnostic accuracy of natriuretic peptides for heart failure. Archives of Internal Medicine. 2004; 164(18):1978-1984	Systematic review of BNP and BNP versus NTproANP cross referenced and all appropriate studies included.
El Mahmoud R, Alibay Y, Brun-Ney D, Boulard JC, Dubourg O, Puy H et al. [Type B natriuretic peptide (BNP) versus n-terminal type B natriuretic propeptide in the diagnosis of cardiac failure in the elderly over 75 population]. Archives Des Maladies Du Coeur Et Des Vaisseaux. 2006; 99(3):201-207	Not in English
Ewald B, Ewald D, Thakkinstian A, Attia J. Meta-analysis of B type natriuretic peptide and N-terminal pro B natriuretic peptide in the diagnosis of clinical heart failure and population screening for left ventricular systolic dysfunction. Internal Medicine Journal. 2008; 38(2):101-113	Systematic review of BNP and NTproBNP. Cross referenced and all appropriate studies included
Gariani K, Delabays A, Perneger TV, Agoritsas T. Use of brain natriuretic peptide to detect previously unknown left ventricular dysfunction in patients with acute exacerbation of chronic obstructive pulmonary disease. Swiss Medical Weekly. 2011; 141:w13298	Indirect population: Screening for LVD in ED patients with a final diagnosis of AECOPD
Golabchi A. Can atrial natriuretic peptides measurement diagnose heart failure at different age groups? Journal of Research in Medical Sciences. 2012; 17(1):116-117	Letter to editor
Green SM, Martinez-Rumayor A, Gregory SA, Baggish AL, O'Donoghue ML, Green JA et al. Clinical uncertainty, diagnostic accuracy, and outcomes in emergency department patients presenting with dyspnea. Archives of Internal Medicine. 2008; 168(7):741-748	Post-hoc analysis of included (PRIDE) study in clinical uncertainty as a prognostic marker
Gutte H, Mortensen J, Jensen CV, von der Recke P, Petersen CL, Kristoffersen US et al. ANP, BNP and D-dimer predict right ventricular dysfunction in patients with acute pulmonary embolism. Clinical Physiology and Functional Imaging. 2010; 30(6):466-472	Screening for RVD in patients with PE
Henzler T, Roeger S, Meyer M, Schoepf UJ, Nance JWJ, Haghi D et al. Pulmonary embolism: CT signs and cardiac biomarkers for predicting right ventricular dysfunction. European Respiratory Journal. 2012; 39(4):919-926	Screening for RVD in patients with PE
Hu Z, Han Z, Huang Y, Sun Y, Li B, Deng A. Diagnostic power of the mid-regional pro-atrial natriuretic peptide for heart failure patients with dyspnea: a meta-analysis. Clinical Biochemistry. 2012; 45(18):1634-1639	Systematic review of MRproANP: Cross checked for all references

Jang TB, Aubin C, Naunheim R, Lewis LM, Kaji AH. The predictive value of physical examination findings in patients with suspected acute heart failure syndrome. Internal and Emergency Medicine. 2012; 7(3):271-274	Indirect reference standard: Criterion standard was pulmonary oedema on CXR
Januzzi JLJ, Chen-Tournoux AA, Moe G. Amino-terminal pro-B-type natriuretic peptide testing for the diagnosis or exclusion of heart failure in patients with acute symptoms. American Journal of Cardiology. 2008; 101(3A):29-38	Review article
Jefic D, Lee JW, Jefic D, Savoy-Moore RT, Rosman HS. Utility of B-type natriuretic peptide and N-terminal pro B-type natriuretic peptide in evaluation of respiratory failure in critically ill patients. Chest. 2005; 128(1):288-295	Indirect population: medical or surgical ICU patients with pulmonary artery catheter in place assessing for contractile dysfunction
Jones DJL, Willingale R, Quinn PA, Lamb JH, Farmer PB, Davies JE et al. Improving the diagnostic accuracy of N-terminal B-type natriuretic peptide in human systolic heart failure by plasma profiling using mass spectrometry. Journal of Proteome Research. 2007; 6(8):3329-3334	Case-control study: Population consists of known CHF patients and healthy controls not suspected heart failure.
Jose JV, Gupta SN, Selvakumar D. Utility of N-terminal pro-brain natriuretic peptide for the diagnosis of heart failure. Indian Heart Journal. 2003; 55(1):35-39	indirect population: Mixed acute and chronic shortness of breath presenting to ED and outpatient departments, no split given
Jourdain P, Funck F, Canault E, Bellorini M, Deschamps P, Duval G et al. [Value of type B natriuretic peptide in the emergency management of patients with suspected cardiac failure. Report of 125 cases]. Archives Des Maladies Du Coeur Et Des Vaisseaux. 2002; 95(9):763-767	Not in English
Jungbauer CG, Buchner S, Birner C, Resch M, Heinicke N, Debl K et al. N-terminal pro-brain natriuretic peptide from fresh urine for the biochemical detection of heart failure and left ventricular dysfunction. European Journal of Heart Failure. 2010; 12(4):331-337	Urinary BNP study
Kamano C, Osawa H, Hashimoto K, Nishimura S, Saito SK, Kashiwagi T et al. N-Terminal pro-brain natriuretic peptide as a predictor of heart failure with preserved ejection fraction in hemodialysis patients without fluid overload. Blood Purification. 2012; 33(1-3):37-43	Indirect population: Screening for HFpEF in haemodialysis patients
Karakilic E, Kepez A, Abali G, Coskun F, Kunt M, Tokgozoglu L. The relationship between B-type natriuretic peptide levels and echocardiographic parameters in patients with heart failure admitted to the emergency department. Anadolu Kardiyoloji Dergisi. 2010; 10(2):143-149	Non diagnostic accuracy study, looks at correlation of BNP levels with echocardiographic parameters
Kevin Rogers R, Stehlik J, Stoddard GJ, Greene T, Collins SP, Peacock WF et al. Adjusting for clinical covariates improves the ability of B-type natriuretic peptide to distinguish cardiac from non-cardiac dyspnoea: a sub-study of HEARD-IT. European Journal of Heart Failure. 2009; 11(11):1043-1049	Duplicate data: From included substudy (HEARD-IT) trial
Knudsen CW, Riis JS, Finsen AV, Eikvar L, Muller C, Westheim A et al. Diagnostic value of a rapid test for B-type natriuretic peptide in patients presenting with acute dyspnoe: effect of age and gender. European Journal of Heart Failure. 2004; 6(1):55-62	Duplicate data: Norwegian data from included study (Breathing Not Properly) data
Korenstein D, Wisnivesky JP, Wyer P, Adler R, Ponieman D, McGinn T. The utility of B-type natriuretic peptide in the diagnosis of heart failure in the emergency department: a systematic review. BMC Emergency Medicine. 2007; 7:6	Systematic review of BNP cross checked for references
Laiho MK, Harjola VP, Graner M, Piilonen A, Raade M, Mustonen P. Helical computerized tomography and NT-proBNP for screening of right ventricular overload on admission and at long term follow-up of acute pulmonary embolism. Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine. 2012; 20:33	Screening for RVD in patients with PE
Latour-Perez J, Coves-Orts FJ, Abad-Terrado C, Abraira V, Zamora J. Accuracy of B-type natriuretic peptide levels in the diagnosis of left ventricular dysfunction and heart failure: a systematic review. European Journal of Heart Failure. 2006; 8(4):390-399	Systematic review of BNP cross checked for references

Lefebvre A, Kural-Menasche S, Darmon M, Thiery G, Feugeas JP, Schlemmer B et al. Use of N-terminal pro-brain natriuretic peptide to detect cardiac origin in critically ill cancer patients with acute respiratory failure. Intensive Care Medicine. 2008; 34(5):833-839	Indirect population: Any cancer patients admitted to ICU not patients with suspected heart failure
Levitt JE, Vinayak AG, Gehlbach BK, Pohlman A, Van Cleve W, Hall JB et al. Diagnostic utility of B-type natriuretic peptide in critically ill patients with pulmonary edema: a prospective cohort study. Critical Care. 2008; 12(1):R3	Indirect target condition: using BNP to distinguish Acute lung Injury/ARDS
Liteplo AS, Marill KA, Villen T, Miller RM, Murray AF, Croft PE et al. Emergency thoracic ultrasound in the differentiation of the etiology of shortness of breath (ETUDES): sonographic B-lines and N-terminal pro-brain-type natriuretic peptide in diagnosing congestive heart failure. Academic Emergency Medicine. 2009; 16(3):201-210	No extractable diagnostic accuracy data. Threshold of NTproBNP not reported alongside sensitivity and specificity. No AUC value given.
Mant J, Doust J, Roalfe A, Barton P, Cowie MR, Glasziou P et al. Systematic review and individual patient data meta-analysis of diagnosis of heart failure, with modelling of implications of different diagnostic strategies in primary care. Health Technology Assessment. 2009; 13(32):1-207	HTA: UK: Cross checked for references
Marantz PR, Kaplan MC, Alderman MH. Clinical diagnosis of congestive heart failure in patients with acute dyspnea. Chest. 1990; 97(4):776-781	Indirect index test: Physical examination manoeuvres compared to reference standard
Martinez-Rumayor AA, Vazquez J, Rehman SU, Januzzi JL. Relative value of amino-terminal pro-B-type natriuretic peptide testing and radiographic standards for the diagnostic evaluation of heart failure in acutely dyspneic subjects. Biomarkers. 2010; 15(2):175-182	Post-hoc analysis of included (PRIDE) study of NTproBNP versus CXR
McCullough PA, Nowak RM, McCord J, Hollander JE, Herrmann HC, Steg PG et al. B-type natriuretic peptide and clinical judgment in emergency diagnosis of heart failure: analysis from Breathing Not Properly (BNP) Multinational Study. Circulation. 2002; 106(4):416-422	Subgroup analysis of included (Breathing Not Properly) study with information recorded for ED physician assessment of probability of heart failure
Merlin, T, Moss, J, Brooks, A, Newton, S, Hedayati, H, and Hiller, J. B-type natriuretic peptide assays in the diagnosis of heart failure. Part A: in the hospital emergency setting. Part B: in the non-hospital setting. Adelaide Health Technology Assessment (AHTA), 2007	HTA: Australia: Cross checked for references
Michaels AD, Rogers R, Stoddard G, Green T, Collins SP, Peacock WF et al. Adjusting for clinical covariates improves the ability of BNP to distinguish cardiac from non-cardiac dyspnea. European Heart Journal. 2009; 30(Suppl 1):131-132	Conference abstract of included study (HEARD-IT)
Michielsen ECHJ, Bakker JA, Kimmenade RRJV, Pinto YM, Dieijen-Visser MPV. The diagnostic value of serum and urinary NT-proBNP for heart failure. Annals of Clinical Biochemistry. 2008; 45(Pt 4):389-394	Case-control study: Population consists of known CHF patients and healthy controls not suspected heart failure.
Mikkelsen KV, Bie P, Moller JE, Ryde H, Videbaek L, Haghfelt T. Diagnostic accuracy of plasma brain natriuretic peptide and aminoterminal-proBNP in mild heart failure depends on assay and introduction of therapy. Scandinavian Journal of Clinical and Laboratory Investigation. 2005; 65(8):633-647	Indirect population; patients referred by GP to HF clinic
Mockel M, Muller R, Vollert JO, Muller C, Carl A, Peetz D et al. Role of N-terminal pro-B-type natriuretic peptide in risk stratification in patients presenting in the emergency room. Clinical Chemistry. 2005; 51(9):1624-1631	Indirect population: Not suspected heart failure: unselected ED patients
Morrison LK, Harrison A, Krishnaswamy P, Kazanegra R, Clopton P, Maisel A. Utility of a rapid B-natriuretic peptide assay in differentiating congestive heart failure from lung disease in patients presenting with dyspnea. Journal of the American College of Cardiology. 2002; 39(2):202-209	Duplicate data: San Diego data from included study (Breathing Not Properly) data
Murray H, Cload B, Collier CP, Sivilotti MLA. Potential impact of N-terminal pro-BNP testing on the emergency department evaluation of acute dyspnea. Canadian Journal of Emergency Medicine. 2006; 8(4):251-258	Indirect reference standard: ED physician rating scale at likelihood of heart failure diagnosis and correlation with NTproBNP levels.

Omland T. B-type natriuretic peptides: prognostic markers in stable coronary artery disease. Expert Review of Molecular Diagnostics. 2008; 8(2):217-225	Prognostic study for BNP in stable coronary artery disease patients
Osca J, Quesada A, Arnau MA, Osa A, Hervas I, Almenar L et al. Brain natriuretic peptide. Diagnostic value in heart failure. Revista Espanola De Cardiologia. 2002; 55(1):7-15	Not in English
O'Shea P, Daly R, Kasim S, Tormey WP. B-type natriuretic peptide in the Cardiology Department. Irish Medical Journal. 2012; 105(10)	Indirect setting and population: GP referrals to cardiology outpatients
Ouanes I, Jalloul F, Ayed S, Dachraoui F, Ouanes-Besbes L, Fekih Hassen M et al. N-terminal proB-type natriuretic peptide levels aid the diagnosis of left ventricular dysfunction in patients with severe acute exacerbations of chronic obstructive pulmonary disease and renal dysfunction. Respirology. 2012; 17(4):660-666	Indirect population: Screening for LVD in patients with COPD and renal dysfucntion
Ozturk TC, Unluer E, Denizbasi A, Guneysel O, Onur O. Can NT-proBNP be used as a criterion for heart failure hospitalization in emergency room? Journal of Research in Medical Sciences. 2011; 16(12):1564-1571	Non diagnostic accuracy study; compares NTproBNP levels in outpatients and those hospitalised
Pahle AS, Sorli D, Omland T, Knudsen CW, Westheim A, Wu AHB et al. Impact of systemic hypertension on the diagnostic performance of B-type natriuretic peptide in patients with acute dyspnea. American Journal of Cardiology. 2009; 104(7):966-971	Post-hoc analysis of included (Breathing Not Properly) study in hypertensive patients
Pang PS, Xue Y, DeFilippi C, Silver M, Januzzi J, Maisel A. The role of natriuretic peptides: from the emergency department throughout hospitalization. Congestive Heart Failure. 2012; 18 Suppl 1:S5-S8	Review article
Park HJ, Baek SH, Jang SW, Kim DB, Shin DI, Shin WS et al. Direct comparison of B-type natriuretic peptide and N-terminal pro-BNP for assessment of cardiac function in a large population of symptomatic patients. International Journal of Cardiology. 2010; 140(3):336-343	Indirect setting and population: Screening for LVSD in patients with dyspnoea in daily clinical practice
Paul B, Soon KH, Dunne J, De Pasquale CG. Diagnostic and prognostic significance of plasma N-terminal-pro-brain natriuretic peptide in decompensated heart failure with preserved ejection fraction. Heart, Lung and Circulation. 2008; 17(6):497-501	Non diagnostic accuracy study studies correlation of NTproBNP with preservation of ejection fraction and correlation with outcomes.
Pfister R, Scholz M, Wielckens K, Erdmann E, Schneider CA. Use of NT-proBNP in routine testing and comparison to BNP. European Journal of Heart Failure. 2004; 6(3):289-293	Indirect population: Screening for LV dysfunction in hospitalised patients undergoing angiography
Rapid HTA on the use of natriuretic peptides for diagnosing cardiac insufficiency in patients with acute dyspnea. Department of Science and Technology - Brazilian Health Technology Assessment General Coordination (DECIT-CGATS), 2009	Not in English
Ray P, Chenevier-Gobeaux C, Claessens Y-E. Natriuretic peptides to diagnose acute heart failure in emergency patients. Annales Francaises De Medecine D'Urgence. 2011; 1(3):200-205	Not in English
Robaei D, Koe L, Bais R, Gould I, Stewart T, Tofler GH. Effect of NT-proBNP testing on diagnostic certainty in patients admitted to the emergency department with possible heart failure. Annals of Clinical Biochemistry. 2011; 48(Pt 3):212-217	Non diagnostic accuracy study, no reference standard: RCT of clinicians blinded versus unblinded to BNP result in cases of suspected heart failure
Sabatasso S, Vaucher P, Augsburger M, Donze N, Mangin P, Michaud K. Sensitivity and specificity of NT-proBNP to detect heart failure at post mortem examination. International Journal of Legal Medicine. 2011; 125(6):849-856	Forensic study of death with heart failure
Sakhuja R, Chen AA, Anwaruddin S, Baggish AL, Januzzi JLJ. Combined use of amino terminal-pro-brain natriuretic peptide levels and QRS duration to predict left ventricular systolic dysfunction in patients with dyspnea. American Journal of Cardiology. 2005; 96(2):263-266	Post-hoc analysis of included (PRIDE) study of combining NTproBNP and QRS duration

Shaikh K, Hanif B, Siddique AA, Shaikh MY, Khan MN. Pro-brain natriuretic peptide plasma levels, left ventricular dimensions and ejection fraction in acute dyspnoea. Journal of the College of Physicians and Surgeons--Pakistan. 2012; 22(12):751-755	Duplicate data: From included study Shaikh 2011[54]
Shetty K, Garber A. B type natriuretic peptide testing was more cost effective than conventional diagnosis in patients with acute dyspnoea: Commentary. Evidence-Based Medicine. 2007; 12(1):28	Economic comment article on included (BASEL) study
Shuai XX, Chen YY, Lu YX, Su GH, Wang YH, Zhao HL et al. Diagnosis of heart failure with preserved ejection fraction: which parameters and diagnostic strategies are more valuable? European Journal of Heart Failure. 2011; 13(7):737-745	Indirect population: Derivation cohort consists of outpatients and inpatients with normal and hypertensive controls. Neither derivation nor validation cohort all suspected heart failure patients
Singer AJ, Thode HCJ, Green GB, Birkhahn R, Shapiro NI, Cairns C et al. The incremental benefit of a shortness-of-breath biomarker panel in emergency department patients with dyspnea. Academic Emergency Medicine. 2009; 16(6):488-494	Indirect index test: SOB biomarker panel not broken down for individual biomarkers
Sonoda H, Ohte N, Goto T, Wakami K, Fukuta H, Kikuchi S et al. Plasma N-terminal pro-brain natriuretic peptide levels identifying left ventricular diastolic dysfunction in patients with preserved ejection fraction. Circulation Journal. 2012; 76(11):2599-2605	Indirect population: Patients undergoing cardiac catheterization for coronary artery disease
Spevack DM, Bowers J, Banerjee A, Talreja A, Altman EJ, Friedman MA et al. Diagnostic accuracy of Doppler echocardiography for determining left ventricular diastolic pressure elevation: prospective comparison to chest radiography, serum B-type natriuretic peptide, and chest auscultation. Echocardiography. 2008; 25(9):946-954	Indirect population: Non-hospitalised patients referred for clinically indicated coronary angiography
Springfield CL, Sebat F, Johnson D, Lengle S, Sebat C. Utility of impedance cardiography to determine cardiac vs. noncardiac cause of dyspnea in the emergency department. Congestive Heart Failure. 2004; 10(2 Suppl 2):14-16	Indirect index test: Impedance cardiography versus clinical assessment
Steg PG, Joubin L, McCord J, Abraham WT, Hollander JE, Omland T et al. B-type natriuretic peptide and echocardiographic determination of ejection fraction in the diagnosis of congestive heart failure in patients with acute dyspnea. Chest. 2005; 128(1):21-29	Duplicate data: From included study (Breathing Not Properly) data
Studler U, Kretzschmar M, Christ M, Breidthardt T, Noveanu M, Schoetzau A et al. Accuracy of chest radiographs in the emergency diagnosis of heart failure. European Radiology. 2008; 18(8):1644-1652	Post-hoc analysis of included (BASEL) study assessing diagnostic utility of chest radiographs
Sultana P, Hoque M, Shafiullah S. Plasma BNP (B-type natriuretic peptide) and heart failure: A case-control study. Journal of Medicine. 2010; 11(1):46-50	Case-control study: Population consists of known CHF patients and healthy controls not suspected heart failure.
Sung EK, Dae GP, Hyun HC, Duck HY, Jun HL, Kyoo RH et al. The best predictor for right ventricular dysfunction in acute pulmonary embolism: Comparison between electrocardiography and biomarkers. Korean Circulation Journal. 2009; 39(9):378-381	Screening for RVD in patients with PE
Trinquart L, Ray P, Riou B, Teixeira A. Natriuretic peptide testing in EDs for managing acute dyspnea: a meta-analysis. American Journal of Emergency Medicine. 2011; 29(7):757-767	Systematic review of BNP or NTproBNP test versus no test on patient outcomes. No diagnostic accuracy data.
Tung RH, Camargo CAJ, Krauser D, Anwaruddin S, Baggish A, Chen A et al. Amino-terminal pro-brain natriuretic peptide for the diagnosis of acute heart failure in patients with previous obstructive airway disease. Annals of Emergency Medicine. 2006; 48(1):66-74	Post-hoc analysis of included (PRIDE) study in patients with known obstructive airways disease
van der Burg-de Graauw, Cobbaert CM, Middelhoff CJFM, Bantje TA, van Guldener C. The additive value of N-terminal pro-B-type natriuretic peptide testing at the emergency department in patients with acute dyspnoea. European	No extractable diagnostic accuracy data, examines additive value of NTproBNP in certain groups

Journal of Internal Medicine. 2009; 20(3):301-306	
Velibey Y, Golcuk Y, Golcuk B, Oray D, Atilla OD, Colak A et al. Determination of a predictive cutoff value of NT-proBNP testing for long-term survival in ED patients with acute heart failure. American Journal of Emergency Medicine. 2013; 31(12):1634-1637	The objective of the study does not match the protocol. This was a prognostic study and not a diagnostic study.
Waldo SW, Beede J, Isakson S, Villard-Saussine S, Fareh J, Clopton P et al. Pro-B-type natriuretic peptide levels in acute decompensated heart failure. Journal of the American College of Cardiology. 2008; 51(19):1874-1882	Prognostic mortality study for BNP, NTproBNP and proBNP
Wang CS, FitzGerald JM, Schulzer M, Mak E, Ayas NT. Does this dyspneic patient in the emergency department have congestive heart failure? JAMA. 2005; 294(15):1944-1956	Systematic review of BNP or NTproBNP cross referenced and all appropriate studies included
Worster A, Balion CM, Hill SA, Santaguida P, Ismaila A, McKelvie R et al. Diagnostic accuracy of BNP and NT-proBNP in patients presenting to acute care settings with dyspnea: a systematic review. Clinical Biochemistry. 2008; 41(4-5):250-259	Systematic review of BNP and NTproBNP in acute care settings cross checked for references
Zaphiriou A, Robb S, Murray-Thomas T, Mendez G, Fox K, McDonagh T et al. The diagnostic accuracy of plasma BNP and NTproBNP in patients referred from primary care with suspected heart failure: results of the UK natriuretic peptide study. European Journal of Heart Failure. 2005; 7(4):537-541	Indirect population: Patients referred to heart failure clinics by GPs
Zhao SQ, Hu YM, Li Q, Liu XR, Wang M, Zhang WY et al. The clinical value of rapid assay for plasma B-type natriuretic peptide in differentiating congestive heart failure from pulmonary causes of dyspnoea. International Journal of Clinical Practice. 2008; 62(2):214-220	Indirect reference standard: PCWP >12mmHg not clinical evaluation

K.2 Echocardiography

Table 74: Studies excluded from the echocardiography clinical review

Reference	Reason for exclusion
Axente L, Sinescu C, Bazacliu G. Heart failure prognostic model. Journal of Medicine and Life. 2011; 4(2):210-225	No addressing earlier vs. later echocardiography
Chiarugi F, Colantonio S, Emmanouilidou D, Martinelli M, Moroni D, Salvetti O. Decision support in heart failure through processing of electro- and echocardiograms. Artificial Intelligence in Medicine. 2010; 50(2):95-104	No addressing earlier vs. later echocardiography
Clendenin DJ, Athiraman U, Zurakowski D, Shapiro F, Sethna NF. Accuracy of preoperative electrocardiographic and chest radiographic screening for prediction of left ventricular dysfunction in patients with suspected neuromuscular disorders. Anesthesia and Analgesia. 2010; 110(4):1116-1120	No addressing earlier vs. later echocardiography
Cocchi A, Zuccala G, Del Sindaco D, Alimenti M, Menichelli P, Carbonin PU. Cross-sectional echocardiography: a window on congestive heart failure in the elderly. Aging. 1991; 3(3):257-262	No addressing earlier vs. later echocardiography
Collins SP, Lindsell CJ, Kontos MC, Zuber M, Kipfer P, Attenhofer Jost C et al. Bedside prediction of increased filling pressure using acoustic electrocardiography. American Journal of Emergency Medicine. 2009; 27(4):397-408	No addressing earlier vs. later echocardiography
Gerdts E, Okin P, Wachtell K, Boman K, Nieminen MS, Dahlof B et al. Combined use of electrocardiogram and echocardiogram to better identify hypertensive patients at high risk for heart failure. Journal of Hypertension. 2010; 28:e214	No addressing earlier vs. later echocardiography

Reference	Reason for exclusion
Hegazy AM, Abdulkader BA. Early improvement of infarct-associated mitral valve regurgitation and likelihood of successful thrombolysis: Color Doppler echocardiographic study. Kuwait Medical Journal. 2007; 39(4):319-326	Ordered for a different question
Hood S, Taylor S, Roeves A, Crook AM, Tlusty P, Cohen J et al. Are there age and sex differences in the investigation and treatment of heart failure? A population-based study. British Journal of General Practice. 2000; 50(456):559-563	Ordered for general background reading
Jeyaseelan S, Struthers AD, Goudie BM, Pringle SD, Sullivan FM, Donnan PT. The accuracy of ECG screening by GPs and by machine interpretation in selecting suspected heart failure patients for echocardiography. British Journal of Cardiology. 2006; 13(3):216-218	Primary care setting and no information about timing
Khunti K, Squire I, Abrams KR, Sutton AJ. Accuracy of a 12-lead electrocardiogram in screening patients with suspected heart failure for open access echocardiography: a systematic review and meta-analysis. European Journal of Heart Failure. 2004; 6(5):571-576	No addressing earlier vs. later echocardiography
Leslie SJ, Snowball VM, Ness A, Reid J, Denvir MA. Patient-focused outcomes following open-access echocardiography for suspected chronic heart failure. British Journal of Cardiology. 2008; 15(3):156-157	No addressing earlier vs. later echocardiography
Lindsay MM, Goodfield NE, Hogg KJ, Dunn FG. Optimising direct access ECHO referral in suspected heart failure. Scottish Medical Journal. 2000; 45(2):43-44	No addressing earlier vs. later echocardiography
Macfarlane PW. Is electrocardiography still useful in the diagnosis of cardiac chamber hypertrophy and dilatation? Cardiology Clinics. 2006; 24(3):401-4ix	No addressing earlier vs. later echocardiography
Nucifora G, Marsan NA, Siebelink HM, van Werkhoven JM, Schuijf JD, Schalij MJ et al. Safety of contrast-enhanced echocardiography within 24 h after acute myocardial infarction. European Journal of Echocardiography. 2008; 9(6):816-818	No addressing earlier vs. later echocardiography
Panoula VF, Daigele AL, Lot AS, Malaweer ASN, Baskara D, Rahma S et al. Pocket-size hand-held cardiac ultrasound in the hands of students and junior doctors: Does it improve diagnostic accuracy over history, physical examination and ECG? Heart. 2012; 98:A55-A56	No addressing earlier vs. later echocardiography
Prondzinsky R, Lemm H, Swyter M, Wegener N, Unverzagt S, Carter JM et al. Intra-aortic balloon counterpulsation in patients with acute myocardial infarction complicated by cardiogenic shock: the prospective, randomized IABP SHOCK Trial for attenuation of multiorgan dysfunction syndrome. Critical Care Medicine. 2010; 38(1):152-160	Ordered for a different question
Razi R, Raider EJ, Doll JA, Spencer KT. Bedside handcarried ultrasound by internal medicine residents vs. traditional clinical assessment for the identification of systolic dysfunction in patients admitted with decompensated heart failure. Journal of the American College of Cardiology. 2011; 57(14 SUPPL. 1):E1181	No addressing earlier vs. later echocardiography
Rinkevich D, Kaul S, Wang XQ, Tong KL, Belcik T, Kalvaitis S et al. Regional left ventricular perfusion and function in patients presenting to the emergency department with chest pain and no ST-segment elevation. European Heart Journal. 2005; 26(16):1606-1611	No addressing earlier vs. later echocardiography
Rovai D, Morales MA, Di Bella G, Prediletto R, De Nes M, Pingitore A et al. Echocardiography and the clinical diagnosis of left ventricular dysfunction. Acta Cardiologica. 2008; 63(4):507-513	No addressing earlier vs. later echocardiography
Senior R, Janardhanan R, Jeetley P, Burden L. Myocardial contrast echocardiography for distinguishing ischemic from nonischemic first-onset acute heart failure: insights into the mechanism of acute heart failure. Circulation. 2005; 112(11):1587-1593	No addressing earlier vs. later echocardiography

Reference	Reason for exclusion
Williams SG, Currie P, Silas JH. Open access echocardiography: a prospective audit of referral patterns from primary care. International Journal of Clinical Practice. 2003; 57(2):136-139	Primary care setting and no information about timing

K.3 Invasive monitoring

Table 75: Studies excluded from the clinical review

Reference	Reason for exclusion
Abraham WT, Adamson PB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW et al. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. Lancet. 2011; 377(9766):658-666	Study population restricted to chronic heart failure.
Allen LA, Rogers JG, Warnica JW, Disalvo TG, Tasissa G, Binanay C et al. High mortality without ESCAPE: the registry of heart failure patients receiving pulmonary artery catheters without randomization. Journal of Cardiac Failure. 2008; 14(8):661-669	This registry was restricted to AHF patients receiving PAC - non-comparative
Barbash IM, Ilia R, Gilutz H, Boyko V, Battler A, Leor J. Cardiogenic shock: single center experience with and without on-site catheterization facilities. Cardiology. 2000; 93(1-2):87-92	Before - after study
Boyd KD, Thomas SJ, Gold J, Boyd AD. A prospective study of complications of pulmonary artery catheterizations in 500 consecutive patients. Chest. 1983; 84(3):245-249	No comparison group.
Drazner MH, Hellkamp AS, Leier CV, Shah MR, Miller LW, Russell SD et al. Value of clinician assessment of hemodynamics in advanced heart failure: the ESCAPE trial. Circulation Heart Failure. 2008; 1(3):170-177	Post hoc prognostic analysis of the ESCAPE trial.
Friesecke S, Heinrich A, Abel P, Felix SB. Comparison of pulmonary artery and aortic transpulmonary thermodilution for monitoring of cardiac output in patients with severe heart failure: validation of a novel method. Critical Care Medicine. 2009; 37(1):119-123	No comparison group.
Kuppahally SS, Michaels AD, Tandar A, Gilbert EM, Litwin SE, Bader FM. Can echocardiographic evaluation of cardiopulmonary hemodynamics decrease right heart catheterizations in end-stage heart failure patients awaiting transplantation? American Journal of Cardiology. 2010; 106(11):1657-1662	Outcomes do not match protocol
Mark S, Calderon-Artero P, Kakinami L, Alexis J, Chen L, Storozynsky E et al. Review of ambulatory pulmonary artery catheterization in the management of advanced heart failure. Congestive Heart Failure. 2012; 18(3):173-178	Review - background reading
Metkus TS, Christopher KB. Pulmonary artery catheter use in the management of critically ill patients at an academic medical center. Journal of Cardiac Failure. 2009; 15(6 SUPPL. 1):S109-S110	Abstract of a descriptive / observational study
Rogers J, Lombardi C, Fiuzat M, Tassisa G, O'Connor C. Mode of death in advanced heart failure: Impact of race, etiology and hemodynamics in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) Trial. European Journal of Heart Failure, Supplement. 2010; 9:S181-S182	Abstract of a post hoc analysis of ESCAPE trial data.
Rogers J, Fiuzat M, Lombardi C, Shaw LK, Felker GM, O'Connor CM. Hemodynamic predictors of heart failure morbidity and mortality: Fluid or flow? European Journal of Heart Failure, Supplement. 2010; 9:S64-S65	Abstract of a post hoc analysis of the ESCAPE trial
Shah MR, Miller L. Use of pulmonary artery catheters in advanced heart failure. Current Opinion in Cardiology. 2007; 22(3):220-224	Review - background reading
Silver MA, Cianci P, Brennan S, Longeran-Thomas H, Ahmad F. Evaluation of impedance cardiography as an alternative to pulmonary artery catheterization in critically ill patients. Congestive Heart Failure. 2004; 10(2 Suppl 2):17-21	Evaluation of all critically ill patients without subgroups relevant to the review protocol.
Temporelli PL, Scapellato F, Eleuteri E, Imparato A, Giannuzzi P. Doppler echocardiography in advanced systolic heart failure: a noninvasive alternative to Swan-Ganz catheter.	Correlation study -

Reference	Reason for exclusion
Circulation Heart Failure. 2010; 3(3):387-394	outcomes not in protocol
Testani JM, Chen J, Wiegers SE, John Sutton MC, Kirkpatrick J. Inferior vena cava inspiratory collapse is poorly correlated with right atrial pressure but significantly predicts outcomes in patients with decompensated heart failure: An application of the evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness trial limited dataset. Journal of the American Society of Echocardiography. 2010; 23(5):B82	Post hoc analysis of ESCAPE data - inferior vena cava inspiratory collapse as a prognostic factor.
Testani JM, Coca SG, Shannon RP, Kimmel SE, Cappola TP. Influence of renal dysfunction phenotype on mortality in the setting of cardiac dysfunction: analysis of three randomized controlled trials. European Journal of Heart Failure. 2011; 13(11):1224-1230	Post hoc analysis of ESCAPE trial - renal function as prognostic factor.
Verdejo HE, Castro PF, Concepcion R, Ferrada MA, Alfaro MA, Alcaino ME et al. Comparison of a radiofrequency-based wireless pressure sensor to swan-ganz catheter and echocardiography for ambulatory assessment of pulmonary artery pressure in heart failure. Journal of the American College of Cardiology. 2007; 50(25):2375-2382	Correlational study of hemodynamic measurements - not in protocol

K.4 Opiates

Table 76: Studies excluded from the clinical review

Reference	Reason for exclusion
Awan NA, Miller RR, DeMaria AN. Effects of morphine and aminophylline on the severity of obstruction to left ventricular outflow in idiopathic hypertrophic subaortic stenosis: Potential adverse effects in treatment of pulmonary edema. Clinical Cardiology. 1978; 1(1):16-21	Before-and-after study. No comparison group.
Beltrame JF, Zeitz CJ, Unger SA, Brennan RJ, Hunt A, Moran JL et al. Nitrate therapy is an alternative to furosemide/morphine therapy in the management of acute cardiogenic pulmonary edema. Journal of Cardiac Failure. 1998; 4(4):271-279	Compares furosemide/morphine vs. nitroglycerine and N-Acetyl Cysteine (NAC). Comparison is not standard initial care comprising nil diuretic and NAC. Discussed with GDG chair.
Berger PE, Archambault P, Poitras J. ARE narcotics harmful in the treatment of acute pulmonary edema? A critically appraised topic. Canadian Journal of Emergency Medicine. 2010; 12 (3):277	Conference abstract for systematic review
Coons JC, McGraw M, Murali S. Pharmacotherapy for acute heart failure syndromes. American Journal of Health-System Pharmacy. 2011; 68(1):21-35	Review article
Grendahl H, Andersen A, Muller C. The effect of intravenous morphine in patients with mitral valvular disease and congestive heart failure. Acta Medica Scandinavica. 1973; 194(1-2):69-74	Before-and-after study. No comparison group.
Hoel BL, Bay G, Refsum HE. The effects of morphine on the arterial and mixed venous blood gas state and on the hemodynamics in patients with clinical pulmonary congestion. Acta Medica Scandinavica. 1971; 190(6):549-554	Before-and-after study. No comparison group.
Klinefelter HF. Morphine for pulmonary edema. JAMA. 1974; 229(6):638	Letter to editor
Lappas DG, Buckley MJ, Laver MB, Daggett WM, Lowenstein E. Left ventricular performance and pulmonary circulation following addition of nitrous oxide to morphine during coronary-artery surgery. Anesthesiology. 1975; 43(1):61-69	Study in intraoperative patients with normal cardiac contractility and not AHF.

Samuelsson S. The danger of using morphine in cor pulmonale. Cardiologia. 1952; 21(6):817-824	Case series
Sosnowski MA. Review article: lack of effect of opiates in the treatment of acute cardiogenic pulmonary oedema. Emergency Medicine Australasia. 2008; 20(5):384-390	Review article
Timmis AD, Rothman MT, Henderson MA, Geal PW, Chamberlain DA. Haemodynamic effects of intravenous morphine in patients with acute myocardial infarction complicated by severe left ventricular failure. BMJ. 1980; 280(6219):980-982	Method of administration is directly into right atrium, not applicable to clinical practice. Only outcome data is haemodynamic and urine output non protocol outcomes.
Vismara LA, Leaman DM, Zelis R. The effects of morphine on venous tone in patients with acute pulmonary edema. Circulation. 1976; 54(2):335-337	Compares healthy subjects with AHF subjects. No comparison within AHF cohort. Uses before-and-after morphine data in AHF cohort.
Zajic F, Bergmann K, Dejdar R, Samanek M. Morphine and the cardiopulmonary system. Cor Et Vasa. 1966; 8(2):104-112	Before-and-after study. No comparison group.

K.5 Diuretic administration

Table 77: Studies excluded from the clinical review

Reference	Reason for exclusion
Abraham W, Ghali J, Braman V, Nirula A, Wisniacki N, Orlandi C. Effects of single dose administration of lixivaptan, a selective V2 receptor antagonist, or furosemide in healthy volunteers. European Journal of Heart Failure. 2010; 9:S198	Population not acute heart failure; "healthy subjects"
Amer M, Adomaityte J, Qayyum R. Continuous infusion versus intermittent bolus furosemide in ADHF: an updated meta-analysis of randomized control trials. Journal of Hospital Medicine. 2012; 7(3):270-275	Low quality meta-analysis; all appropriate trials included
Bagatin J, Sardelic S, Gancevic I, Rumboldt Z, Polic S, Miric D et al. Diuretic efficiency of furosemide in continuous intravenous infusion vs. bolus injection in congestive heart failure: Results of a pilot study. Pharmaca. 1993; 31(3-4):279	Not in English
Biadi O, Sighieri C, Mariani M. Comparison between two diuretic drugs: A double-blind clinical experimentation. Drugs Under Experimental and Clinical Research. 1981; 7(6):763-772	Nil route of administration comparison; oral versus oral
Cardoso JN, Ochiai ME, Morgado PC, Munhoz RT, Oliveira MT, Curuatti M et al. Weight-change guided tailored diuretic therapy to decompensated congestive heart failure: A randomized trial. Journal of the American College of Cardiology. 2011; 1):E223	Conference abstract only
Channer KS, McLean KA, Lawson-Matthew P, Richardson M. Combination diuretic treatment in severe heart failure: a randomised controlled trial. British Heart Journal. 1994; 71(2):146-150	Nil route of administration comparison; oral versus oral
Chaudhury RR, Chugh KS, Gupta GS, Sodhi P, Gupta KK. A controlled clinical trial comparing the diuretic furosemide and hydrochlorothiazide. Journal of the Association of Physicians of India. 1968; 16(2):157-163	Nil route of administration comparison; oral versus oral
Chugh KS, Gupta KK, Chaudhury RR. A controlled clinical trial comparing the diuretic ethacrynic acid and furosemide in patients with congestive heart failure. Indian Journal of Medical Research. 1969; 57(4):784-788	Nil route of administration comparison; oral versus oral
Cienki JJ, Hebert K, Ta AK, Diskin AL. A randomized comparison of continuous IV infusion of furosemide versus repeated IV bolus furosemide in acutely decompensated congestive heart failure. Annals of Emergency Medicine. 2009;	Conference abstract only

1):S29-S30	
Di Sipio P, Beltrami M, Paganini G, Calabro A, Franci B, Nuti R et al. Different loop diuretic administration in patients with acute heart failure: Effects on bnp levels, renal function and hospitalization. Giornale Italiano Di Cardiologia. 2011; 3):e257	Conference abstract only
Engelmeier RS, Le TT, Kamalay SE, Utecht KN, Nikstad TP, Kaliebe JW et al. Randomized trial of high dose furosemide-hypertonic saline in acute decompensated heart failure with advanced renal disease. Journal of the American College of Cardiology. 2012; 1):E958	Conference abstract only
Fasullo S, Basile I, Sarullo F, Vitrano G, Terrazzino G, Maringhini G et al. Sodium management in acute and chronic phases in patients with new york heart association class III (class C) heart failure. Short- and long-term findings. Giornale Italiano Di Cardiologia. 2011; 1):7S	Conference abstract only
Fauchald P, Lind E. Double-blind crossover study on the diuretic effect of Bay g 2821 and furosemide in patients with cardiac oedema. Pharmatherapeutica. 1977; 1(7):409-414	Nil route of administration comparison; oral versus oral
Givertz MM, Teerlink JR, Albert NM, Westlake Canary CA, Collins SP, Colvin-Adams M et al. Acute decompensated heart failure: update on new and emerging evidence and directions for future research. Journal of Cardiac Failure. 2013; 19(6):371-389	Background reading: cross-checked for new trials
Gottlieb SS, Stebbins A, Voors AA, Hasselblad V, Ezekowitz JA, Califf RM et al. Effects of nesiritide and predictors of urine output in acute decompensated heart failure: results from ASCEND-HF (acute study of clinical effectiveness of nesiritide and decompensated heart failure). Journal of the American College of Cardiology. 2013; 62(13):1177-1183	Nesiritide is not currently used as a diuretic in treatment of AHF in the UK
Gupta A, Stehlik J, McNulty S, Lee KL, Gilbert EM, Budge D et al. Does obesity affect response to treatment in acute decompensated heart failure? A diuretic optimization strategies evaluation (DOSE) trial substudy. Journal of the American College of Cardiology. 2011; 1):E199	Conference abstract analysis of Felker 2011 included study
Hariman RJ, Bremner S, Louie EK, Rogers WJ, Kostis JB, Nocero MA et al. Dose-response study of intravenous torsemide in congestive heart failure. American Heart Journal. 1994; 128(2):352-357	Nil route of administration comparison; IV versus IV
Holzer-Richling N, Holzer M, Herkner H, Riedmuller E, Havel C, Kaff A et al. Randomized placebo controlled trial of furosemide on subjective perception of dyspnoea in patients with pulmonary oedema because of hypertensive crisis. European Journal of Clinical Investigation. 2011; 41(6):627-634	Nil route of administration comparison; furosemide versus placebo
Homeida M, Roberts CJ, Dombey SL. A single dose comparison of piretanide and bumetanide in congestive cardiac failure. British Journal of Clinical Pharmacology. 1979; 8(2):173-178	Nil route of administration comparison; oral versus oral
Inomata T, Izumi T, Matsuzaki M, Hori M, Hirayama A, Tolvaptan I. Phase III clinical pharmacology study of tolvaptan. Cardiovascular Drugs and Therapy. 2011; 25 Suppl 1:S57-S65	Nil route of administration comparison; dose finding study of tolvaptan
Kociol RD, McNulty SE, Hernandez AF, Lee KL, Redfield MM, Tracy RP et al. Markers of congestion, symptom relief and clinical outcomes among patients hospitalized with acute heart failure: Data from the diuretic optimal strategy evaluation in acute heart failure study. Journal of the American College of Cardiology. 2011; 1):E220	Conference abstract analysis of Felker 2011 included study
Kramer WG, Smith WB, Ferguson J, Serpas T, Grant AG, III, Black PK et al. Pharmacodynamics of torsemide administered as an intravenous injection and as a continuous infusion to patients with congestive heart failure. Journal of Clinical Pharmacology. 1996; 36(3):265-270	Population not acute heart failure; “stable compensated heart failure”
Marsh JD, Nesto R, Glynn MA, Smith TW. Comparison of intravenous piretanide and furosemide in patients with congestive heart failure. Journal of Cardiovascular Pharmacology. 1982; 4(6):949-954	Nil route of administration comparison; IV versus IV

Marti C, Cole R, Kalogeropoulos A, Georgiopoulou V, Butler J. Medical therapy for acute decompensated heart failure: what recent clinical trials have taught us about diuretics and vasodilators. Current Heart Failure Reports. 2012; 9(1):1-7	Discussion of literature; all trials included
Matsuzaki M, Hori M, Izumi T, Fukunami M, Tolvaptan I. Efficacy and safety of tolvaptan in heart failure patients with volume overload despite the standard treatment with conventional diuretics: a phase III, randomized, double-blind, placebo-controlled study (QUEST study). Cardiovascular Drugs and Therapy. 2011; 25 Suppl 1:S33-S45	Nil route of administration comparison; tolvaptan versus placebo
McFarland MD. A clinical trial of furosemide in patients with congestive heart failure. Missouri Medicine. 1968; 65(8):655-659	Nil route of administration comparison; oral versus oral
Mojtahedzadeh M, Salehifar E, Vazin A, Mahidiani H, Najafi A, Tavakoli M et al. Comparison of hemodynamic and biochemical effects of furosemide by continuous infusion and intermittent bolus in critically ill patients. Journal of Infusion Nursing. 2004; 27(4):255-261	Population not restricted to acute heart failure; "critically ill patients in ICU with patients included if the attending physicians decided furosemide was clinically indicated"; agreed with GDG chair
Mojtahedzadeh M. The relationship between pharmacokinetics variables and pharmacodynamics profiles of bolus versus continuous infusion of furosemide in critically ill patients. Journal of Infusion Nursing. 2005; 13:127-132	Population not restricted to acute heart failure; "critically ill patients who required diuretic therapy"; agreed with GDG chair
Ostermann M, Alvarez G, Sharpe MD, Martin CM. Frusemide administration in critically ill patients by continuous compared to bolus therapy. Nephron Clinical Practice. 2007; 107(2):c70-c76	Population not restricted to acute heart failure; "critically ill patients who required IV diuresis"; agreed with GDG chair
Paterna S, Di Pasquale P, Parrinello G, Amato P, Cardinale A, Follone G et al. Effects of high-dose furosemide and small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as a bolus, in refractory congestive heart failure. European Journal of Heart Failure. 2000; 2(3):305-313	Same recruitment period and study group as Licata 2003. Licata recruited for longer with increased numbers of patients; same rationale applied as Cochrane review Salvador 2005[152]
Paterna S, Fasullo S, Di Pasquale P. High-Dose Torasemide is Equivalent to High-Dose Furosemide with Hypertonic Saline in the Treatment of Refractory Congestive Heart Failure. Clinical Drug Investigation. 2005; 25(3):165-173	Nil route of administration comparison; HSS infusion versus HSS infusion
Paterna S, Fasullo S, Parrinello G et al. Short-Term Effects of Hypertonic Saline Solution in Acute Heart Failure and Long-Term Effects of a Moderate Sodium Restriction in Patients With Compensated Heart Failure With New York Heart Association Class III (Class C) (SMAC-HF Study). American Journal of Medical Sciences. 2011; 342 (1):27-37	Recruited from 2000-2008. No differentiation of control arm between furosemide bolus and infusion. Reported as IV furosemide. Included Pirandello 2011 and Paterna 2005 as split reporting to bolus and infusion.
Ravnan SL, Ravnan MC. Management of adult heart failure: Bolus versus continuous infusion loop diuretics, a review of the literature. Hospital Pharmacy. 2000; 35(8):832-836	Review article
Sagar S, Sharma BK, Sharma PL, Wahi PL. A comparative randomized double-blind clinical trial of bumetanide and furosemide in congestive cardiac failure and other edema states. International Journal of Clinical Pharmacology, Therapy and Toxicology. 1984; 22(9):473-478	Nil route of administration comparison; oral versus oral
Salvador DRK, Rey NR, Ramos GC, Punzalan FER. Continuous infusion versus bolus injection of loop diuretics in congestive heart failure. Cochrane Database of Systematic Reviews. 2005;(3):CD003178	Cochrane review of continuous versus bolus infusion strategies in congestive heart failure; all appropriate trials in acute heart failure included
Schuller D, Lynch JP, Fine D. Protocol-guided diuretic management: comparison of furosemide by continuous infusion and intermittent bolus. Critical Care Medicine. 1997; 25(12):1969-1975	Population not restricted to acute heart failure; "cardiogenic and non-cardiogenic pulmonary

	oedema and patients with acute or chronic renal failure with fluid overload "; agreed with GDG chair
Shah RV, McNulty S, Lee K, Michael Felker G, O'Connor CM, Givertz MM. Effect of admission oral diuretic dose on response to continuous versus bolus intravenous diuretics in acute heart failure: An analysis from DOSE-AHF. Journal of the American College of Cardiology. 2011; 1):E216	Conference abstract analysis of Felker 2011 included study
Stauch M, Stiehl L. Controlled, double-blind clinical trial on the efficacy and tolerance of torasemide in comparison with furosemide in patients with congestive heart failure - a multicenter study. Progress in Pharmacology and Clinical Pharmacology. 1990; 8(1):121-126	Nil route of administration comparison; oral versus oral
Stewart JH, Edwards KD. Clinical comparison of frusemide with bendrofluazide, mersalyl, and ethacrynic acid. BMJ. 1965; 2(5473):1277-1281	Non-randomised
Stringer KA, Watson W, Gratton M, Wolfe R. Intravenous torsemide as adjunctive therapy in patients with acute pulmonary edema. Journal of Clinical Pharmacology. 1994; 34(11):1083-1087	Nil route of administration comparison; IV versus IV
Stroobandt R, Dodion L, Kesteloot H. Clinical efficacy of torasemide, a new diuretic agent, in patients with acute heart failure: a double blind comparison with furosemide. Archives Internationales De Pharmacodynamie Et De Therapie. 1982; 260(1):151-158	Nil route of administration comparison; IV versus IV
Tepper D. Frontiers in congestive heart failure. Prevention and Management of Congestive Heart Failure. 1996; 2(5):50-51	Comment on Dormans 1996 (included study)
Udelson JE, Bilsker M, Hauptman PJ, Sequeira R, Thomas I, O'Brien T et al. A multicenter, randomized, double-blind, placebo-controlled study of tolvaptan monotherapy compared to furosemide and the combination of tolvaptan and furosemide in patients with heart failure and systolic dysfunction. Journal of Cardiac Failure. 2011; 17(12):973-981	Nil route of administration comparison; oral versus oral
Vaduganathan M, Gheorghiade M, Pang PS, Konstam MA, Zannad F, Swedberg K et al. Efficacy of oral tolvaptan in acute heart failure patients with hypotension and renal impairment. Journal of Cardiovascular Medicine. 2012; 13(7):415-422	Nil route of administration comparison; Tolvaptan versus placebo
van Meyel JJ, Dormans T, Smits P, Gerlag PGG, Russel FGM, Gribnau FWJ. Diuretic efficacy of different modes of administratin of furosemide in patients with compensated and decompensated heart failure. Clinical Pharmacology and Therapeutics. 1993; 55(2):162	Conference abstract only
Vargo DL, Brater DC, Rudy DW, Swan SK. Dopamine does not enhance furosemide-induced natriuresis in patients with congestive heart failure. Journal of the American Society of Nephrology. 1996; 7(7):1032-1037	Nil route of administration comparison; Infusion versus infusion and dopamine
Verel D, Stentiford NH, Rahman F, Saynor R. A Clinical Trial of Frusemide. Lancet. 1964; 2(7369):1088-1089	Nil route of administration comparison; oral versus oral
Verma SP, Silke B, Hussain M, Nelson GI, Reynolds GW, Richmond A et al. First-line treatment of left ventricular failure complicating acute myocardial infarction: a randomised evaluation of immediate effects of diuretic, venodilator, arteriodilator, and positive inotropic drugs on left ventricular function. Journal of Cardiovascular Pharmacology. 1987; 10(1):38-46	Nil route of administration comparison; Furosemide versus hydralazine versus isosorbide dinitrate versus prenalterol
Ziakas G, Zioutas G, Arvanitidis T, Zurukzoglu W. Muzolimine in patients with cardiac edema: A comparison with furosemide in a repeated-dose, single-blind study. Clinical Nephrology. 1983; 19(Suppl. 1):S85-S91	Nil route of administration comparison; oral versus oral

K.6 Vasodilators

Table 78: Studies excluded from the clinical review

Reference	Reason for exclusion
Abraham WT, Cheng ML, Smoluk G, Vasodilation in the Management of Acute Congestive Heart Failure (VMAC) Study Group. Clinical and hemodynamic effects of nesiritide (B-type natriuretic peptide) in patients with decompensated heart failure receiving beta blockers. Congestive Heart Failure. 2005; 11(2):59-64	Included trial VMAC 2002 RCT subgroup analysis
Beltrame JF, Zeitz CJ, Unger SA, Brennan RJ, Hunt A, Moran JL et al. Nitrate therapy is an alternative to furosemide/morphine therapy in the management of acute cardiogenic pulmonary edema Journal of Cardiac Failure. 1998; 4(4):271-279	Nil placebo control
Bolognese L, Sarasso G, Rognoni G, Makmur J, Fornaro G, Perucca A et al. Sustained beneficial hemodynamic effects of low transdermal nitroglycerin doses compared with placebo in patients with congestive heart failure. Clinical Cardiology. 1988; 11(2):79-85	Non-AHF population: chronic stable heart failure
Borzak S. Intravenous nitroglycerin for acute myocardial infarction. Henry Ford Hospital Medical Journal. 1991; 39(3-4):206-209	SR of nitrates in myocardial infarction; all appropriate trials included
Cotter G, Metzkor E, Kaluski E, Faigenberg Z, Miller R, Simovitz A et al. Randomised trial of high-dose isosorbide dinitrate plus low-dose furosemide versus high-dose furosemide plus low-dose isosorbide dinitrate in severe pulmonary oedema. Lancet. 1998; 351(9100):389-393	Nil placebo control
De Luca L, Fonarow GC, Mebazaa A, Shin DD, Collins SP, Swedberg K et al. Early pharmacological treatment of acute heart failure syndromes: A systematic review of clinical trials. Acute Cardiac Care. 2007; 9(1):10-21	Review of clinical trials; all appropriate trials included
Durrer JD, Lie KI, van Capelle FJ, Durrer D. Effect of sodium nitroprusside on mortality in acute myocardial infarction. New England Journal of Medicine. 1982; 306(19):1121-1128	Non-AHF population: acute myocardial infarction preventing AHF and not concomitant AHF
Elkayam U, Akhter MW, Singh H, Khan S, Usman A. Comparison of effects on left ventricular filling pressure of intravenous nesiritide and high-dose nitroglycerin in patients with decompensated heart failure. American Journal of Cardiology. 2004; 93(2):237-240	Analysis of VMAC 2002; Included trial
Elkayam U, Bitar F, Akhter MW, Khan S, Patrus S, Derakhshani M. Intravenous nitroglycerin in the treatment of decompensated heart failure: potential benefits and limitations. Journal of Cardiovascular Pharmacology and Therapeutics. 2004; 9(4):227-241	Nitroglycerin in AHF review; All appropriate trials included
Flaherty JT, Becker LC, Bulkley BH, Weiss JL, Gerstenblith G, Kallman CH et al. A randomized clinical trial of intravenous nitroglycerin in patients with acute myocardial infarction: benefits of early treatment. Zeitschrift Fur Kardiologie. 1983; 72 Suppl 3:131-136	Non-AHF population: acute myocardial infarction
Franciosa JA, Goldsmith SR, Cohn JN. Contrasting immediate and long-term effects of isosorbide dinitrate on exercise capacity in congestive heart failure. American Journal of Medicine. 1980; 69(4):559-566	Non-AHF population: chronic heart failure
Franciosa JA, Nordstrom LA, Cohn JN. Nitrate therapy for congestive heart failure. JAMA. 1978; 240(5):443-446	Non-AHF population: chronic heart failure, patients treated for 8 weeks
Garadah T, Ghaisas NK, Mehana N, Foley B, Crean P, Walsh M. Impact of intravenous nitroglycerin on pulsed Doppler indexes of left ventricular filling in acute anterior myocardial infarction. American Heart Journal. 1998;	Non-AHF population: Anterior myocardial infarction

136(5):812-817	
Garadah T, Ghaisas NK, Mehana N, Foley B, Crean P, Walsh M. Impact of intravenous nitroglycerin on pulsed Doppler indexes of left ventricular filling in acute anterior myocardial infarction. American Heart Journal. 1998; 136(5):812-817	Non-AHF population: Anterior myocardial infarction excluding pulmonary oedema and cardiogenic shock
Heikkila J, Pellinen TJ, Blake P, McAllister A, Yardley J. Increase of cardiac output by afterload reduction in patients with severe congestive heart failure using nitroglycerin discs. A double-blind placebo-controlled haemodynamic study. Annals of Clinical Research. 1987; 19(3):203-207	Non-AHF population: chronic heart failure
Held P. Effects of nitrates on mortality in acute myocardial infarction and in heart failure. British Journal of Clinical Pharmacology. 1992; 34 Suppl 1:25S-28S	Old/low quality meta-analysis; all appropriate trials included
Hiremath JS, Patki SA, Gokhale SV, Gulati RB. Use of sodium nitroprusside in resistant congestive cardiac failure. Indian Heart Journal. 1987; 39(1):15-17	Nitroprusside trial; nil placebo control
Jordan RA, Seith L, Henry DA, Wilen MM, Franciosa JA. Dose requirements and hemodynamic effects of transdermal nitroglycerin compared with placebo in patients with congestive heart failure. Circulation. 1985; 71(5):980-986	Non-AHF population: chronic heart failure
Jordan RA, Seth L, Casebolt P, Hayes MJ, Wilen MM, Franciosa J. Rapidly developing tolerance to transdermal nitroglycerin in congestive heart failure. Annals of Internal Medicine. 1986; 104(3):295-298	Non-AHF population: chronic heart failure
Lahiri A, Crawley JC, Sonecha TN, Raftery EB. Acute and chronic effects of sustained action buccal nitroglycerin in severe congestive heart failure. International Journal of Cardiology. 1984; 5(1):39-48	Non-AHF population: chronic heart failure
Leier CV, Huss P, Magorien RD, Unverferth DV. Improved exercise capacity and differing arterial and venous tolerance during chronic isosorbide dinitrate therapy for congestive heart failure. Circulation. 1983; 67(4):817-822	Non-AHF population: chronic heart failure
Lindvall K, Eriksson SV, Lagerstrand L, Sjogren A. Efficacy and tolerability of transdermal nitroglycerin in heart failure. A noninvasive placebo controlled double-blind cross over study. European Heart Journal. 1988; 9(4):373-379	Non-AHF population: chronic heart failure
Massoudy P, Zahler S, Freyholdt T, Henze R, Barankay A, Becker BF et al. Sodium nitroprusside in patients with compromised left ventricular function undergoing coronary bypass: reduction of cardiac proinflammatory substances. Journal of Thoracic and Cardiovascular Surgery. 2000; 119(3):566-574	Non-AHF population: patients with compromised left ventricular function undergoing coronary artery bypass graft
Miller AH, Nazeer S, Pepe P, Estes B, Gorman A, Yancy CW. Acutely decompensated heart failure in a county emergency department: a double-blind randomized controlled comparison of nesiritide versus placebo treatment. Annals of Emergency Medicine. 2008; 51(5):571-578	Nesiritide versus placebo RCT
Sackner-Bernstein JD, Skopicki HA, Aaronson KD. Risk of worsening renal function with nesiritide in patients with acutely decompensated heart failure. Circulation. 2005; 111(12):1487-1491	Non-intervention specific meta-analysis; all appropriate trials included
Sanghera SS, Goldberg AA, Parsons DG. Buccal nitroglycerin in congestive cardiac failure: a multicentre study. Journal of International Medical Research. 1986; 14(5):274-278	Non-AHF population: chronic heart failure. Nil placebo control

Schneider AJ, Teule GJ, Groeneveld AB, Nauta J, Luth WJ, Thijs LG. The immediate effect of nitroglycerin on total body blood volume distribution in patients with congestive heart failure: a non-invasive study. European Heart Journal. 1987; 8(10):1119-1125	Nil protocol outcomes; blood volume redistribution study
Vogt A, Arnold T, Neuhaus K-L, Stepien J. Acute haemodynamic effects of a new formulation of isosorbide dinitrate spray in patients with heart failure. Drug Investigation. 1993; 6(3):149-155	Non-AHF population: Chronic heart failure
Wakai A, McMahon G. Nitrates for acute heart failure. Cochrane Database of Systematic Reviews. 2005; Issue 1:CD005151. DOI:10.1002/14651858.CD005151	Cochrane Review Protocol
Win S, Anand I, Rector T, Furst H, Cohn J, Taylor AL. Combination of isosorbide dinitrate and hydralazine reduces 30 day hospital readmissions and increases time to hospital readmission in blacks with heart failure. Journal of the American College of Cardiology. 2012; 59(13 SUPPL. 1):E1042	Conference abstract. Non-AHF population: chronic heart failure
Ya-Li H, Feng-Xia L, Zhi-Zhang Y, Zhi-Shen Z, Guo-Qiang L, Hui-Ru S et al. The effects of Shengmai injection and sodium nitroprusside in 36 patients with heart failure of ischemic heart disease. Integrated Traditional Chinese and Western Medicine in Practice of Critical Care Medicine. 1998; 5(3):139-140	Not in English Language
Young JB. Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: A randomized controlled trial. JAMA. 2002; 287(12):1531-1540	Included trial: VMAC 2002

K.7 Inotropes and vasopressors

Table 79: Studies excluded from the clinical review

Reference	Reason for exclusion
Aroutunov AG. Pilot randomized study of estimation of heart rate control on decompensated heart failure patiens needed inotropic support. Short term results. European Journal of Heart Failure, Supplement. 2009; 8:ii419	Abstract – none of the critical outcomes reported in the abstract. Unclear which inotrope was used.
Aziz EF, Alviar CL, Herzog E, Cordova JP, Bastawrose JH, Pamidimukala CK et al. Continuous infusion of furosemide combined with low-dose dopamine compared to intermittent boluses in acutely decompensated heart failure is less nephrotoxic and carries a lower readmission at thirty days. Hellenic Journal of Cardiology. 2011; 52(3):227-235	Retrospective case review
Bader FM, Gilbert EM, Mehta NA, Bristow MR. Double-blind placebo-controlled comparison of enoximone and dobutamine infusions in patients with moderate to severe chronic heart failure. Congestive Heart Failure. 2010; 16(6):265-270	Chronic heart failure population (mean duration of condition >30 months)
Bayram M, De Luca L, Massie MB, Gheorghiade M. Reassessment of dobutamine, dopamine, and milrinone in the management of acute heart failure syndromes. American Journal of Cardiology. 2005; 96(6A):47G-58G	Review - cross-checked for references
Choraria SK, Taylor D, Pilcher J. Haemodynamic effects of oral enoximone in severe congestive heart failure [abstract]. British Journal of Clinical Pharmacology. 1986; 22:209P-210P	Abstract - severe rather than decompensated heart failure
Cleland JGF, Takala A, Apajasalo M, Zethraeus N, Kobelt G. Intravenous levosimendan treatment is cost-effective compared with dobutamine in severe low-output heart failure: an analysis based on the international LIDO trial. European Journal of Heart Failure. 2003; 5(1):101-108	Abstract - levosimendan vs. dobutamine without placebo control group
Cotter G, Weissgarten J, Metzkor E, Moshkovitz Y, Litinski I, Tavori U et al. Increased toxicity of high-dose furosemide versus low-dose dopamine in the treatment of refractory congestive heart failure. Clinical Pharmacology &	Refractory rather than decompensated heart failure

Therapeutics. 1997; 62(2):187-193	
Cowley AJ, Skene AM. Treatment of severe heart failure: quantity or quality of life? A trial of enoximone. Enoximone Investigators. British Heart Journal. 1994; 72(3):226-230	Population consists of patients with severe rather than decompensated heart failure
Cuffe MS, Califf RM, Adams KF, Bourge RC, Colucci W, Massie B et al. Rationale and design of the OPTIME CHF trial: outcomes of a prospective trial of intravenous milrinone for exacerbations of chronic heart failure. American Heart Journal. 2000; 139(1 Pt 1):15-22	Rationale and design of the OPTIME-HF trial
Di BR, Shabetai R, Kostuk W, Moran J, Schlant R, Wright R. Oral milrinone and digoxin in heart failure: results of a placebo-controlled, prospective trial of each agent and the combination. Circulation. 1987; 76(suppl IV):IV-256	Abstract - unobtainable
Economou D, Karayannis G, Giamouzis G, Nastas I, Tsaknakis T, Skoularigis J et al. The combination of low dose furosemide and low dose dopamine is effective and prevents worsening of renal function and hypokalemia during hospitalization for acute decompensated heart failure. European Journal of Heart Failure, Supplement. 2009; 8:ii397	Abstract of reference Giamouzis et al, 2010
Elis A, Bental T, Kimchi O, Ravid M, Lishner M. Intermittent dobutamine treatment in patients with chronic refractory congestive heart failure: a randomized, double-blind, placebo-controlled study. Clinical Pharmacology and Therapeutics. 1998; 63(6):682-685	Chronic refractory rather than acute decompensated heart failure
Elkayam U, Ng TMH, Hatamizadeh P, Janmohamed M, Mehra A. Renal vasodilatory action of dopamine in patients with heart failure: Magnitude of effect and site of action. Circulation. 2008; 117(2):200-205	Not randomised and population is chronic heart failure
Erlemeier HH, Kupper W, Bleifeld W. Intermittent infusion of dobutamine in the therapy of severe congestive heart failure--long-term effects and lack of tolerance. Cardiovascular Drugs and Therapy. 1992; 6(4):391-398	Severe rather than acute decompensated heart failure
Felker GM, Benza RL, Chandler AB, Leimberger JD, Cuffe MS, Califf RM et al. Heart failure etiology and response to milrinone in decompensated heart failure: results from the OPTIME-CHF study. Journal of the American College of Cardiology. 2003; 41(6):997-1003	Post hoc analysis of the OPTIME-HF trial according to aetiology of decompensated heart failure
Gheorghiade M, Gattis WA, Klein L. OPTIME in CHF trial: rethinking the use of inotropes in the management of worsening chronic heart failure resulting in hospitalization. European Journal of Heart Failure. 2003; 5(1):9-12	Commentary on the OPTIME-CHF trial
Giamouzis G, Economou D, Karayannis G, Rovithis D, Nastas I, Kyrlidis T et al. The combination of low dose furosemide and low dose dopamine is effective and prevents worsening of renal function and hypokalemia during hospitalization for acute decompensated heart failure. European Heart Journal. 2009; 30:431	Abstract of reference Giamouzis et al, 2010
Goldberg Li, McDonald RHJ, Zimmerman AM. Sodium diuresis produced by dopamine in patients with congestive heart failure. New England Journal of Medicine. 1963; 269:1060-1064.	Not randomised
Klein L, O'Connor CM, Leimberger JD, Gattis-Stoμgh W, Pina IL, Felker GM et al. Lower serum sodium is associated with increased short-term mortality in hospitalized patients with worsening heart failure: results from the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study. Circulation. 2005; 111(19):2454-2460	Retrospective analysis from the OPTIME-HF trial
Konstam MA, Cody RJ. Short-term use of intravenous milrinone for heart failure. American Journal of Cardiology. 1995; 75(12):822-826	Review of milrinone
Landmesser U, Drexler H. Update on inotropic therapy in the management of acute heart failure. Current Treatment Options in Cardiovascular Medicine. 2007; 9(6):443-449	Clinical update summary
Leier CV, Binkley PF, Carpenter J, Randolph PH, Unverferth DV. Cardiovascular pharmacology of dopexamine in low output congestive heart failure. American Journal of Cardiology. 1988; 62(1):94-99	Type of inotrope (dopexamine) not used in current practice

Leier CV, Huss P, Lewis RP, Unverferth DV. Drug-induced conditioning in congestive heart failure. Circulation. 1982; 65(7):1382-1387	Population chronic heart failure - mean duration of symptoms > 30 months
Leier CV, Lima JJ, Meiler SE, Unverferth DV. Central and regional hemodynamic effects of oral enoximone in congestive heart failure: a double-blind, placebo-controlled study. American Heart Journal. 1988; 115(5):1051-1059	Chronic heart failure
Levy B, Perez P, Perny J, Thivilier C, Gerard A. Comparison of norepinephrine-dobutamine to epinephrine for hemodynamics, lactate metabolism, and organ function variables in cardiogenic shock. A prospective, randomized pilot study. Critical Care Medicine. 2011; 39(3):450-455	Comparison not in protocol
Liang C, Sherman LG, Doherty JU. Sustained improvement of cardiac function in patients with congestive heart failure after short-term infusion of dobutamine. Circulation. 1984; 69(1):113-119	Patients with stable chronic congestive heart failure
López-Candales A, Vora T, Gibbons W, Carron C, Simmons P, Schwartz J. Symptomatic improvement in patients treated with intermittent infusion of inotropes: a double-blind placebo controled pilot study. Journal of Medicine. 2002; 33(1-4):129-146	Stable patients with heart failure
Metra M, Eichhorn E, Abraham WT, Linseman J, Bohm M, Corbalan R et al. Effects of low-dose oral enoximone administration on mortality, morbidity, and exercise capacity in patients with advanced heart failure: the randomized, double-blind, placebo-controlled, parallel group ESSENTIAL trials. European Heart Journal. 2009; 30(24):3015-3026	Population advanced rather than decompensated heart failure
Midtbo KA, Silke B, Verma P, Reynolds G, Taylor SH. Haemodynamic dose-response effects of dobutamine and amrinone in acute heart failure [abstract]. British Journal of Clinical Pharmacology. 1986; 22:209P	Abstract - details unobtainable
Nanas JN, Tsagalou EP, Kanakakis J, Nanas SN, Terrovitis JV, Moon T et al. Long-term intermittent dobutamine infusion, combined with oral amiodarone for end-stage heart failure: a randomized double-blind study. Chest. 2004; 125(4):1198-1204	Advanced rather than decompensated heart failure
Nieminen MS, Akkila J, Hasenfuss G, Kleber FX, Lehtonen LA, Mitrovic V et al. Hemodynamic and neurohumoral effects of continuous infusion of levosimendan in patients with congestive heart failure. Journal of the American College of Cardiology. 2000; 36(6):1903-1912	Population consists of patients with stable congestive heart failure
O'Connor CM, Gattis WA, Uretsky BF, Adams KFJ, McNulty SE, Grossman SH et al. Continuous intravenous dobutamine is associated with an increased risk of death in patients with advanced heart failure: insights from the Flolan International Randomized Survival Trial (FIRST). American Heart Journal. 1999; 138(1 Pt 1):78-86	Post hoc subgroup analysis of a randomised trial
Oliva F, Latini R, Politi A, Staszewsky L, Maggioni AP, Nicolis E et al. Intermittent 6-month low-dose dobutamine infusion in severe heart failure: DICE multicenter trial. American Heart Journal. 1999; 138(2 Pt 1):247-253	Severe rather than acute decompensated heart failure
Robinson T, Gariballa S, Fancourt G, Potter J, Castleden M. The acute effects of a single dopamine infusion in elderly patients with congestive cardiac failure. British Journal of Clinical Pharmacology. 1994; 37(3):261-263	Advanced rather than decompensated heart failure
Sindone, A, Keogh, A, MacDonald, P et al. Inotropic therapy improves neuroendocrine abnormalities in severe heart failure [abstract]. Australian and New Zealand Journal of Medicine. 1999; 29:174	Abstract - severe rather than decompensated heart failure
Sindone, A, MacDonald, P, K, A. Haemodynamic, neurohumoral and symptomatic effects of dobutamine, dopamine and milrinone in severe heart failure [abstract]. Australian and New Zealand Journal of Medicine. 1998; 28:113	Abstract - severe rather than decompensated heart failure
Tacon CL, McCaffrey J, Delaney A. Dobutamine for patients with severe heart failure: a systematic review and meta-analysis of randomised controlled trials. Intensive Care Medicine. 2012; 38(3):359-367	Population in the systematic review does not match protocol population
Takano TE. Efficacy and Pharmacokinetics of Continuous Intravenous Infusion of Milrinone in Patients with Acute Heart Failure: A Late Phase II Study. Japanese	Abstract of reference Seino et al, 1996

Journal of Clinical and Experimental Medicine). 1994; 71(3):798-813	
Thackray S, Easthaugh J, Freemantle N, Cleland JGF. The effectiveness and relative effectiveness of intravenous inotropic drugs acting through the adrenergic pathway in patients with heart failure-a meta-regression analysis. European Journal of Heart Failure. 2002; 4(4):515-529	Meta regression review but patients not restricted to acute heart failure - cross checked for references
Uretsky BF, Jessup M, Konstam MA, Benotti JR, Sandberg JA. Multicenter trial of oral enoximone in patients with moderately severe congestive heart failure: lack of benefit compared to placebo. Circulation. 1989; 80(suppl II):II-174	Population consists of severe rather than decompensated heart failure patients
van de Borne P, Oren R, Somers VK. Dopamine depresses minute ventilation in patients with heart failure. Circulation. 1998; 98(2):126-131	Crossover study using 'normal' as well as people with severe rather than decompensated heart failure
Vargo DL, Brater DC, Rudy DW, Swan SK. Dopamine does not enhance furosemide-induced natriuresis in patients with congestive heart failure. Journal of the American Society of Nephrology. 1996; 7(7):1032-1037	Population people with chronic heart failure
Velez-Roa S, van de Borne P, Somers VK. Dobutamine potentiates the peripheral chemoreflex in patients with congestive heart failure. Journal of Cardiac Failure. 2003; 9(5):380-383	Stable congestive heart failure
White HD, Ribeiro JP, Hartley LH, Colucci WS. Immediate effects of milrinone on metabolic and sympathetic responses to exercise in severe congestive heart failure. American Journal of Cardiology. 1985; 56(1):93-98	Severe rather than decompensated heart failure
Wimmer A, Stanek B, Kubecova L, Vitovec J, Spinar J, Yilmaz N et al. Effects of prostaglandin E1, dobutamine and placebo on hemodynamic, renal and neurohumoral variables in patients with advanced heart failure. Japanese Heart Journal. 1999; 40(3):321-334	Population advanced rather than decompensated heart failure
Zwolfer W, Dressler HT, Keznickl P, Dieterich HA. Enoximone versus epinephrine/nitroglycerin in cardiac low-output states following valve replacement. Clinical Cardiology. 1995; 18(3):145-149	Post-operative administration of enoximone (following valve replacement)

K.8 Non-invasive ventilation

Table 17: Excluded clinical studies – non-invasive ventilation

Reference	Reason for exclusion
Austin MA, Wills KE. Effect of continuous positive airway pressure on mortality in the treatment of acute cardiogenic pulmonary edema in the prehospital setting: Randomized controlled trial. Academic Emergency Medicine. 2012; 19:S283	Conference abstract - sufficient fully published evidence available
Chadda K, Annane D, Hart N, Gajdos P, Raphaël JC, Lofaso F. Cardiac and respiratory effects of continuous positive airway pressure and noninvasive ventilation in acute cardiac pulmonary edema. Critical Care Medicine. 2002; 30(11):2457-2461	Outcomes do not match inclusion criteria and it is a crossover RCT
Cydulka RK. Noninvasive ventilation in cardiogenic pulmonary edema: a multicenter randomized trial. Annals of Emergency Medicine. 2005; 45(2):227-228	Abstract only - sufficient fully published evidence available
Ferrer M, Valencia M, Nicolas JM, Bernadich O, Badia JR, Torres A. Early noninvasive ventilation averts extubation failure in patients at risk: A randomized trial. American Journal of Respiratory and Critical Care Medicine. 2006; 173(2):164-170	Patient population does not match the protocol
Guervilly C, Forel J-M, Hraiech S, Demory D, Allardet-Servent J, Adda M et al. Right ventricular function during high-frequency oscillatory ventilation in adults with acute respiratory distress syndrome. Critical Care Medicine. 2012; 40(5):1539-1545	Intervention not in protocol

Hubble MW, Richards ME, Wilfong DA. Estimates of cost-effectiveness of prehospital continuous positive airway pressure in the management of acute pulmonary edema. Prehospital Emergency Care. 2008; 12(3):277-285	Incorrect study design
Kelly C, Newby DE, Boon NA, Douglas NJ. Support ventilation versus conventional oxygen. Lancet. 2001; 357(9262):1126	Letter to editor - full study published 2002
Khayat RN, Abraham WT, Patt B, Pu M, Jarjoura D. In-hospital treatment of obstructive sleep apnea during decompensation of heart failure. Chest. 2009; 136(4):991-997	Specific sub-population of people with decompensated heart failure as well as sleep apnea
L'Her E, Jaffrelot M. Should we still initiate noninvasive ventilation for acute respiratory distress related to cardiogenic pulmonary edema? Reanimation. 2009; 18(8):720-725	Not a systematic review
Lin M, Chiang HT. The efficacy of early continuous positive airway pressure therapy in patients with acute cardiogenic pulmonary edema. Journal of the Formosan Medical Association = Taiwan Yi Zhi. 1991; 90(8):736-743	Since dates overlap - study population same as Lin 1995
Mackay C, Mackay T, Barr K, Newby D, McDonagh T, Douglas N. Randomized controlled trial of CPAP vs conventional therapy in acute pulmonary edema. American Journal of Respiratory and Critical Care Medicine. 2000; 161(3 Suppl.):A416	Conference abstract - sufficient fully published evidence available
Mariani J, Macchia A, Belziti C, Deabreu M, Gagliardi J, Doval H et al. Noninvasive ventilation in acute cardiogenic pulmonary edema: a meta-analysis of randomized controlled trials. Journal of Cardiac Failure. 2011; 17(10):850-859	Systematic review - unclear study quality assessment cross checked for references
Moritz F, Benichou J, Vanheste M, Richard JC, Line S, Hellot MF et al. Boussignac continuous positive airway pressure device in the emergency care of acute cardiogenic pulmonary oedema: a randomized pilot study. European Journal of Emergency Medicine. 2003; 10(3):204-208	Outcomes do not match the protocol - very short follow-up 30 mins
Park, M, Sangean, M, Volpe, M et al. Randomized, prospective trial of oxygen, continuous and bilevel positive airway pressure in the treatment of cardiogenic acute pulmonary edema [abstract]. American Journal of Respiratory and Critical Care Medicine. 2002; 165(8 Suppl):A27	Abstract of an included study (Park 2004)
Radke PW, Hanrath P. Management of acute mitral regurgitation. Intensiv- Und Notfallbehandlung. 2005; 30(1):11-18	Ordered as background reading for another review question
Simpson PM, Bendall JC. Prehospital non-invasive ventilation for acute cardiogenic pulmonary oedema: an evidence-based review. Emergency Medicine Journal. 2011; 28(7):609-612	Review paper - cross-checked for references
Thys F, Roeseler J, Reynaert M, Liistro G, Rodenstein DO. Noninvasive ventilation for acute respiratory failure: a prospective randomised placebo-controlled trial. European Respiratory Journal. 2002; 20(3):545-555	Not review population, Not review population - > 50% diagnosed as COPD
Trevisan CE, Vieira SR. Noninvasive mechanical ventilation may be useful in treating patients who fail weaning from invasive mechanical ventilation: A randomized clinical trial. Critical Care. 2008; 12(2)	Population not in protocol
Uy CA, Limpin MEB, Guzman AV, Guia TS. Continuous positive airway pressure (CPAP) among patients with cardiogenic pulmonary oedema [Abstract]. European Respiratory Journal. 2003; 22(Suppl 45)	Abstract - sufficient fully published evidence available
Uy CA, Limpin MB, Guzman AV, Guia TS. Continuous positive airway pressure amoung patients with cadiogenic pulmonary edema [Abstract]. American Thoracic Society 100th International Conference, May 21-26, 2004, Orlando. 2004;C23	Abstract - sufficient fully published evidence available

Vaisanen IT, Rasanen J. Continuous positive airway pressure and supplemental oxygen in the treatment of cardiogenic pulmonary edema. Chest. 1987; 92(3):481-485	Incorrect study design
Zhu L, Hou J, Wang Q, Niu S. The treatment of patients with severe cadiogenic pulmonary edema and shock via mechanical ventilation [Abstract]. Respirology. 2005; 10(Suppl. 3):A191	Abstract - sufficient fully published evidence available

K.9 Mechanical ventilation

Table 80: Studies excluded from the clinical review

Reference	Reason for exclusion
Abdelbary A, Ayoub W, Nassar Y, et al. Can we predict left ventricular dysfunction-induced weaning failure? Invasive and echocardiographic evaluation. Crit Care 2011;15:S58.	Non AHF population: Conference abstract on echocardiographic and PA catheter criteria as predictors of extubation failure in mechanically ventilated patients
Boissier F, Ben GH, Razazi K, et al. Predictive factors for extubation failure in medical ICU patients. Intensive Care Med 2012;38:S195.	Non AHF population: Conference abstract of predictive factors of extubation failure in mechanically ventilated patients.
Bresson D, Sibellas F, Bastien O, et al. Clinical outcomes in advanced acute heart failure (AHF) patients stratified by INTERMACS classification. Eur Heart J 2011;32:138.	Indirect population: Conference abstract of risk stratification of patients with cardiogenic shock secondary to acute decompensated heart failure. 27/87 patients mechanically ventilated no analysis of this cohort in conference abstract
Brugnaro L, Frizzarin N, Marangon C, et al. Heart failure (HF) in the intensive cardiac care unit (ICCU): Predictors of the length of stay (LOS) and mortality. EUR J CARDIOVASC NURS 2011;10:S32.	Indirect population: Conference abstract of characteristics of patients admitted to ICU with a diagnosis of HF, not mechanically ventilated patients
Geppert A, Dorninger A, Delle-Karth G, et al. Plasma concentrations of interleukin-6, organ failure, vasopressor support, and successful coronary revascularization in predicting 30-day mortality of patients with cardiogenic shock complicating acute myocardial infarction. Crit Care Med 2006;34:2035-42.	Indirect population: Patients in ICU with cardiogenic shock complicating myocardial infarction only 27/38 were mechanically ventilated.
Gerbaud E, Erickson M, Grenouillet-Delacre M, et al. Echocardiographic evaluation and N-terminal pro-brain natriuretic peptide measurement of patients hospitalized for heart failure during weaning from mechanical ventilation. Minerva Anestesiol 2012;78:415-25.	Study examines NTproBNP and echocardiographic criteria to predict weaning failure. No multivariate analysis conducted.
Mekontso DA, Roche-Campo F, Kouatchet A, et al. Natriuretic peptide-driven fluid management during ventilator weaning: a randomized controlled trial. Am J Respir Crit Care Med 2012 Dec 15;186:1256-63.	Non prognostic study: RCT designed to evaluate difference between BNP guided and non BNP guided weaning from mechanical ventilation.
Mekontso-Dessap A, de PN, Girou E, Braconnier F, Lemaire F, Brun-Buisson C et al. B-type natriuretic peptide and weaning from mechanical ventilation. Intensive Care Medicine. 2006; 32(10):1529-1536	Indirect population: All mechanically ventilated patients in ICU not acute heart failure patients.

Rose L, Gray S, Atzema C, et al. Mechanical ventilation in the emergency department: A prospective observational pilot study. Acad Emerg Med 2011;18:S208-S209.	Indirect population: Conference abstract on patients treated with invasive ventilation and non-invasive ventilation in the ED. No aetiological stratification or subgroup presented in conference abstract.
Shirakabe A, Hata N, Yokoyama S, et al. Predicting the success of noninvasive positive pressure ventilation in emergency room for patients with acute heart failure. J Cardiol 2011;57:107-14.	Study looks at comparisons between NIV systems, and NIV success and failure cohorts.
Taneja A, Kumar G, Patel J, et al. Outcomes of congestive heart failure requiring mechanical ventilation. Crit Care Med 2010;38:A184.	Non prognostic study: Conference abstract comparing outcomes between invasive and non-invasively ventilated cohorts after adjustment.
Zahger D, Maimon N, Novack V, et al. Clinical characteristics and prognostic factors in patients with complicated acute coronary syndromes requiring prolonged mechanical ventilation. Am J Cardiol 2005;96:1644-8.	Indirect population: all patients admitted for ACS and required 3 days of mechanical ventilation, not specifically due to acute heart failure.
Zapata L, Vera P, Roglan A, et al. B-type natriuretic peptides for prediction and diagnosis of weaning failure from cardiac origin. Intensive Care Med 2011;37:477-85.	Study assessing BNP and NTproBNP to predict weaning failure, Nil multivariable analysis conducted only sensitivity, specificity reported.

K.10 Ultrafiltration

Table 81: Studies excluded from the clinical review

Reference	Reason for exclusion
Bart BA, Goldsmith SR, Lee KL, Redfield MM, Felker GM, O'Connor CM et al. Cardiorenal rescue study in acute decompensated heart failure: rationale and design of CARRESS-HF, for the Heart Failure Clinical Research Network. Journal of Cardiac Failure. 2012; 18(3):176-182	Included RCT protocol
Bartone C, Menon SG, Kereiakes DJ, O'Brien TM, Mazur W, McClellan M et al. Target weight guided treatment of acute heart failure using ultrafiltration or usual care: Results of a randomized pilot study. Journal of Cardiac Failure. 2010; 1):S106	Conference abstract only
Bartone C, Saghir S, Menon SG, et al. Comparison of ultrafiltration, nesiritide, and usual care in acute decompensated heart failure. Congest Heart Fail. 2008;14:298–301.	Retrospective analysis
Clark WR, Paganini E, Weinstein D, Bartlett R, Sheinfeld G, Ronco C. Extracorporeal ultrafiltration for acute exacerbations of chronic heart failure: report from the Acute Dialysis Quality Initiative. Int J Artif Organs. 2005; 28(5):466-476	Review article
Cosentino ER, Rinaldi ER, Degli Esposti D, Santi F, Ferramosca E, Colombo G et al. Preliminary report on the effects of ultrafiltration in severe HF refractory to conventional diuretic therapy: The Continuous Ultrafiltration for cOngestive heaRt failurE (CUORE) trial. European Journal of Heart Failure. 2011; 10(Suppl):S112	Conference abstract only
Costanzo MR, Saltzberg MT, Jessup M, Teerlink JR, Sobotka PA, Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure I. Ultrafiltration is associated with fewer rehospitalizations than continuous diuretic infusion in patients with decompensated heart failure: results from UNLOAD. Journal of Cardiac Failure. 2010; 16(4):277-284	Post Hoc subgroup analysis of included RCT

Dahal KB, Riella C, Chebib F, Revenco D, Susantitaphong P, Tsao L et al. Extracorporeal ultrafiltration vs. intravenous diuretics for treatment of acute decompensated heart failure: A meta-analysis of randomized controlled trials. Journal of Cardiac Failure. 2012; 1):S96	Abstract of a meta-analysis
Givertz MM, Teerlink JR, Albert NM, Westlake Canary CA, Collins SP, Colvin-Adams M et al. Acute decompensated heart failure: update on new and emerging evidence and directions for future research. Journal of Cardiac Failure. 2013; 19(6):371-389	Background reading: cross-checked for new trials
Gottlieb SS, Stebbins A, Voors AA, Hasselblad V, Ezekowitz JA, Califf RM et al. Effects of nesiritide and predictors of urine output in acute decompensated heart failure: results from ASCEND-HF (acute study of clinical effectiveness of nesiritide and decompensated heart failure). Journal of the American College of Cardiology. 2013; 62(13):1177-1183	Nesiritide is not currently used as a diuretic in treatment of AHF in the UK
Pepi M, Marenzi GC, Agostoni PG, Doria E, Barbier P, Muratori M et al. Sustained cardiac diastolic changes elicited by ultrafiltration in patients with moderate congestive heart failure: pathophysiological correlates. Br Heart J. 1993; 70(2):135-140	Indirect population: individuals with clinically silent but radiologically evident increased interstitial lung water
Rogers HL, Marshall J, Bock J, Dowling TC, Feller E, Robinson S et al. A randomized, controlled trial of the renal effects of ultrafiltration as compared to furosemide in patients with acute decompensated heart failure. Journal of Cardiac Failure. 2008; 14(1):1-5	Single centre results of included multicentre RCT
Stein AC, Mostarda C, Alves B, De CE, Araujo L, Eick R et al. Ultrafiltration treatment in decompensated heart failure: Changes in heart rate variability and survival. Hypertension. 2011; 58(5):e64	Conference abstract only

K.11 Beta-blockers

K.11.1 Excluded clinical studies – continuing / reducing or discontinuing beta-blockers

Table 11: Studies excluded from the clinical review

Reference	Reason for exclusion
Ansari M, Shlipak MG, Heidenreich PA, Van OD, Pohl EC, Browner WS et al. Improving guideline adherence: a randomized trial evaluating strategies to increase beta-blocker use in heart failure. Circulation. 2003; 107(22):2799-2804	Not relevant comparison
Butler J, Young JB, Abraham WT, Bourge RC, Adams KF, Jr., Clare R et al. Beta-blocker use and outcomes among hospitalized heart failure patients. Journal of the American College of Cardiology. 2006; 47(12):2462-2469	Beta-blocker comparison not randomised and n<2000
Krantz MJ, Ambardekar AV, Kaltenbach L, Hernandez AF, Heidenreich PA, Fonarow GC. Patterns and predictors of evidence-based medication continuation among hospitalized heart failure patients (from get with the guidelines-heart failure). American Journal of Cardiology. 2011; 107(12):1818-1823	Patients continuing beta-blockers not compared with those discontinuing
Metra M, Torp-Pedersen C, Cleland JGF, Di Lenarda A, Komajda M, Remme WJ et al. Influence of beta-blocker continuation or withdrawal on outcomes in patients hospitalized with heart failure: findings from the OPTIMIZE-HF program	Beta-blocker comparison not randomised and

Reference	Reason for exclusion
Use of beta-blockers and reduction in all-cause mortality in hospitalized Medicare beneficiaries with acute diastolic heart failure: A propensity-matched study of the OPTIMIZE-HF. European Journal of Heart Failure. 2007; 9(9):901-909	n<2000
Orso F, Baldasseroni S, Fabbri G, Gonzini L, Lucci D, D'Ambrosi C et al. Influence of beta-blocker continuation or withdrawal on outcomes in patients hospitalized with heart failure: findings from the OPTIMIZE-HF program Use of beta-blockers and reduction in all-cause mortality in hospitalized Medicare beneficiaries with acute diastolic heart failure: A propensity-matched study of the OPTIMIZE-HF. European Journal of Heart Failure. 2009; 11(1):77-84	Beta-blocker comparison not randomised and n<2000
Williams RE. Influence of beta-blocker continuation or withdrawal on outcomes in patients hospitalized with heart failure: findings from the OPTIMIZE-HF program	Comment and review

K.11.2 Excluded clinical studies – commencing beta-blockers

Table 12: Studies excluded from the clinical review

Reference	Reason for exclusion
Ansari M, Shlipak MG, Heidenreich PA, Van OD, Pohl EC, Browner WS et al. Improving guideline adherence: a randomized trial evaluating strategies to increase beta-blocker use in heart failure. Circulation. 2003; 107(22):2799-2804	Not relevant comparison
Bohm M, Link A, Cai D, Nieminen MS, Filippatos GS, Salem R et al. Beneficial association of -blocker therapy on recovery from severe acute heart failure treatment: data from the Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support trial. Critical Care Medicine. 2011; 39(5):940-944	Beta-blocker comparison not randomised and n<2000
Johnson D, Jin Y, Quan H, Cujec B. Beta-blockers and angiotensin-converting enzyme inhibitors/receptor blockers prescriptions after hospital discharge for heart failure are associated with decreased mortality in Alberta, Canada. Journal of the American College of Cardiology. 2003; 42(8):1438-1445	Not comparison of pre-versus post-discharge beta-blockers
Williams RE. Influence of beta-blocker continuation or withdrawal on outcomes in patients hospitalized with heart failure: findings from the OPTIMIZE-HF program Use of beta-blockers and reduction in all-cause mortality in hospitalized Medicare beneficiaries with acute diastolic heart failure: A propensity-matched study of the OPTIMIZE-HF. Journal of Clinical Hypertension. 2005; 7(9):520-530	Not relevant comparison
Yilmaz MB, Laribi S, Mebazaa A. Managing beta-blockers in acute heart failure: when to start and when to stop? Current Heart Failure Reports. 2010; 7(3):110-115	Review – background reading

Hamaguchi S, Kinugawa S, Tsuchihashi-Makaya M, Goto K, Goto D, Yokota T et al. Spironolactone use at discharge was associated with improved survival in hospitalized patients with systolic heart failure. American Heart Journal. 2010; 160(6):1156-1162	Observational study with less than 2,000 participants

K.12 ACE inhibitors

Table 82: Studies excluded from the clinical review

Reference	Reason for exclusion
Johnson D, Jin Y, Quan H, and Cujec B. Beta-blockers and angiotensin-converting enzyme inhibitors/receptor blockers prescriptions after hospital discharge for heart failure are associated with decreased mortality in Alberta, Canada. Journal of the American College of Cardiology: 42: 1438-1445.	Study did not use 'at discharge' or later prescription rather used within 3 months after discharge as the time period
O'Connor CM, Abraham WT, Albert NM, Clare R, Gattis Stough W, Gheorghiade M, Greenberg BH, Yancy CW, Young JB, and Fonarow GC. Predictors of mortality after discharge in patients hospitalized with heart failure: an analysis from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). American Heart Journal: 2008; 156: 662-673.	Study evaluated effectiveness, but did not address timing

K.13 MRA

Table 83: Studies excluded from the clinical review

Reference	Reason for exclusion
Gislason GH, Rasmussen JN, Abildstrom SZ, Schramm TK, Hansen ML, Buch P et al. Persistent use of evidence-based pharmacotherapy in heart failure is associated with improved outcomes. Circulation. 2007; 116(7):737-744	Study did not use 'at discharge' or later prescription used within 3 months after discharge as the time period.
Kadir S, Christopoulos C, Foster S, Devadathan SEN. In Hospital use of Eplerenone. European Journal of Heart Failure, Supplement. 2010; 9:S13	Abstract of a study with 60 participants
Pitt B, White H, Nicolau J, Martinez F, Gheorghiade M, Aschermann M et al. Eplerenone reduces mortality 30 days after randomization following acute myocardial infarction in patients with left ventricular systolic dysfunction and heart failure. Journal of the American College of Cardiology. 2005; 46(3):425-431	RCT concerned with effectiveness rather than timing

K.14 Aortic stenosis

Table 84: Studies excluded from the clinical review

Reference	Reason for exclusion
Barbanti M, Ussia GP, Capodanno D, Mignosa C, Gentile M, Aruta P etal. Transcatheter aortic valve implantation versus surgical aortic valve replacement in patients with severe aortic stenosis. Giornale Italiano DiCardiologia. 2011; 12(12 SUPPL. 3):e240	Abstract of a non-randomised study

Reference	Reason for exclusion
Bourantas CV, Farooq V, Onuma Y, Piazza N, Van Mieghem NM, Serruys PW. Transcatheter aortic valve implantation: new developments and upcoming clinical trials. EuroIntervention. 2012; 8(5):617-627	Review – cross-checked
Castiglioni A, Verzini A, Colangelo N, Nascimbene S, Laino G, Alfieri O. Comparison of minimally invasive closed circuit versus standard extracorporeal circulation for aortic valve replacement: a randomized study. Interactive Cardiovascular and Thoracic Surgery. 2009; 9(1):37-41	Non-randomised trial
Cook M, Brasseur P, Busca R. The burden of not treating patients with severe aortic stenosis: Comparison of secondary care resource consumption in TAVI versus medical management cohort of 30 patients in a UK NHS setting. European Heart Journal. 2011; 32:896	Cost analysis without randomised data
Eggebrecht H, Schmermund A, Kahlert P, Erbel R, Voigtlander T, Mehta RH. Emergent cardiac surgery During Transcatheter aortic valve implantation (TAVI): A weighted meta-analysis of 9,251 patients from 46 studies. EuroIntervention. 2013; 8(9):1072-1080	Meta-analysis cross checked for randomised controlled trials
Eggebrecht H, Schmermund A, Voigtlander T, Kahlert P, Erbel R, Mehta RH. Risk of stroke after transcatheter aortic valve implantation (TAVI): a meta-analysis of 10,037 published patients. EuroIntervention. 2012; 8(1):129-138	Meta-analysis cross checked for randomised controlled trials
Elmariah S, Passeri J, Hueter I, Margey R, Inglessis I, Baker J et al. Relationship of transcatheter and surgical aortic valve replacement with left ventricular function in high-risk patients with aortic stenosis. Journal of the American College of Cardiology. 2012; 60:B29	Abstract of a non-randomised study
Green P, Woglom AE, Genereux P, Daneault B, Paradis JM, Schnell S et al. The impact of frailty status on survival after transcatheter aortic valve replacement in older adults with severe aortic stenosis: a single-center experience. JACC Cardiovascular Interventions. 2012; 5(9):974-981	Non randomised controlled study
Hamon M, Lipiecki J, Carrie D, Burzotta F, Durel N, Coutance G et al. Silent cerebral infaRCT after cardiac catheterization: a randomized comparison of radial and femoral approaches. American Heart Journal. 2012; 164(4):449-454	Comparison not in protocol
Head SJ, Mokhles MM, Osnabrugge RLJ, Pibarot P, Mack MJ, TakkenbergJJM et al. The impact of prosthesis-patient mismatch on long-term survival after aortic valve replacement: a systematic review and meta-analysis of 34 observational studies comprising 27 186 patients with 133 141 patient-years. European Heart Journal. 2012; 33(12):1518-1529	Review included only observational studies
Khatri PJ, Webb JG, Rodes-Cabau J, Fremes SE, Ruel M, Lau K et al. Adverse effects associated with transcatheter aortic valve implantation: a meta-analysis of contemporary studies. Annals of Internal Medicine. 2013; 158(1):35-46	Meta-analysis cross checked for randomised controlled trials
McGregor M and Esfandiari S. Transcatheter Aortic Valve Implantation (TAVI) at the MUHC: a Health Technology Assessment. Technology Assessment Unit of the McGill University Health Centre (MUHC), 2009	Health technology assessment cross checked for references
Mealing S, Watt M, Eaton J, Sculpher M, Brasseur P, Busca R et al. A United Kingdom-based cost utility analysis of TAVI for inoperable patents with severe Aortic Stenosis treated by medical management. EuroIntervention. 2011; 7:M225	Economic
Neyt M, Van Brabandt H, Devriese S, Van De Sande S. A cost-utility analysis of transcatheter aortic valve implantation in Belgium: focusing on a well-defined and identifiable population. BMJ Open. 2012; 2(3)	Economic
Rajani R. In people with severe aortic stenosis unsuitable for surgery transcatheter aortic valve implantation reduces 1-year mortality compared with standard care. Evidence-Based Medicine. 2011; 16(3):74-75	Not a randomised controlled study
Schofer J, Fajadet J, Colombo A, Klugmann S, Bijuklic K, Tuebler T et al. 30-day outcome of the 18 f-direct flow medical valve in patients with severe aortic	Comparison not in protocol

Reference	Reason for exclusion
stenosis-results from the discover trial. Journal of the American College of Cardiology. 2012; 60:B236	
Sharma UC, Barenbrug P, Pokharel S, Dassen WRM, Pinto YM, Maessen JG. Systematic review of the outcome of aortic valve replacement in patients with aortic stenosis. Annals of Thoracic Surgery. 2004; 78(1):90-95	Systematic review cross checked for references
Vilela AT, Grande AJ, Palma JH, Buffolo E, Riera R. Transcatheter valve implantation versus aortic valve replacement for aortic stenosis in high-risk patients. Cochrane Database of Systematic Reviews. 2013; Issue 1:CD010304. DOI:10.1002/14651858.CD010304	Review protocol
Wu YC, Zhang JF, Shen WF, Zhao Q. Transcatheter aortic valve implantation versus surgical aortic valve replacement for severe aortic stenosis: a meta-analysis. Chinese Medical Journal. 2013; 126(6):1171-1177	Meta-analysis cross checked for randomised controlled trials
Zierer A, Wimmer-Greinecker G, Martens S, Moritz A, Doss M. Is transapical aortic valve implantation really less invasive than minimally invasive aortic valve replacement? Journal of Thoracic and Cardiovascular Surgery. 2009; 138(5):1067-1072	Not a randomised controlled trial

K.15 Mitral regurgitation

Table 85: Studies excluded from the clinical review

Reference	Reason for exclusion
Buerke M, Prondzinsky R, Lemm H, Dietz S, Buerke U, Ebelt H et al. Intra-aortic balloon counterpulsation in the treatment of infarction-related cardiogenic shock--review of the current evidence. Artificial Organs. 2012; 36(6):505-511	Pre-ordered for another question
Coats AJS, Shewan LG. Inconsistencies in the development of the ESC Clinical Practice Guidelines for Heart Failure. International Journal of Cardiology. 2013; 168(3):1724-1727	Review of guideline development process differences.
Deja MA, Grayburn PA, Sun B, Rao V, She L, Krejca M et al. Influence of mitral regurgitation repair on survival in the surgical treatment for ischemic heart failure trial. Circulation. 2012; 125(21):2639-2648	Comparison not in protocol: surgery with or without mitral repair
Douglas PS, Waugh RA, Bloomfield G, Dunn G, Davis L, Hahn RT et al. Implementation of echocardiography core laboratory best practices: a case study of the PARTNER I trial. Journal of the American Society of Echocardiography. 2013; 26(4):348-358	Ordered for the aortic stenosis review update, but excluded due to non-matching study focus.
Feldman T, Foster E, Qureshi M, Whisenant B, Williams J, Glower D et al. The everest ii randomized controlled trial (RCT): Three year outcomes. Journal of the American College of Cardiology. 2012; 60:B229-B230	Abstract of included study
Foster E, Kwan D, Feldman T, Weissman NJ, Grayburn PA, Schwartz A et al. Percutaneous mitral valve repair in the initial EVEREST cohort: evidence of reverse left ventricular remodeling. Circulation Cardiovascular Imaging. 2013; 6(4):522-530	Study design is not matching the protocol (non-randomised study)
Glower D, Ailawadi G, Argenziano M, Mack M, Trento A, Wang A et al. EVEREST II randomized clinical trial: predictors of mitral valve replacement in de novo surgery or after the MitraClip procedure. Journal of Thoracic and Cardiovascular Surgery. 2012; 143(4 Suppl):S60-S63	Abstract of included study
Hahn RT, Pibarot P, Stewart WJ, Weissman NJ, Gopalakrishnan D, Keane MG et al. Comparison of transcatheter and surgical aortic valve replacement in severe aortic	Excluded see aortic stenosis update

Reference	Reason for exclusion
stenosis: a longitudinal study of echocardiography parameters in cohort A of the PARTNER trial (placement of aortic transcatheter valves). Journal of the American College of Cardiology. 2013; 61(25):2514-2521	
Hu X, Zhao Q. Systematic comparison of the effectiveness of percutaneous mitral balloon valvotomy with surgical mitral commissurotomy. Swiss Medical Weekly. 2011; 141:w13180	Systematic review – cross checked for references
Janatzek S, Thomas S, and Mad P. Percutaneous repair of mitral regurgitation with the MitraClip. Ludwig Boltzmann Institut fuer Health Technology Assessment (LBIHTA), 2010	HTA – cross checked for references
Kar S, Lim DS, Rinaldi M, Foster E, Mauri L, Glower D et al. Impact of experience of percutaneous reduction of mitral regurgitation with the mitraclip device on procedural results. Catheterization and Cardiovascular Interventions. 2012; 79:S102	Abstract of non-randomised study
LaPar DJ, Kron IL. Should all ischemic mitral regurgitation be repaired? When should we replace? Current Opinion in Cardiology. 2011; 26(2):113-117	Non-systematic review
Lim S, Foster E, Glower D, Feldman T. Transcatheter mitral valve repair versus surgery in the elderly. Catheterization and Cardiovascular Interventions. 2011; 77:S143-S144	General review – cross checked for references
Maisano F, Taramasso M, Cioni M, Buzzatti N, Denti P, Colombo A et al. Review of the MitraClip clinical evidence. Minerva Cardioangiologica. 2012; 60(1):85-93	Review – cross checked for references
Mauri L, Garg P, Massaro JM, Foster E, Glower D, Mehoudar P et al. The EVEREST II Trial: design and rationale for a randomized study of the evalve mitraclip system compared with mitral valve surgery for mitral regurgitation. American Heart Journal. 2010; 160(1):23-29	Protocol of included study
Mookadam F, Raslan SF, Jiamsripong P, Jalal U, Murad MH. Percutaneous closure of mitral paravalvular leaks: a systematic review and meta-analysis. Journal of Heart Valve Disease. 2012; 21(2):208-217	Systematic review – cross checked for references
Murphy G and Cunningham J. Percutaneous heart valve replacement for valvular heart disease: a review of the clinical effectiveness, cost-effectiveness, and guidelines. Canadian Agency for Drugs and Technologies in Health (CADTH), 2010	Review – cross checked for references
O'Gara PT. Randomized trials in moderate ischemic mitral regurgitation: Many questions, limited answers. Circulation. 2012; 126(21):2452-2455	Commentary – cross checked
Tietge WJ, de Heer LM, van Hessen MWJ, Jansen R, Bots ML, van Gilst W et al. Early mitral valve repair versus watchful waiting in patients with severe asymptomatic organic mitral regurgitation; rationale and design of the Dutch AMR trial, a multicenter, randomised trial. Netherlands Heart Journal. 2012; 20(3):94-101	Protocol of a not yet published trial
Tsutsui JM, Maciel RR, Costa JM, Andrade JL, Ramires JF, Mathias WJ. Hand-carried ultrasound performed at bedside in cardiology inpatient setting - a comparative study with comprehensive echocardiography. Cardiovascular Ultrasound. 2004; 2:24	Ordered for another question
Whitlow P, Kar S, Pedersen W, Lim S, Kipperman R, Smalling R et al. MitraClip therapy in the EVEREST II high risk registry: One year results. Catheterization and Cardiovascular Interventions. 2010; 75:S154-S155	Abstract of included study
Whitlow PL, Feldman T, Pedersen WR, Lim DS, Kipperman R, Smalling R et al. Acute and 12-month results with catheter-based mitral valve leaflet repair: the EVEREST II (Endovascular Valve Edge-to-Edge Repair) High Risk Study. Journal of the American College of Cardiology. 2012; 59(2):130-139	EVEREST-II compared to a retrospective control group – not RCT

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K.16 Mechanical assist devices

Table 86: Excluded clinical studies - mechanical cardiac support

Reference	Reason for exclusion
Abraham WT, Anand I, Aranda JMJ, Boehmer J, Costanzo MR, DeMarco T et al. Randomized controlled trial of ventricular elastic support therapy in the treatment of symptomatic heart failure: rationale and design. American Heart Journal. 2012; 164(5):638-645	Rationale and design of an RCT which was excluded as the population did not match the protocol
Acker MA, Jessup M, Bolling SF, Oh J, Starling RC, Mann DL et al. Mitral valve repair in heart failure: five-year follow-up from the mitral valve replacement stratum of the Acorn randomized trial. Journal of Thoracic and Cardiovascular Surgery. 2011; 142(3):569-574	Follow-up study of an RCT which was excluded as the intervention did not match the protocol
Al Masri HH, Al Masri AH, Al Masri EH, Zourob FI. Hemodynamic support requires integrated approach comparing plvad vs. IABP in patients experiencing left ventricular failure. Heart Surgery Forum. 2012; 15:S36	Conference abstract: sufficient fully published evidence available
Bahekar A, Singh M, Singh S, Bhuriya R, Ahmad K, Khosla S et al. Cardiovascular outcomes using intra-aortic balloon pump in high-risk acute myocardial infarction with or without cardiogenic shock: A meta-analysis. Journal of Cardiovascular Pharmacology and Therapeutics. 2012; 17(1):44-56	Systematic review which includes all study designs: individual RCTs checked for reference
Baldwin JT, Mann DL. NHLBI's program for VAD therapy for moderately advanced heart failure: the REVIVE-IT pilot trial. Journal of Cardiac Failure. 2010; 16(11):855-858	This is a document of intent for an RCT
Brouwers C, Denollet J, de Jonge N, Caliskan K, Kealy J, Pedersen SS. Patient-reported outcomes in left ventricular assist device therapy: a systematic review and recommendations for clinical research and practice. Circulation Heart Failure. 2011; 4(6):714-723	Systematic review: majority covered are observational studies
Buerke M, Prondzinsky R, Lemm H, Dietz S, Buerke U, Ebelt H et al. Intra-aortic balloon counterpulsation in the treatment of infarction-related cardiogenic shock--review of the current evidence. Artificial Organs. 2012; 36(6):505-511	No indication that this is a systematic review
Cheng JM, den Uil CA, Hoeks SE, van der Ent M, Jewbali LSD, van Domburg RT et al. Percutaneous left ventricular assist devices vs. intra-aortic balloon pump counterpulsation for treatment of cardiogenic shock: a meta-analysis of controlled trials. European Heart Journal. 2009; 30(17):2102-2108	Meta-analysis: superseded by a more recent systematic review
Christenson JT, Simonet F, Schmuziger M. Economic impact of preoperative intraaortic balloon pump therapy in high-risk coronary patients. Annals of Thoracic Surgery. 2000; 70(2):510-515	The focus is on health economics
Christenson JT, Schmuziger M, Simonet F. Effective surgical management of high-risk coronary patients using preoperative intra-aortic balloon counterpulsation therapy. Cardiovascular Surgery. 2001; 9(4):383-390	The focus is on revascularisation
Christenson JT, Simonet F, Badel P, Schmuziger M. Evaluation of preoperative intra-aortic balloon pump support in high risk coronary patients. European Journal of Cardio-Thoracic Surgery. 1997; 11(6):1097-1104	Population does not match the protocol – majority of participants had unstable angina
Clegg AJ. The clinical and cost-effectiveness of left ventricular assist devices for end-stage heart failure: a systematic review and economic evaluation. NIHR Health Technology Assessment programme, 2005 Available from: http://www.hta.ac.uk/1250	Systematic review: majority covered are observational studies
Clegg AJ, Scott DA, Loveman E, Colquitt J, Royle P, Bryant J. Clinical and cost-	Superseded by a more

effectiveness of left ventricular assist devices as destination therapy for people with end-stage heart failure: a systematic review and economic evaluation. International Journal of Technology Assessment in Health Care. 2007; 23(2):261-268	recent systematic review. Majority of studies included are non-RCTs
Costanzo MR, Maybaum S, Bank A, Anand I, Rayburn B, Ivanhoe R et al. Ventricular elastic support therapy (VEST) in Stage C heart failure-analysis from the PEERLESS-HF study. Journal of Cardiac Failure. 2010; 16(11):912	Sub-group analysis of an RCT with population that does not match the protocol
Costanzo MR, Ivanhoe RJ, Kao A, Anand IS, Bank A, Boehmer J et al. Prospective evaluation of elastic restraint to lessen the effects of heart failure (PEERLESS-HF) trial. Journal of Cardiac Failure. 2012; 18(6):446-458	Population does not match the protocol - chronic heart failure and not acute
Cowger J, Sundareswaran K, Rogers JG, Park SJ, Pagani FD, Bhat G et al. Predicting survival in patients receiving continuous flow left ventricular assist devices. Journal of the American College of Cardiology. 2013; 6(3):313-321.	Pooled analysis of participants from several trials to derive a model of survival prediction
de Waha S, Desch S, Eitel I, Fuernau G, Lurz P, de Waha A et al. What is the evidence for IABP in STEMI with and without cardiogenic shock? Therapeutic Advances in Cardiovascular Disease. 2012; 6(3):123-132	Review: no firm evidence of this being a systematic review
Dixon S, Maini B, Palacios I, O'Neill W, Gregory D. Quality of life improvements with impella hemodynamic support compared with intra-aortic balloon pump in high risk patients receiving PCI: Results from the protect II trial. Catheterization and Cardiovascular Interventions. 2012; 79:S20	Conference abstract: population does not match the protocol - had 3 vessel disease
Elahi MM, Lam J, Asopa S, Matata BM. Levosimendan versus an intra-aortic balloon pump in adult cardiac surgery patients with low cardiac output. Journal of Cardiothoracic and Vascular Anesthesia. 2011; 25(6):1154-1162	Review: no firm evidence of this being a systematic review
French JK, Feldman HA, Assmann SF, Sanborn T, Palmeri ST, Miller D et al. Influence of thrombolytic therapy, with or without intra-aortic balloon counterpulsation, on 12-month survival in the SHOCK trial. American Heart Journal. 2003; 146(5):804-810	Intervention of our interest was not allocated randomly to participants
Fuernau G, Thiele H. Intra-Aortic Balloon Pump (IABP) in cardiogenic shock. Current Opinion in Critical Care. 2013; 19(5):404-409	Review and interpretation of literature – background reading
Gazzoli F, Vigano M, Pagani F, Alloni A, Silvaggio G, Panzavolta M et al. Initial results of clinical trial with a new left ventricular assist device (LVAD) providing synchronous pulsatile flow. International Journal of Artificial Organs. 2009; 32(6):344-353	This is neither an RCT nor a systematic review
Girling AJ, Freeman G, Gordon JP, Poole-Wilson P, Scott DA, Lilford RJ. Modeling payback from research into the efficacy of left-ventricular assist devices as destination therapy. International Journal of Technology Assessment in Health Care. 2007; 23(2):269-277	The focus is on health economics
Greenberg B, Czerska B, Abraham WT, Neaton JD, Delgado RM, Mather P et al. Rationale, design, and methods for a pivotal randomized clinical trial of continuous aortic flow augmentation in patients with exacerbation of heart failure: the MOMENTUM trial. Journal of Cardiac Failure. 2007; 13(9):715-721	Rationale, design and methods of an RCT which has been excluded
Greenberg B, Czerska B, Delgado RM, Bourge R, Zile MR, Silver M et al. Effects of continuous aortic flow augmentation in patients with exacerbation of heart failure inadequately responsive to medical therapy: results of the Multicenter Trial of the Orqis Medical Cancion System for the Enhanced Treatment of	The intervention is unlikely to be available widely as the company which developed the device is

Heart Failure Unresponsive to Medical Therapy (MOMENTUM). Circulation. 2008; 118(12):1241-1249	currently out of business and there is limited information regarding licensing and use of this device.
Gregory D, Scotti DJ, de LG, Palacios I, Dixon S, Maini B et al. A value-based analysis of hemodynamic support strategies for high-risk heart failure patients undergoing a percutaneous coronary intervention. American Health and Drug Benefits. 2013; 6(2)	Population does not match the protocol - had 3 vessel disease
Hochman JS, Buller CE, Sleeper LA, Boland J, Dzavik V, Sanborn TA et al. Cardiogenic shock complicating acute myocardial infarction--etiologies, management and outcome: a report from the SHOCK Trial Registry. SHould we emergently revascularize Occluded Coronaries for cardiogenic shocK? Journal of the American College of Cardiology. 2000; 36(3 Suppl A):1063-1070	Overview report of an RCT
Hochman JS, Sleeper LA, White HD, Dzavik V, Wong SC, Menon V et al. One-year survival following early revascularization for cardiogenic shock. JAMA. 2001; 285(2):190-192	Intervention of our interest was not allocated randomly to participants
Hutchinson J, Scott DA, Clegg AJ, Loveman E, Royle P, Bryant J et al. Cost-effectiveness of left ventricular-assist devices in end-stage heart failure. Expert Review of Cardiovascular Therapy. 2008; 6(2):175-185	The focus is on health economics
Ivanhoe RJ, Costanza MR, Abraham WT, Rayburn BK. Ventricular restraint improves outcomes in HF patients with CRT. Journal of Cardiac Failure. 2011; 17(8 SUPPL. 1):S41-S42	Conference abstract of an RCT which has been included
Jaworska E, Wlodarczyk A, Budasz-Swiderska M. Clinical and cost-effectiveness of third-generation, implantable left ventricular assist devices for people with end-stage heart failure: A systematic review. Value in Health. 2012; 15(7):A345	Systematic review: not restricted to RCTs
John R, Naka Y, Smedira NG, Starling R, Jorde U, Eckman P et al. Continuous flow left ventricular assist device outcomes in commercial use compared with the prior clinical trial. Annals of Thoracic Surgery. 2011; 92(4):1406-1413	Follow-up study of an RCT which has been excluded as the population does not match the protocol
John R, Long JW, Massey HT, Griffith BP, Sun BC, Tector AJ et al. Outcomes of a multicenter trial of the Levitronix CentriMag ventricular assist system for short-term circulatory support. Journal of Thoracic and Cardiovascular Surgery. 2011; 141(4):932-939	This is neither an RCT nor a systematic review
Kaul U, Sahay S, Bahl VK, Sharma S, Wasir HS, Venugopal P. Coronary angioplasty in high risk patients: comparison of elective intraaortic balloon pump and percutaneous cardiopulmonary bypass support--a randomized study. Journal of Interventional Cardiology. 1995; 8(2):199-205	Study population and comparator do not match the protocol
Lazar RM, Shapiro PA, Jaski BE, Parides MK, Bourge RC, Watson JT et al. Neurological events during long-term mechanical circulatory support for heart failure: the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) experience. Circulation. 2004; 109(20):2423-2427	Sub-study of an RCT which has been excluded as the population did not match the protocol
Lomivorotov VV, Boboshko VA, Kornilov IA, Kniazkova LG, Deryagin MN, Cherniavsky AM. Levosimendan versus intraaortic balloon pump in high risk cardiac patients operated under cardiopulmonary bypass: Preliminary report. Intensive Care Medicine. 2010; 36:S238	Conference abstract: medication studied not part of standard care in UK
Long JW, Kfoury AG, Slaughter MS, Silver M, Milano C, Rogers J et al. Long-term destination therapy with the HeartMate XVE left ventricular assist device:	Report of long-term outcomes of an RCT which

improved outcomes since the REMATCH study. Congestive Heart Failure. 2005; 11(3):133-138	has been excluded as the population did not match the protocol
Maini B, O'Neill W, Dixon S, Palacios I, Schreiber T, Gregory DA et al. Cost-effectiveness and clinical outcomes of impella hemodynamic support compared with intra-aortic balloon pump in high risk patients receiving PCI: Results from the PROTECT II trial. Journal of the American College of Cardiology. 2011; 1):B131-B132	Conference abstract: population does not match the protocol – had 3 vessel disease
Maini BS, O'Neill W, Palacios I, Dixon S, Gregory D. Cost-effectiveness and quality of life improvements: Impella hemodynamic support compared with intra-aortic balloon pump in high risk patients receiving PCI. Journal of the American College of Cardiology. 2012; 59(13):E68	Conference abstract: population does not match the protocol - had 3 vessel disease
Mann DL, Acker MA, Jessup M, Sabbah HN, Starling RC, Kubo SH. Clinical evaluation of the CorCap Cardiac Support Device in patients with dilated cardiomyopathy. Annals of Thoracic Surgery. 2007; 84(4):1226-1235	Study population does not match the protocol - chronic heart failure rather than acute
Mann DL, Kubo SH, Sabbah HN, Starling RC, Jessup M, Oh JK et al. Beneficial effects of the CorCap cardiac support device: five-year results from the Acorn Trial. Journal of Thoracic and Cardiovascular Surgery. 2012; 143(5):1036-1042	Follow-up study of an RCT which has been excluded as the intervention did not match the protocol
Marek J, Saba S, Schwartzman D, Jain SK, Adelstein EC, Onishi T et al. Resynchronization is strongly associated with clinical outcome benefit in echoguided lead placement: Results from starter randomized controlled trial. Circulation. 2012; 126(21 SUPPL. 1)	The intervention is neither an IABP nor an LVAD
Oz MC, Gelijns AC, Miller L, Wang C, Nickens P, Arons R et al. Left ventricular assist devices as permanent heart failure therapy: the price of progress. Annals of Surgery. 2003; 238(4):577-585	The focus is on health economics
Park SJ, Tector A, Piccioni W, Raines E, Gelijns A, Moskowitz A et al. Left ventricular assist devices as destination therapy: a new look at survival. Journal of Thoracic and Cardiovascular Surgery. 2005; 129(1):9-17	Follow-up study of an RCT which has been excluded as the population did not match the protocol
Perera D, Stables R, Thomas M, Booth J, Pitt M, Blackman D et al. Elective intra-aortic balloon counterpulsation during high-risk percutaneous coronary intervention: a randomized controlled trial. JAMA. 2010; 304(8):867-874	The focus of the study was on revascularisation
Pettit S, Japp A, Hawkins N, Gardner R, Haj-Yahia S, McMurray J et al. Systematic review of bridging to heart transplantation with long-term continuous flow left ventricular assist devices. European Journal of Heart Failure. 2013; 12:S35	Conference abstract of a systematic review
Prondzinsky R, Unverzagt S, Lemm H, Wegener NA, Schlitt A, Heinroth KM et al. Interleukin-6, -7, -8 and -10 predict outcome in acute myocardial infarction complicated by cardiogenic shock. Clinical Research in Cardiology. 2012; 101(5):375-384	The outcomes did not match the protocol
Ramanathan K, Farkouh ME, Cosmi JE, French JK, Harkness SM, Dzavik V et al. Rapid complete reversal of systemic hypoperfusion after intra-aortic balloon pump counterpulsation and survival in cardiogenic shock complicating an acute myocardial infarction. American Heart Journal. 2011; 162(2):268-275	The study design did not match the protocol: retrospective analysis of trial registry data
Ranucci M, Castelvecchio S, Biondi A, de Vincentiis C, Ballotta A, Varrica A et al. A randomized controlled trial of preoperative intra-aortic balloon pump in coronary patients with poor left ventricular function undergoing coronary	The population does not match the protocol.

artery bypass surgery*. Critical Care Medicine. 2013; 41(11):2476-2483	
Rao V, Naka Y, Catanese KA, Flannery MA, Oz MC. Economic costs associated with implantable left ventricular assist device therapy. Journal of Congestive Heart Failure and Circulatory Support. 2001; 2(1):31-34	The focus is on health economics
Rogers JG, Bostic RR, Tong KB, Adamson R, Russo M, Slaughter MS. Cost-effectiveness analysis of continuous-flow left ventricular assist devices as destination therapy. Circulation. 2012; Heart failure. 5(1):10-16	The focus is on health economics
Romeo F, Acconcia MC, Sergi D, Romeo A, Muscoli S, Valente S et al. The outcome of intra-aortic balloon pump support in acute myocardial infarction complicated by cardiogenic shock according to the type of revascularization: a comprehensive meta-analysis. American Heart Journal. 2013; 165(5):679-692	Systematic review which includes all study designs: individual RCTs checked for reference
Samson D. Cost-Effectiveness of Left-Ventricular Assist Devices as Destination Therapy for End-Stage Heart Failure. Chicago,Il.. Technology Assessment Centre, BlueCross BlueShield Association, 2004	The focus is on health economics
Sanborn TA, Sleeper LA, Bates ER, Jacobs AK, Boland J, French JK et al. Impact of thrombolysis, intra-aortic balloon pump counterpulsation, and their combination in cardiogenic shock complicating acute myocardial infarction: a report from the SHOCK Trial Registry. SHould we emergently revascularize Occluded Coronaries for cardiogenic shocK? Journal of the American College of Cardiology. 2000; 36(3 Suppl A):1123-1129	Retrospective analysis of trial registry data
Sas G, Lambert LJ, Boothroyd LJ, Ducharme A, Charbonneau E, Carrier M et al. What can the patient with chronic end-stage heart failure expect from a long-term left ventricular assist device? A systematic review of current evidence. Canadian Journal of Cardiology. 2012; 28(5 SUPPL. 1):S337-S338	Conference poster of a systematic review
Seyfarth M, Sibbing D, Bauer I, Frohlich G, Bott-Flugel L, Byrne R et al. A randomized clinical trial to evaluate the safety and efficacy of a percutaneous left ventricular assist device versus intra-aortic balloon pumping for treatment of cardiogenic shock caused by myocardial infarction. Journal of the American College of Cardiology. 2008; 52(19):1584-1588	Conference abstract of an RCT which has already been included
Sharples L, Buxton M, Caine N, Cafferty F, Demiris N, Dyer M et al. Evaluation of the ventricular assist device programme in the UK. Health Technology Assessment. 2006; 10(48):1-119, iii	Systematic review: majority covered are observational studies
Sjauw KD, Engström AE, Vis MM, van der Schaaf RJ, Baan J Jr, Koch KT, de Winter RJ et al. A systematic review and meta-analysis of intra-aortic balloon pump therapy in ST-elevation myocardial infarction: should we change the guidelines? European Heart Journal. 2009; 30:459-468.	Systematic review: population does not match the study protocol
Westaby S, Kharbanda R, Banning AP. Cardiogenic shock in ACS. Part 1: prediction, presentation and medical care. Nature Reviews Cardiology. 2012; 9(3):158-171.	Neither an RCT nor a systematic review.
Westaby S, Anastasiadis K, Wieselthaler GM. Cardiogenic shock in ACS. Part 2: role of mechanical circulatory support. Nature Reviews Cardiology. 2012; 9(4):195-208.	Neither an RCT nor a systematic review.
Westaby S. Rotary blood pumps as definitive treatment for severe heart failure. Future Cardiology. 2013; 9(2):199-213.	Neither an RCT nor a systematic review.
Westaby S, Deng M. Continuous flow blood pumps: the new gold standard for advanced heart failure? European Journal of Cardio-Thoracic Surgery. 2013; 44(1):4-8.	Neither an RCT nor a systematic review.
Zile MR, Colombo PC, Mehra M, Greenberg B, Brown S, Konstam MA.	The intervention is unlikely

Progressive improvement in cardiac performance with continuous aortic flow augmentation (aortic flow therapy) in patients hospitalized with severe heart failure: results of the Multicenter Trial of the Orqis Medical Cancion System for the Enhanced Treatment of Heart Failure Unresponsive to Medical Therapy (MOMENTUM). Journal of Heart and Lung Transplantation. 2010; 29(1):86-92	to be available widely as the company which developed the device is currently out of business and there is limited information regarding licensing and use of this device.

K.17 Specialist management

Table 87: Studies excluded from the clinical review

Reference	Reason for exclusion
Abrahamyan L, Trubiani G, Witteman W, Mitsakakis N, Krahn M, Wijeysundera HC. Insights into the contemporary management of heart failure in specialized multidisciplinary ambulatory clinics. Canadian Journal of Cardiology. 2013; 29(9):1062-1068	Mainly on CHF management
Auerbach AD, Hamel MB, Califf RM, Davis RB, Wenger NS, Desbiens N et al. Patient characteristics associated with care by a cardiologist among adults hospitalized with severe congestive heart failure. SUPPORT Investigators. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments. Journal of the American College of Cardiology. 2000; 36(7):2119-2125	Multivariate predictors of factors associated with attending cardiologist care
Bellotti P, Badano LP, Acquarone N, Griffo R, Lo Pinto G, Maggioni AP et al. Specialty-related differences in the epidemiology, clinical profile, management and outcome of patients hospitalized for heart failure; the OSCUR study. Oucome dello Scompenso Cardiaco in relazione all'Utilizzo delle Risore. European Heart Journal. 2001; 22(7):596-604	Univariate descriptive / epidemiological study
De Geest S, Scheurweghs L, Reynders I, Pelemans W, Droogne W, Van Cleemput J et al. Differences in psychosocial and behavioral profiles between heart failure patients admitted to cardiology and geriatric wards. European Journal of Heart Failure. 2003; 5(4):557-567	Univariate descriptive analysis
Di Lenarda A, Scherillo M, Maggioni AP, Acquarone N, Ambrosio GB, Annicchiarico M et al. Current presentation and management of heart failure in cardiology and internal medicine hospital units: a tale of two worlds--the TEMISTOCLE study. American Heart Journal. 2003; 146(4):E12	Abstract of a univariate descriptive study
El-Banayosy A, Cobaugh D, Zittermann A, Kitzner L, Arusoglu L, Morshuis M et al. A multidisciplinary network to save the lives of severe, persistent cardiogenic shock patients. Annals of Thoracic Surgery. 2005; 80(2):543-547	Comparison not in protocol (network between local hospital and specialist heart centres)
Feldman DE, Huynh T, Des Lauriers J, Giannetti N, Frenette M, Grondin F et al. Gender and other disparities in referral to specialized heart failure clinics following emergency department visits. Journal of Women's Health. 2013; 22(6):526-531	Study on prognostic factors and not on effectiveness
Fonseca C, Ceia F, Sarmento PM, Marques F, Covas R, Aleixo A. Translating guidelines into clinical practice: benefits of an acute heart failure unit. Revista Portuguesa De Cardiologia. 2007; 26(11):1111-1128	Before and after univariate analysis
Gregory D, Ordway LJ, McGillivray M, Konstam MA, Denofrio D. A cost-saving strategy for inpatient management of advanced decompensated heart failure patients: the Cardiomyopathy Unit. Journal of Cardiac Failure. 2009; 15(5):428-434	Cost analysis
Jaarsma T. Multidisciplinary approach in heart failure: Evidence, experiences	Abstract of a review

Reference	Reason for exclusion
and challenges. Journal of Cardiac Failure. 2010; 16(9 SUPPL. 1):S131	
Jondeau G, Arnoult F, Caligiuri G, Phan G, Mercadier JJ, Aumont MC et al. Impact of a mobile team of cardiologist using echocardiography for managing patients with acute heart failure. the EMEPIC randomized controlled trial. European Heart Journal. 2011; 32:447	Abstract of a study with a comparison that is not in the protocol
Kleet A, Borenstein K, Manole F, Fearon-Clarke J, Langlois E, Henry A et al. The chronic care disconnect in heart failure therapy. Journal of Cardiac Failure. 2010; 16(8 SUPPL. 1):S95	Abstract – skilled nursing in transition care.
Liljeroos M, Andreae C. Does multiprofessional standard care plans improve the care of heart failure patients? A case record study. Scandinavian Cardiovascular Journal. 2010; 44:38	Abstract of a descriptive before and after study
McDonald K, Ledwidge M, Cahill J, Quigley P, Maurer B, Travers B et al. Heart failure management: multidisciplinary care has intrinsic benefit above the optimization of medical care. Journal of Cardiac Failure. 2002; 8(3):142-148	Multidisciplinary education and follow-up
Nicol ED, Fittall B, Roughton M, Cleland JGF, Dargie H. NHS heart failure survey: a survey of acute heart failure admissions in England, Wales and Northern Ireland. Heart. 2008; 94(2)	Univariate analysis of length of stay by attending physician
Philbin EF, Rocco J, Lindenmuth NW, Ulrich K, McCall M, Jenkins PL. The results of a randomized trial of a quality improvement intervention in the care of patients with heart failure. American Journal of Medicine. 2000; 109(6):443-449	Intervention not in the protocol: a general improvement programme
Piepoli MF, Villani GQ, Aschieri D, Bennati S, Groppi F, Pisati MS et al. Multidisciplinary and multisetting team management programme in heart failure patients affects hospitalisation and costing. International Journal of Cardiology. 2006; 111(3):377-385	Post discharge from hospital, i.e. non-acute population
Sutton SS, Franklin M, Reeder CE, Laws F. Effects of multidisciplinary care of heart failure patients at high risk for hospital admission. Drug Benefit Trends. 2008; 20(2):54-59	Health care costs
Thomas R, Huntley A, Mann M, Huws D, Paranjothy S, Elwyn G et al. Specialist clinics for reducing emergency admissions in patients with heart failure: a systematic review and meta-analysis of randomised controlled trials. Heart. 2013; 99(4):233-239	Systematic review – excluded since all studies are conducted in community or outpatient settings (secondary prevention)
Zarrinkoub R, Wettermark B, Wandell P, Mejhert M, Szulkin R, Ljunggren G et al. The epidemiology of heart failure, based on data for 2.1 million inhabitants in Sweden. European Journal of Heart Failure. 2013; 15(9):995-1002	Background information
Zuily S, Jourdain P, Decup D, Agrinier N, Loiret J, Groshens S et al. Impact of heart failure management unit on heart failure-related readmission rate and mortality. Archives of Cardiovascular Diseases. 2010; 103(2):90-96	Before and after univariate analysis

Appendix L: Excluded economic studies

L.1 Natriuretic peptides

Table 88: Studies excluded from the economic review

Reference	Reason for exclusion
Behnes M, Brueckmann M, Ahmad-Nejad P, Lang S, Wolpert C, Elmas E et al. Diagnostic performance and cost effectiveness of measurements of plasma N-	Superseded by other available evidence in

Reference	Reason for exclusion
terminal pro brain natriuretic peptide in patients presenting with acute dyspnea or peripheral edema. International Journal of Cardiology. 2009; 135(2):165-174	terms of its applicability and/or methodological quality

L.2 Ultrafiltration

Table 89: Studies excluded from the economic review

Reference	Reason for exclusion
Bradley SM, Levy WC, Veenstra DL. Cost-consequences of ultrafiltration for acute heart failure: a decision model analysis. Circulation: Cardiovascular Quality and Outcomes. 2009; 2(6):566-573	Superseded by other available evidence in terms of its applicability and/or methodological quality

L.3 Aortic stenosis

Table 90: Studies excluded from the economic review

Reference	Reason for exclusion
Doble B, Blackhouse G, Goeree R, Xie F. Cost-effectiveness of the Edwards SAPIEN transcatheter heart valve compared with standard management and surgical aortic valve replacement in patients with severe symptomatic aortic stenosis: a Canadian perspective. Journal of Thoracic and Cardiovascular Surgery. Canada 2013; 146(1):52-60	Superseded by other available evidence in terms of its applicability and/or methodological quality
Hancock-Howard RL, Feindel CM, Rodes-Cabau J, Webb JG, Thompson AK, Banz K. Cost effectiveness of transcatheter aortic valve replacement compared to medical management in inoperable patients with severe aortic stenosis: Canadian analysis based on the PARTNER Trial Cohort B findings. Journal of Medical Economics. 2013; 16(4):566-574	Superseded by other available evidence in terms of its applicability and/or methodological quality
Neyt M, Van Brabandt H, Devriese S, Van De Sande S. A cost-utility analysis of transcatheter aortic valve implantation in Belgium: focusing on a well-defined and identifiable population. BMJ Open. 2012; 2(3):e001032	Superseded by other available evidence in terms of its applicability and/or methodological quality
Sehatzadeh S, Doble B, Xie F, Blackhouse G, Campbell K, Kaulback K et al. Transcatheter aortic valve implantation (TAVI) for treatment of aortic valve stenosis: an evidence-based Analysis (part B). Ontario Health Technology Assessment Series. 2012; 12(14):1-62	Superseded by other available evidence in terms of its applicability and/or methodological quality

L.4 Mechanical assist devices

Table 91: Studies excluded from the economic review

Reference	Reason for exclusion
Alba AC, Alba LF, Delgado DH, Rao V, Ross HJ, Goeree R. Cost-effectiveness of	Superseded by other

Reference	Reason for exclusion
ventricular assist device therapy as a bridge to transplantation compared with nonbridged cardiac recipients. Circulation. 2013; 127(24):2424-2435	available evidence in terms of its applicability and/or methodological quality
Christopher F and Clegg A. Left ventricular assist devices (LVADs) for end stage heart failure: conclusion of the Development and Evaluation Committee. Southampton. Wessex Institute for Health Research and Development, 1999	Superseded by other available evidence in terms of its applicability and/or methodological quality
Clegg AJ, Scott DA, Loveman E, Colquitt J, Hutchinson J, Royle P et al. The clinical and cost-effectiveness of left ventricular assist devices for end-stage heart failure: a systematic review and economic evaluation. Health Technology Assessment. 2005; 9(45):1-132	Superseded by other available evidence in terms of its applicability and/or methodological quality
Sharples L, Buxton M, Caine N, Cafferty F, Demiris N, Dyer M et al. Evaluation of the ventricular assist device programme in the UK. Health Technology Assessment. 2006; 10(48):1-119	Superseded by other available evidence in terms of its applicability and/or methodological quality

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Appendix M: Cost-effectiveness analysis

M.1 Introduction

Patients presenting to the emergency department with acute dyspnoea and no overt sign of lung injury or chest trauma may be suspected of having acute heart failure or respiratory conditions for which the management is different. Differentiation of acute heart failure from other causes at the diagnostic work-up is therefore important to help ensure optimised intervention.

Testing for elevated serum natriuretic peptide can assist diagnostic work-up by ruling out heart failure and is available to two-thirds of NHS Trusts in England and Health Boards in Wales [Unpublished, NICOR].[115] However, while natriuretic peptide testing could potentially decrease the number of incorrect acute heart failure diagnoses through the use of a rule-out threshold, it represents an additional cost to standard diagnostic investigations.

Economic evaluations identified in a systematic literature search suggest natriuretic peptide testing is cost effective, but this has not been demonstrated from the NHS perspective and assessment has not included patient health-related quality of life, the preferred methodology of the National Institute for Health and Care Excellence.[118]

It has been reported that people admitted for acute heart failure who are seen by specialists are more likely to be initiated on appropriate drug therapy. The National Heart Failure Audit of patients admitted to acute Trusts in England and Wales quantifies this disparity in prescribing and shows a large variation amongst providers in access to specialist heart failure services.[31] However, a systematic search did not identify any relevant analysis of health benefit and cost.

This evaluation uses a two-part model to assess the cost effectiveness of a more specialist staffing arrangement of inpatient heart failure care versus a standard arrangement; and the cost effectiveness of serum natriuretic peptide testing versus standard clinical investigations.

M.2 Methods

M.2.1 Model overview

A cost-utility analysis was undertaken to explore two economic questions in acute heart failure management:

1. Is the serum natriuretic peptide test used in addition to standard clinical investigations cost effective compared to standard clinical investigations alone?
2. Is specialist management cost effective compared to standard management?

The model addresses both questions by combining the two analyses: NP testing and Specialist Management.

M.2.1.1 Comparators

Four strategies which combine the two economic questions were selected. The abbreviated names for the strategies are given in parenthesis.

1. Standard management (STM)
2. Standard management with natriuretic peptide testing (STM-NP)
3. Specialist management (SPM)
4. Specialist management with natriuretic peptide testing (SPM-NP)

Both standard and specialist management strategies include care given by a specialist heart failure team, although to different proportions of patients and in different ward settings. In the model a specialist heart failure team is described as a cardiology team to reflect common interpretation; it mainly comprises a cardiologist (although in some settings, this may be any physician with an interest in heart failure) and heart failure specialist nurses (HFSN). If care is not provided by the specialist heart failure team then it is provided by a general medical team, led by a general physician who does not specialise in heart failure (and who may have a non-heart failure subspecialty).

M.2.1.2 Population

The analysis considers the adult population of England and Wales who present to the emergency department with acute dyspnoea and who are suspected of acute heart failure, that is, they have no clear alternative diagnosis. Patients with a known history of heart failure who may be presenting with acute decompensation of heart failure are excluded. Therefore only the incident population is considered. The model does not consider NHS Trusts without accident and emergency and cardiology inpatient services.

M.2.1.3 Time horizon, treatment period, perspective, discount rates used

A time horizon of 4 years was used in the base case (primary analysis). This is the currently available follow-up period for patients included in the national heart failure audit and was considered long enough to capture the differences between strategies in costs and QALYs resulting from a single (index) admission. The national heart failure audit finds that approximately forty per cent of patients surviving the index admission remain alive at 4 years post-discharge.[31] A sensitivity analysis examined cost effectiveness over a 10 year time horizon.

Patients who are initiated on treatment during the index hospital admission are assumed to remain on treatment throughout. In the base case, patients who are not initiated on treatment at the index admission continue untreated.

Costs and quality-adjusted life years (QALYs) were considered from a UK NHS perspective. The analysis follows the standard assumptions of the NICE reference case including discounting at 3.5% for costs and health effects, and incremental analysis.[118]

M.2.1.4 Deviations from NICE reference case

The modelling methodology does not deviate from the NICE reference case requirements.[118]

M.2.2 Approach to modelling

M.2.2.1 Differences in comparators incorporated in the model

Diagnostic work-up (assessment preceding admission)

In all strategies the emergency physician (admitting physician) performing the diagnostic work-up uses standard clinical investigations, such as physical examination, electrocardiography, chest radiography and routine blood tests. However, strategies 2 and 4 model the emergency physician using the serum natriuretic peptide test in addition to standard investigations. The base case assesses the B-type natriuretic peptide (BNP) test using a rule-out threshold of 100 ng/L (where results of less than 100 ng/L indicate that the patient does not have acute heart failure).[104] A sensitivity analysis assesses the NT-proBNP test using a rule-out threshold of 300 ng/L.

Management of inpatient care (care following diagnostic work-up)

Strategies 1 and 2 model standard management while strategies 3 and 4 model specialist management. In the base case, both standard and specialist management provide cardiology ward beds to 50 per cent of presenting patients whose work-up is positive for acute heart failure, but they differ in respect of the remaining 50 per cent of patients. Table 92 shows how the involvement of cardiology and general medical teams differs between specialist and standard management.

Table 92: Staff and ward setting differences between Specialist and Standard management

Type of management	Ward setting	Care team(s)
Standard	50% cardiology ward	Cardiology team
	50% general medical ward	General medical team
Specialist	50% cardiology ward	Cardiology team
	50% general medical ward	General medical team, and Cardiology team (operating as an 'outreach' team)

The cardiology team operating off the cardiology ward is described as an 'outreach' team.

Both standard and specialist management deal the same way with patients whose diagnostic work-up is negative for acute heart failure: they are admitted to non-cardiology wards and receive care from general medical teams only.

M.2.2.2 Model structure

Structure Overview

A two-part decision analytic model was constructed using Microsoft Excel (Microsoft Corporation, Redmond, WA). Data on individual patient health status and resource utilisation was not available so a cohort approach was chosen in which conservative estimates were obtained from a range of sources. A decision tree was used to divide a starting cohort of 1000 patients into distinct subgroups for which outcomes might be different owing to condition, diagnostic work-up and the resultant

care. Subgroups were fed into a long term model which simulated patient wellbeing between pre-defined health states. Each health state is characterised by distinct resource utilisation and health-related quality of life. The probability of transition between health states was dependent on characteristics of the subgroup, and transition could occur at the end of cycles of three months. The simulation was run through sixteen cycles, totalling four years.

Specialist management and left ventricular systolic dysfunction (LVSD)

The systematic search of the literature identified evidence favouring improved outcomes for patients whose care was lead or had input from specialists in acute heart failure, compared to care solely from non-heart failure specialising physicians.[1,12,23,30,31,76,97,174] The guideline development group judged that the most applicable and highest quality identified source was the National Heart Failure Audit (NHFA), so this was the primary source used for the model[31].

While mortality was an available outcome of the NHFA the guideline development group considered the differential prescribing of LVSD disease-modifying drugs between cardiology teams and general medical teams was the more conservative outcome with which to model. Interventions for patients with LVSD are effective and well established, and the NHFA shows that LVSD is the underlying cause of approximately two-thirds of patients discharged with a diagnosis of acute heart failure.[114,116] However, for the remaining one-third of patients with non-LVSD causes of acute heart failure causes of heart failure, available interventions are comparatively disparate and the treatment effects are difficult to quantify.[104] For this reason this model does not include the impact on health by specialist management for these patients; but as precaution includes their costs.

Non-heart failure causes of dyspnoea

Evidence included in the clinical review shows that 53 per cent of patients presenting to the emergency department with acute dyspnoea, and who are suspected of acute heart failure, do not have acute heart failure.[103] In the model all alternative causes of dyspnoea are combined as a single 'Other condition' with common utility, mortality, readmission risk, and cost. This is a simplification which is discussed more fully in the Limitations and Interpretation section (M.4.2).

The Decision Tree

In order to estimate the expected costs and QALYs of the different strategies it is necessary to differentiate patients according to their true underlying condition, even though this is not necessarily observed in the clinic, because the true underlying cause will determine the effectiveness of the intervention, and because we assume that other conditions are not dealt with by the cardiology team. Therefore the first node of the tree divides patients into those who truly have acute heart failure and those who do not.

The second decision node divides patients with acute heart failure into those with left ventricular systolic dysfunction (LVSD) and those with another cause, because the interventions considered by the model are specific to LVSD.

The third decision node deals with the accuracy of diagnostic work-up because this also dictates the choice of intervention, and the timing of its initiation. Evidence from the clinical review indicates that the accuracy of diagnostic work-up may be improved with the addition of the natriuretic peptide test (Refer to the Diagnosis, Assessment and Monitoring chapter). There are four alternative outcomes of the diagnostic work-up because it is not perfect:

1. The patient truly has acute heart failure and receives a diagnostic work-up positive for AHF (true positive)
2. The patient truly has acute heart failure and receives a diagnostic work-up negative for AHF (false negative)

3. The patient has another condition and receives a diagnostic work-up positive for AHF (false positive)
4. The patient has another condition and receives a diagnostic work-up negative for AHF (true negative)

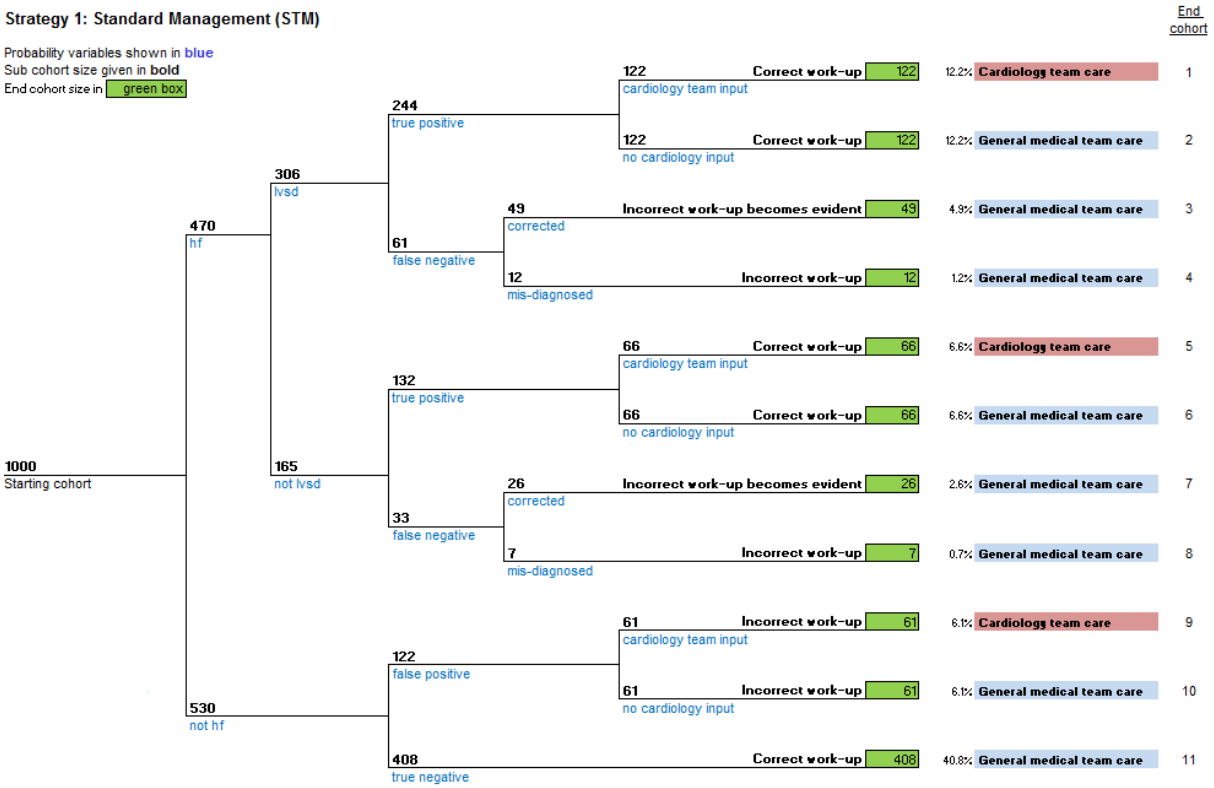
The fourth decision node concerns the later correction of a false work-up and is used to include the reality that the true underlying condition often becomes clear during the hospital stay. This node allows the modelling of an extended hospital stay as a result of a delay in appropriate treatment for patients whose incorrect work-up is not identified.

The fifth and final decision node distributes patients to the type of care arrangement they are to receive on admission, and this is determined by the strategy itself. Patients entering the state transition model can enter into care from a cardiology team or from a general medical team (as described in Table 92); and standard and specialist management strategies have different level of involvement of each team. All patients with a negative diagnostic work-up (correct or incorrect) receive care from a general medical team, irrespective of work-up correction.

Table 93: The decision tree defined 11 cohorts likely to achieve different health outcomes

Subgroup	AHF or not AHF?	LVSD or not LVSD?	Positive or Negative work-up?	False work-up corrected or not?	Cardiology team input or not?
1	Yes	Yes	True positive	N/A	Yes
2				N/A	No
3			False negative	Corrected	No
4				Uncorrected	No
5		No	True positive	N/A	Yes
6				N/A	No
7			False negative	Corrected	No
8				Uncorrected	No
9	No	N/A	False positive	N/A	Yes
10				N/A	No
11			True negative	N/A	No

Figure 205: The decision tree apportioned patients according five sequential decisions



State transition model

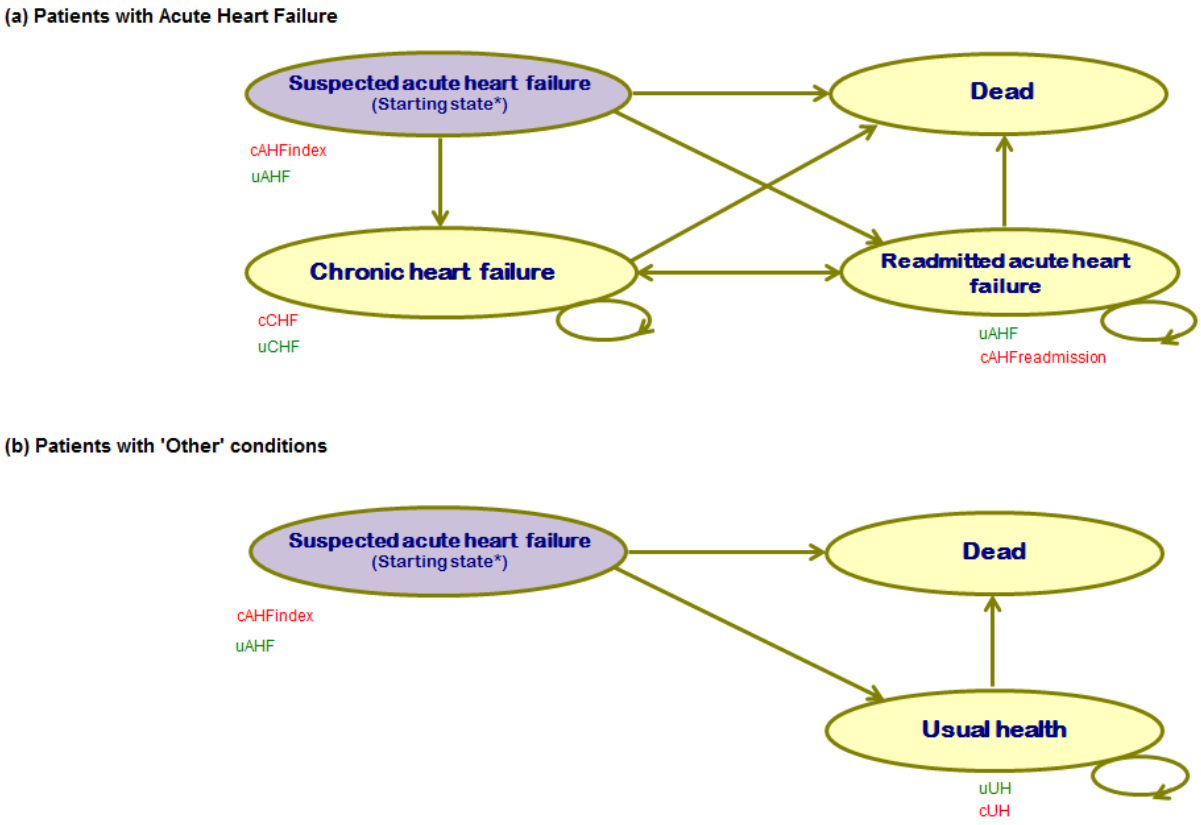
A state transition model was constructed for each of 11 decision tree end-points (described in Table 93 and Figure 205) to calculate the quality-adjusted life-years and costs from the point of hospital admission to the end of the time horizon. In a state transition model a set of mutually exclusive health states are defined that describe what can happen to the population of interest over time. People in the model can only exist in one of these health states at a time. Possible transitions are defined between health states and the probability of transition during a pre-specified time (cycle) is assigned and may be time-dependent.

Figure 206 illustrates the key health states in the model for patients with acute heart failure and for those with other conditions, with the possible transitions between them. Patients who present to the emergency department and who are suspected of acute heart failure but do not have it transition differently (Figure 206 panel b). This was driven by the assumption that these patients would not be admitted for acute heart failure on a subsequent occasion. A 3-month cycle duration was used to reflect a typical period in which a readmission for heart failure might occur. The population entering the model are people who are admitted due to the suspicion of acute heart failure, so all of the simulation population (1,000 patients) start in the 'Suspected acute heart failure' state at cycle one. From this state they can transition to the 'Chronic heart failure', 'Readmission', 'Usual health' or 'Dead' states.

The model was run for sixteen cycles (4 years). For each cycle the relevant cost and utility are applied to the number of patients in each state. The costs and QALYs are then aggregated for all cycles. This was repeated for each of the 11 cohorts defined by the decision tree.

Because each strategy in the model distributes the starting population into the 11 cohorts in different proportions, and because each cohort has a unique set of transition probabilities, the number of patients existing in each health state is different across the strategies at any given time. This method allows the resulting cost and QALY accumulations to be calculated and an incremental analysis can then be performed to identify the most cost effective strategy.

Figure 206: Diagrammatic representation of the state transition model



Key for Figure 206: States of the model are represented by ovals, transitions between states represented by arrows. Circular arrows indicate that patients may remain in the state for consecutive cycles. Quality of life weights, or utilities, (in green) and costs (in red) are specific for each health state. Patients who are not alive do not accrue costs and have zero utility. Transition probabilities are represented by the labels shown in blue. *All patients start in this state and cannot return to it. (a) patients with Acute Heart Failure; (b) patients with other conditions.

The standard limitations of state transition models (also known as Markov models) apply to this model: that is each member of the cohort can undergo only 1 transition per cycle (3-moths); so cannot experience more than 4 hospitalisations per year. State transition models also do not preserve memory of past events, so the risk of experiencing a further readmission is equal whether they have previously experienced 1 readmission or several.

Furthermore, cohort simulation models such as state transition models necessarily represent the costs, quality of life and risk of future readmission of a typical 'average' patient, whilst in practice there is a spectrum of severities.

M.2.2.3 Uncertainty

The model was also built probabilistically to take account of the uncertainty around input parameter point estimates. A probability distribution was defined for each model input parameter. When the model was run, a value for each input was randomly selected simultaneously from its respective probability distribution; mean costs and mean QALYs were calculated using these values. The model was run 1,000 times for the base case and results were summarised. We checked for convergence by plotting the ICER for pair-wise comparisons of strategies on a graph and noted early convergence at approximately 250 iterations.

The way in which distributions are defined reflects the nature of the data. For example, utilities were given a beta distribution, which is bounded by zero and one, reflecting that a mean utility will not be outside this range. Probability distributions in the analysis were parameterised using error estimates

from data sources. Details of the distributional parameters of variables that were probabilistic are detailed in Table 94.

Table 94: Description of the type and properties of distributions used in the probabilistic sensitivity analysis

Parameter	Type of distribution	Properties of distribution
Prevalence of AHF Prevalence of LVSD Sensitivity of work-up test Specificity of work-up test Probability of false negative work-up being identified during the hospital stay Probability of death Probability of drug prescription	Beta	Bounded between 0 and 1. The distribution parameters were calculated as: Alpha=Number of patients experiencing the event Beta=Number of patients not experiencing the event
Mean utility value	Beta	Bounded between 0 and 1. Derived using the method of moments, the distribution parameters were defined as: Alpha = $mean^2$ *(1-(mean/SE^2)-mean Beta = Alpha *((1-mean)/mean)
Mean staff time Unit costs Mean utility decrement	Gamma	Bounded at 0, positively skewed. Derived from mean and its standard error, the distribution parameters were defined as: Alpha = $(mean/SE)^2$ Beta = SE^2/Mean
Hazard ratio of in-hospital death Hazard ratio of drug treatment (mortality and readmission)	Lognormal	Bounded at zero, positively skewed. The mean of the distribution was calculated as follows: Mean = ln(HR) – $(SE)^2/2$ The standard error (SE) of the natural log of the hazard ratio was calculated by: SE = [ln(HRupper 95%CL) – ln(HRlower 95%CL)]/(1.96*2) CL=confidence limit; Ln=natural log; HR=hazard ratio.

Where the parameter source did not report a standard error, or its equivalent, it was conservatively assumed that the standard error was equal to the mean divided by 4. In addition, deterministic sensitivity analyses were undertaken to test the robustness of model assumptions. This was done in two ways: by varying every probabilistic input individually by 10%; by testing pre-selected inputs with alternative estimates from alternative literature sources or expert opinion from the GDG economic subgroup. Each time an input is changed and the analysis rerun to evaluate the impact on results.

M.2.3 Model inputs

M.2.3.1 Evidence base

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 by clinical members of the guideline development group throughout the model's development.

M.2.3.2 Initial cohort settings

In line with the means from the most recent annual national heart failure audit (N = 41,932) the starting age in the model was 75 years for men and 80 years for women; 44% of the starting cohort were female; 65% have LVSD.[31]

M.2.3.3 Baseline event rates

Mortality - LVSD

For patients with LVSD, the baseline mortality (all-cause mortality) was that of the untreated population recorded in the national audits 2009 to 2013, and is illustrated in Figure 207 and shown in Table 95. This data was obtained from a secondary analysis of national heart failure audits 2009-2013.[116] These are patients discharged from hospitals in England and Wales who had not been initiated on drug treatment at the point of discharge.

Figure 207: Four year Kaplan-Meier survival of patients who survived to discharge, LVSD - no treatment (Time is measured in days from discharge, and survival is illustrated as a probability of being alive at time *x*)

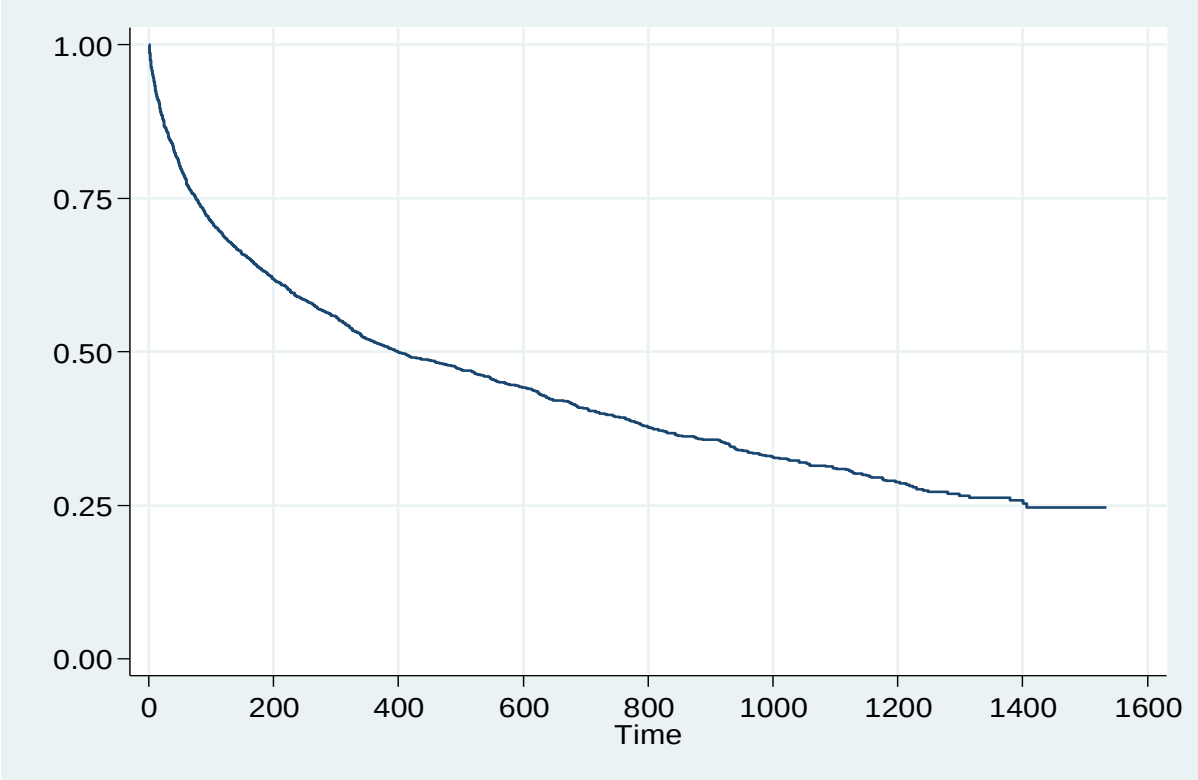


Table 95: Baseline CV-mortality of patients with LVSD (no treatment)[116]

3-month cycle	Probability of survival at the end of the cycle (no treatment) [(a)]	3-month rate of CV-mortality (no treatment)
1	0.72	0.261
2	0.64	0.100
3	0.57	0.086
4	0.52	0.081
5	0.49	0.040
6	0.46	0.050
7	0.43	0.054
8	0.41	0.048
9	0.38	0.051
10	0.37	0.032
11	0.34	0.057
12	0.31	0.074
13	0.29	0.053

3-month cycle	Probability of survival at the end of the cycle (no treatment) [(a)]	3-month rate of CV-mortality (no treatment)
14	0.27	0.072
15	0.26	0.031
16	0.24	0.048

Mortality – Non-LVSD heart failure

For patients with heart failure due to causes other than LVSD, we used a time-dependent mortality rate from the cohort of non-LVSD patients in the National Heart Failure Audit who were seen on a non-cardiology ward.

Mortality – conditions other than heart failure

For patients with other conditions the baseline mortality was the age and gender adjusted all-cause mortality in the general population (Table 96), using Office for National Statistics population estimates and registrations of death for England and Wales.[125,126] The transition probability (Table 97) was calculated from the annual mortality rate using the methodology described in the section headed Computations (page 448).

Table 96: Mortality from all causes in life tables of the general population[125,126]

Item	Males	Females
Proportion of population	54%	44%
Age	75 – 79	80 – 84
Category population in England and Wales (by gender)	810,600	788,100
Deaths from all causes (age categorised)	33,466	41,482

Table 97: Mortality of patients with other conditions

Underlying condition	1-year rate of death from any cause weighted for age and gender	3-month mortality probability of death from any cause
Other	0.0463	1.15%

Readmission for worsening heart failure

For patients with acute heart failure the baseline time-dependent rate of readmission for worsening heart failure was taken from a population-based study of hospitalisations in incident chronic heart failure patients (n = 332) living in the Bromley district of South London.[35] Patients in this 1997 study received an unknown level of LVSD drug therapy, but it was conservatively assumed that this was the baseline rate of readmission for an untreated LVSD population. Beyond two years a Weibull parametric curve was fitted to the available data to extrapolate a readmission rate for years three and four.

M.2.3.4 Relative treatment effects

Mortality - LVSD

Cardiology team treatment effect during the index admission

The national heart failure audit showed the mortality of patients during their index hospital stay is improved when care included input from a cardiologist, other physician with an interest in heart failure, or heart failure specialist nurse.[31] A secondary statistical analysis of the national heart failure audit was supplied by the National Institute for Outcomes Research (NICOR) so that a separate effect could be applied for LVSD patients and so that the control group were patients who had not received

any specialist heart failure or cardiologist care.[115] From this analysis a hazard ratio was calculated for in-hospital mortality when under a general medical team versus a cardiology team; this was 1.94. This ratio was applied to the baseline rate (in-hospital mortality under a cardiology team) to provide the mortality estimates for the index hospital episode (Table 86). Note that the in-hospital mortality of patients under the general medical team care was calculated using a population of patients who had not received *any* input from a physician with an interest in heart failure, a cardiologist, or a heart failure specialist nurse.

In-hospital treatment effect was applied only to the index admission and reflected only a period of 15 days, which approximates the mean index length of hospitalisation in England and Wales.[31] In the base case analysis it was conservatively assumed that there was no survival benefit from having received specialist input for patients with non-LVSD heart failure.

Table 98: Mortality during the index admission (first 15 days of cycle 1)

LVSD drug class	LVSD[(a)]	Non-LVSD[(a)]
Hospitalised period (first 15 days)		
Probability of death *with* cardiology team involvement (baseline)	3.3%	5.3%
Probability of death *without* cardiology team involvement	6.3%	10.1%[(b)]

(a) Adjusted for confounders: Systolic blood pressure; heart rate, haemoglobin; NHYA class; urea; creatinine; serum sodium; serum potassium; age >75; gender; previous COPD, MI, ischemic heart disease, vascular disease.
(b) In the base case analysis 5.3% was used, that is there was assumed to be no survival benefit for patients with non-LVSD heart failure.

Cardiology team treatment effect for the post-discharge period

The national heart failure audit also shows an improvement in post-discharge mortality when care included input from a cardiologist, other physician with an interest in heart failure, or heart failure specialist nurse.[31] However the model based mortality on the probability of receiving an LVSD drug by the time of discharge, and therefore applied survival benefit only to patients with LVSD. For each drug class logistic regression modelling was conducted using the National Heart Failure Audit to estimate the propensity of being prescribed the drug with or without specialist care and controlling for potential confounders (systolic blood pressure; haemoglobin; NHYA class; urea; creatinine; serum sodium; serum potassium; age; gender; previous COPD, MI, ischemic heart disease, vascular disease). An original analysis was conducted for this model by NICOR so that potential confounders were controlled, as this was not otherwise available.[115]

Table 99: Probability of receiving LVSD drug treatment, by class and type of care[116]

LVSD drug class	Care from a Cardiologist[(a)]	Care from a Non-cardiologist[(a)]
Angiotensin Converting Enzyme inhibitor (ACEi) or Angiotensin Receptor Antagonist (ARA) [(b)]	78.0% (n=5493)	60.7% (n=1462)
Beta Blocker (BB)	86.6% (n=5399)	58.6% (n=1433)
Mineralocorticoid Receptor Agonist (MRA)	37.9% (n=5389)	17.9% (n=1444)

(a) Adjusted for confounders: Systolic blood pressure; haemoglobin; NHYA class; urea; creatinine; serum sodium; serum potassium; age; gender; previous COPD, MI, ischemic heart disease, vascular disease
(b) Angiotensin receptor antagonists are also known as angiotensin receptor blockers

Cardiovascular mortality was selected by the guideline development group as the most appropriate effect measure to apply treatment, being the mortality outcome most influenced by established interventions. Effect size estimates were obtained from the literature according to a pre-specified search protocol. In the absence of existing systematic reviews which included the major trials *and* reported the relevant outcomes, we pooled together the results of trials that met the following criteria:

- Placebo-controlled

- All patients have chronic heart failure with reduced left ventricular ejection fraction
- N>=1000 per arm
- Include a relevant outcome (HF admission and/or CV mortality)

We excluded trials that focused on an acute MI population.

Risk ratios from contributing trials were meta-analysed and weight-adjusted according to trial size, and these are shown in Table 100 along with the literature source of effect size. Note that no published meta-analyses were identified whioch met the protocol requirements for the model.

Forest plots of risk ratios for individual trials and their meta-analyses are given below in Figure 208,Figure 209 and Figure 210, and these were converted to hazard ratios using the methodology described in section M.2.4.

Table 100: Cardiovascular-cause mortality hazard ratios of LVSD drugs versus placebo

LVSD drug class	Risk ratio of CV mortality (drug versus placebo) [95% CI]	Trials included in original meta-analysis	Rationale
Angiotensin Converting Enzyme inhibitor (ACEi) or Angiotensin Receptor Antagonist (ARA)	0.91 [0.85, 0.97]	CHARM[182] Val-HEFT[33 50] SOLVD-T[105,169]	Existing published meta-analysis either included trials whose population presented predominantly for acute myocardial infarction, or did not report cardio-vascular mortality or admissions for worsening heart failure. Of the major trials of ACEi versus placebo; TRACE and SAVE were considered to have indirect populations because patients presented with AMI. CONSENSUS was excluded because there were fewer than 1000 patients per arm. A low proportion of patients in SOLVD-Treatment were on background LVSD therapy but this trial represented the model population most closely and reported risk reductions are comparable to that of trials of more medicated populations, albeit in less direct populations. A recent Cochrane meta-analysis met the criteria for use in the model to inform the effect size of the ARA drug class, but did not include two major applicable trials: CHARM-LowLVEF and excluded Val-HEFT.
Beta Blocker (BB)	0.78 [0.71, 0.86]	BEST[2] CIBIS-2 COPERNICUS[129(a)] MERIT-HF[105(b)]	No existing published meta-analyses identified in a systematic review included the four major trials of beta blockers whose population was judged most direct to that of the model (BEST, MERIT-HF, CIBIS-2 and COPERNICUS) and also reported outcomes of interest.. CAPRICORN was excluded an original meta-analysis because it recruited patients with recent acute myocardial infarction, and SENIORS was excluded because it included some patients without reduced LVEF.
Mineralocorticoid Receptor Agonist (MRA)	0.80 [0.65, 0.98]	EMPHASIS[184]	No exiting published meta-analyses identified in a systematic review included the three major placebo trials in the class (RALE, EPHESUS and EMPHASIS); possibly because of the heterogeneity between trial populations. EPHESUS was excluded from original meta-analysis because patients were early post myocardial infarction, and was RALE was excluded because it recruited less than 1000 patients per arm and background beta blocker therapy was very low. Therefore only EMPHASIS was used to inform the treatment effect size for the MRA drug class in the model.

LVSD drug class	Risk ratio of CV mortality (drug versus placebo) [95% CI]	Trials included in original meta-analysis	Rationale

(a) Reported only HF admissions, not CV mortality in the original published analysis.
(b) Reported only CV mortality, not HF admissions in the original analysis

Figure 208: Forest plot of comparison: ACEis and ARAs versus placebo (CV mortality)

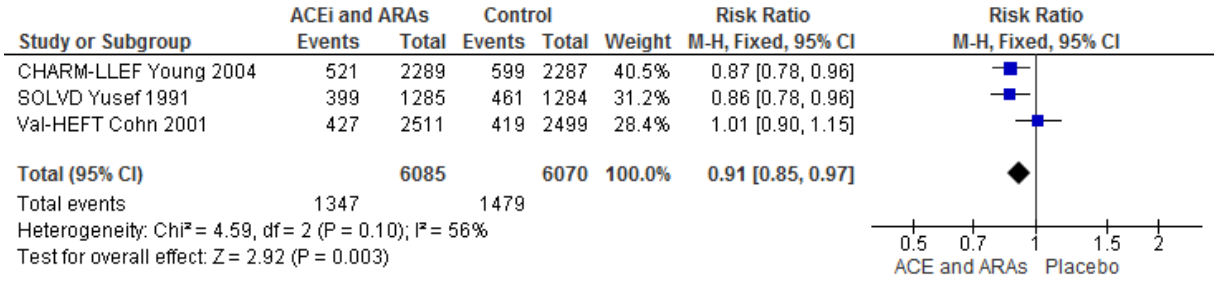


Figure 209: Forest plot of comparison: BBs versus placebo (CV mortality)

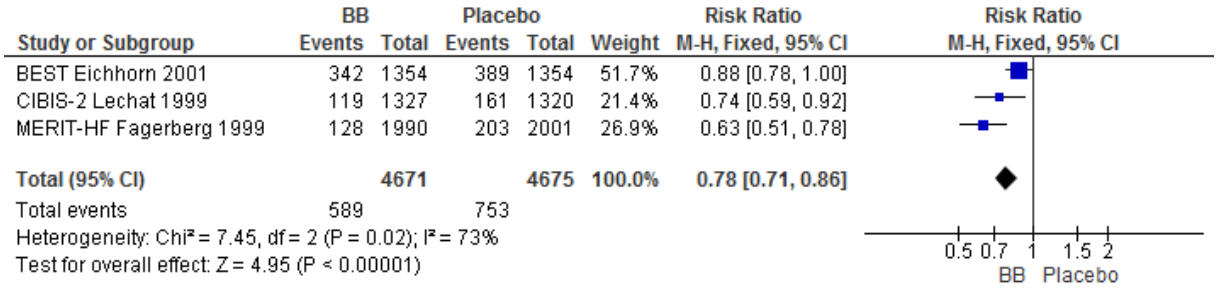
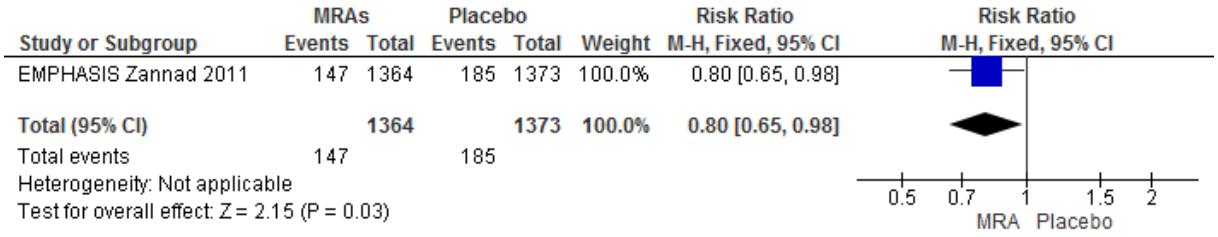


Figure 210: Forest plot of comparison: MRAs versus placebo (CV mortality)



In order to attain the treatment effect of care teams from the therapeutic effect, the cardiovascular mortality hazard ratios of the LVSD drugs were proportionally reduced in accordance with the proportion of patients receiving treatment. Hazard ratios for individual drug classes were multiplied to achieve a combined effect. These adjusted hazard ratios represent the treatment effect of the type of care (cardiology team and general medical team), and are shown in Table 101.

Care hazard ratios were applied to the proportion of deaths in the baseline mortality that were of cardiovascular origin, which was calculated using data from the captopril arm of the ELITE II study (n=1574, mean age 71.5 years), in which 80% (199/250) of patients on captopril who died, died from a cardiovascular cause.[136] This trial was chosen because the National Heart Failure audit does not collect data on cardiovascular deaths and because the mean age of the population was closer to that of our target population than any of the other heart failure trials that have a long enough follow-up.

Table 101: Cardiovascular mortality hazard ratio of type of care versus no LVSD drug

LVSD drug class	Hazard ratio CV mortality: Care from a cardiology team	Hazard ratio CV mortality: Care from a General medical team
Angiotensin Converting Enzyme inhibitor (ACEi)	0.920	0.938

LVSD drug class	Hazard ratio CV mortality: Care from a cardiology team	Hazard ratio CV mortality: Care from a General medical team
or Angiotensin Receptor Antagonist (ARA)		
Beta Blocker (BB)	0.798	0.863
Mineralocorticoid Receptor Agonist (MRA)	0.920	0.962

Mortality –Non-LVSD

In the base case analysis treatment benefits associated with specialist management were not included for patients with heart failure not due to LVSD. However in a sensitivity analysis, survival benefits from the National Heart Failure Audit were included for both in-hospital (hazard ratio=0.51) and post-discharge periods (hazard ratio=0.91).

Readmission for worsening heart failure - LVSD

The treatment effect of the cardiology team versus the general medical team on the risk of readmissions for worsening heart failure was also based on the probability of receiving LVSD treatment by discharge; and as with mortality this effect was only attributed to patients with LVSD.[116] 'Readmission treatment effect' was applied for two years only, beyond which the baseline readmission rate was applied to all.

Table 99 above details the confounder adjusted probability of receiving an LVSD drug treatment by drug class and by the type of care received. Table 102 below shows the risk ratios of readmissions for worsening heart failure by drug class and by the type of care received. The search protocol used to identify evidence to estimate the treatment effect size for cardiovascular mortality was used for heart failure readmission (See Table 88).

Table 103 shows the risk ratios for care type that result when adjustment is made for the probability of receiving the drug. Table 104 details the time dependent probability of readmission (transition probabilities) when the respective hazard ratios are applied to the baseline probability, based on expert clinical opinion.

Table 102: Readmissions for worsening heart failure hazard ratios of LVSD drugs versus placebo

LVSD drug class	Risk ratio of HF readmissions, drug versus placebo	Trials included in original meta-analysis
Angiotensin Converting Enzyme inhibitor (ACEi) or Angiotensin Receptor Antagonist (ARA)	0.80	CHARM[182] Val-HeFT[33,50] SOLVD-T[169]
Beta Blocker (BB)	0.77	BEST[2] CIBIS-2[29] [COPERNICUS[129(a)]] [MERIT-HF[105(a)]]
Mineralocorticoid Receptor Agonist (MRA)	0.65	EMPHASIS[184]

(a) Reported only HF admissions, not CV mortality in the original published analysis.

Table 103: Readmission for worsening heart failure risk ratio by care type versus no LVSD drug

LVSD drug class	Risk ratio for readmission under Cardiology team care	Risk ratio for readmission under General medical team care
Angiotensin Converting Enzyme inhibitor (ACEi) or Angiotensin Receptor Antagonist (ARA)	0.84	0.88

LVSD drug class	Risk ratio for readmission under Cardiology team care	Risk ratio for readmission under General medical team care
Beta Blocker (BB)	0.80	0.87
Mineralocorticoid Receptor Agonist (MRA)	0.87	0.94

Table 104: Transition probability for readmission due to worsening heart failure for patients with LVSD by type of care given (shown with baseline probability)

Cycle of 3-months	Baseline probability of a HF readmission	Probability of a readmission having had Cardiologist team care	Probability of a readmission having had Non-cardiologist team care
1	0.18	0.10	0.13
2	0.08	0.05	0.06
3	0.07	0.04	0.05
4	0.06	0.03	0.04
5	0.03	0.02	0.02
6	0.06	0.03	0.04
7	0.02	0.01	0.02
8	0.06	0.04	0.04
Beyond 2 years the baseline probability of readmission was extrapolated but no treatment effect was applied			
9	0.04	Equal to baseline	
10	0.04		
11	0.03		
12	0.03		
13	0.03		
14	0.03		
15	0.03		
16	0.03		

Readmission for worsening heart failure – Non-LVSD

Non-LVSD heart failure patients were assumed to be readmitted, but with the same probability as LVSD patients under a general medical team. It was conservatively assumed that the cardiology team would not reduce re-admission rates for these patients.

Re-admissions were not modelled for patients without heart failure.

M.2.3.5 Diagnostic work-up

The sensitivity and specificity of the serum BNP test (and NT-proBNP) were taken from a diagnostic meta-analysis based on evidence identified in the systematic review undertaken for the guideline (See Diagnosis, assessment and monitoring chapter). In the base case the sensitivity and specificity of the physician using standard clinical investigations was taken from the receiver-operator curve from the Breathing Not Properly (BNP) multinational study.[103] Sensitivity and specificity were read at the point of greatest test accuracy: where the curve is closest to 100% sensitivity and 100% specificity. Input parameters for both methods of diagnostic work-up are shown in Table 105.

Table 105: Sensitivity and specificity of the diagnostic work-up using the BNP test and the physician using standard clinical investigations

Method diagnostic work-up	Specificity	Sensitivity	Source
BNP Test	0.95	0.63	Guideline meta-analysis. See Diagnosis, Assessment and Monitoring chapter
Physician with access to standard clinical investigations (ECG, E-ray, clinical examination)	0.80	0.77	Breathing Not Properly Trial.[103] This trial was the only large trial included in the clinical review to report a ROC curve for the diagnostic accuracy of the physician working without an NP test.

The prevalence of acute heart failure in the presenting population was also taken from the Breathing Not Properly trial and used to calculate the distribution of correct (true) and incorrect (false) working diagnoses.[103] The resulting distributions are shown in Table 106.

Table 106: Distribution of true and false diagnoses, by those with and without acute heart failure (A. BNP test; B. Physician using standard investigations)

A. BNP test

Test result / True underlying condition	AHF	Not AHF
Test positive	45% (true positives)	20% (false positives)
Test negative	2% (false negatives)	33% (true negatives)

B. Physician using only standard clinical investigations

Test result / True underlying condition	AHF	Not AHF
Test positive	38% (true positives)	12% (false positives)
Test negative	9% (false negatives)	41% (true negatives)

An incorrect (false) diagnostic work-up was judged to have a detrimental consequence for the following parameters in the model:

- Length of index admission (all patients)
- Mortality during hospitalisation (LVSD cause AHF patients only)
- Mortality post-discharge (LVSD cause AHF patients only)
- Risk of readmission for worsening heart failure (LVSD cause AHF patients only)

The key assumptions regarding the size of detriment were based on expert clinical opinion of the guideline development group, and are shown in Table 107.

The guideline development group also advised that 20 per cent of patients incorrectly labelled as not having acute heart failure would leave hospital without their AHF being diagnosed. No patients leave the hospital with a false positive diagnosis, since all patients deemed to be positive for AHF after work-up are assumed to have an echocardiogram during the admission.

Table 107: Key assumptions of detrimental effect for incorrect (false) diagnostic work-up

Assumption	Expert consensus of opinion	Population applied to
Increased index admission length of hospitalisation		
False positive	2 days	• Patients with AHF

Assumption	Expert consensus of opinion	Population applied to
False negative	2 days	• Patients with AHF
Mortality		
False positive	No detriment	
False negative (if uncorrected*)	Equivalent to untreated population post-discharge, applied for 3 months (cycles 1)	• Patients with LVSD (No detriment for non-LVSD AHF)
Risk of readmission for worsening heart failure		
False positive	No detriment	
False negative (if uncorrected*)	Elevated to 33% risk during the first 3 months post-discharge (cycle 1)	• Patients with LVSD

*80% of patients with a false negative work-up may be identified during the hospitalised period and their treatment plan corrected

M.2.3.6 Utilities

The utility attributed to patients in the 'Chronic heart failure' health state was based on the distribution of NYHA classes (I-IV) in the BATTLESCARRED trial and the class utility weights from a directly applicable study included in the clinical review.[88,166]

The utility attributed to the 'Suspected acute heart failure' and 'Readmitted acute heart failure' health states was equal to the chronic state less the disutility associated with a single episode of acute heart failure. This decrement was calculated from EQ5-D data collected in the SHIFT trial which showed an acute admission for worsening heart failure was associated with a 6 week dip in utility: adjusted to a 3-month cycle this was 0.064.[156]

Patients with other underlying conditions were given the same utility as those in the acute heart failure states for the index cycle and that of chronic heart failure state for all other cycles. These cycles are described as the 'Usual health' state. This matching of utility is a simplification, but since the model structure does not include different costs or effects for this group (between strategies) the utility is arbitrary.

The health state utilities used in the model are shown in Table 108.

Table 108: Health state utilities

Health state	Utility score
Heart failure patients	
Suspected AHF	0.688
Readmitted AHF	0.688
CHF	0.752
Other condition patients	
Suspected AHF	0.688
Usual health	0.752
Dead	
Dead	0

M.2.3.7 Resource use and costs

Diagnostic work-up costs

The cost of standard clinical investigations (ECG, radiography and clinical exam) was not included because they are common to all strategies. The cost of serum natriuretic peptide testing in the acute setting was included for all presenting patients in strategies 2 and 4. The cost of echocardiograms

was included for all patients with a diagnostic work-up suggesting acute heart failure, plus those patients with acute heart failure whose work-up was negative, but whose condition becomes evident during hospitalisation.

The unit cost of serum natriuretic peptide testing and echocardiograms is given in Table 109.

Table 109: Unit cost of included diagnostic tests/imaging

Diagnostic	Unit cost	Source
BNP or NT-proBNP test	£28.13	St Georges NHS Trust
Departmental simple trans-thoracic echocardiogram	£62.60	NHS Reference costs schedule 2012-13[42]

Acute care staffing costs

The cost of staffing standard management and specialist management arrangements of care were not available in the literature, so original evidence was sought.

The guideline development group selected the general physician, the cardiologist and the heart failure specialist nurse (HFSN) as the key roles whose time requirement would differ between standard and specialist arrangements of inpatient heart failure care. Other roles and disciplines were considered but excluded on the basis that the level and nature of their input would not differ.

On behalf of the NCGC, the National Institute for Cardiology Outcomes Research (NICOR) conducted an online survey of 145 NHS Trusts in England and NHS Health Boards in Wales in order to estimate how much time each discipline spent on patient related activities per patient per week in cardiology and general medical wards. The guideline development group formulated the questions. 53 Trusts submitted usable responses. Estimates are shown in Table 110.

Table 110: Time spent on patient related activities by discipline

Ward setting	Discipline	Median time on patient related activities (minutes per patient per week)
Cardiology ward	Cardiologist	20
	General physician	23
	HFSN	30
General medical wards (and other non-cardiology wards)	Cardiologist	20
	General physician[(a)]	15
	HFSN	30

(a) The general physician was assumed to consult only 20% of AHF patients based on cardiology wards

The cost per hour of a Cardiologist and General physician is the same, and Consultant grade was selected as a conservative simplification. The HFSN was assumed to be NHS Agenda for Change Band 7. Hourly rates were obtained from the Personal Social Services Research Unit Handbook 2013 and are shown below in Table 111.[37]

Table 111: Unit cost of hospital staff included in the model

Staff role and discipline	Unit cost (per hour)[(a)]
Consultant Cardiologist	£132
Consultant General physician	£132
Heart failure specialist nurse	£52

(a) Sourced from the Personal Social Services Research Unit Handbook 2013[37]

Acute care bed costs

The model included hospital costs other than staff, treatments and diagnostic tests in order to reflect the additional cost of extended length of hospitalisation resultant from incorrect diagnostic work-up. The weighted unit cost for a bed day was calculated from the NHS reference costs EB03H and EB03I (Heart Failure or Shock with and without complications) and was £232.09.[42] The median length of stay was 8 days, and the consequence of incorrect diagnosis was an additional 2 days stay, as advised by the guideline development group.[31]

Drug therapy costs

The cost of LVSD disease modifying drug therapy was included for LVSD patients during the hospitalised periods and the non-hospitalised periods. Three classes of LVSD drug were included because they form the gold standard of care in this group of patients. The weighted average cost per day was calculated using the Prescription Cost Analysis for England 2012.[74] The cost of each drug was weighted by number of prescriptions (although it was not possible to isolate this to prescriptions specifically for heart failure). Unit costs are shown in Table 112 and 90 day treatment costs, by management strategy are given in Table 113.

Table 112: Unit cost of LVSD drugs

Drug class	Drugs	Weighted average cost per day[(a)]
ACE inhibitor / Angiotensin receptor antagonist	Enalapril maleate, lisinopril, perindopril erbumine, ramipril / candesartan cilexetil, irbesartan, losartan potassium, valsartan	£0.11
Beta blocker	Bisoprolol fumarate, carvedilol, nebivolol	£0.07
Mineralocorticoid receptor antagonist	Eplerenone, spironolactone	£0.20

(a) Prescription cost analysis England 2012[74]

Table 113: LVSD drug treatment cost by care received

Type of care given	90-day LVSD treatment cost[(a)]
Cardiology team	£24.56
General medical team	£16.18

(a) Based on the probability of being prescribed treatment (National heart failure audit)[116]

The cost of other standard drugs such as diuretics was not included because the level of their use was assumed to be equivalent in standard and specialist management.

Follow-on costs

Costs arising during non-hospitalised periods, as a result of an acute admission, were judged to include the following on the basis that they would differ between standard and specialist management:

LVSD drug therapy (described above)

Hospital out-patient visits

Primary care GP visits

Community HFSN visits

The cost of cardiac rehabilitation was not included because the uptake of this service is low (11%) and cost is uncertain.[31] Although it is likely specialist management would lead to some increased take-up of rehabilitation, the health benefits of this increased take-up as well as the costs are not included in this model.

The occurrence and frequency of health system contacts other than acute admissions were specific to whether or not referral had been made to follow-on services. The national heart failure audit 2013 provides the probability of being referred to cardiology and heart failure nurse services - Table 114.

Table 114: Probability of being referred to follow-on services[31]

Follow-on service	Cardiology team on a cardiology ward (NHFA 2012-13)	Cardiology team on a general ward (inferred)	General medical team on a general ward (NHFA 2012-13)
Cardiology follow-up	71%	50%	22%
Heart Failure nurse follow-up[(a)]	68%	71%	23%

(a) HFSN follow-up was costed as a home visiting based service

The frequency of service contacts and associated use of tests for referred patients based on the expert clinical opinion of the guideline development group, and is given in Table 115.

Table 115: Number of follow-on service contacts per annum

Follow-on service/type of contact	Receiving service	Not receiving service
Cardiology follow-up		
Outpatient visits (first year)	2	0
Outpatient visits (subsequent years)	1	0
NP tests (first year)	2	0
Blood tests (first year)	2	0
Heart Failure nurse follow-up		
Community HFSN visits	4	0
GP visits	3	7

The unit costs of follow-on services and tests are given in Table 116.

Table 116: Unit cost of follow-on services

Follow-on service/type of contact	Unit cost	Source
GP visit	£37	Personal Social Services Research Unit Handbook 2013.[37] 11.7 minute consultation.
Community HFSN visit	£42	Personal Social Services Research Unit Handbook 2013.[37] Nurse Specialist (Community), 1 hour.
Hospital outpatient visit	£131	NHS Reference costs schedule 2012-13.[42] Cardiology outpatient visit.

M.2.3.8 Parameter distributions

The point estimates, selected distribution, and the distribution parameters for each input variable of the probabilistic model are shown in Table 117.

1 **Table 117: Overview of parameters and parameter distributions used in the model**

Parameter description	Point estimate	Probability distribution	Distribution parameters
Diagnosis parameters			
Prevalence of AHF in patients presenting to ED with acute dyspnoea suspected of AHF	47%	Beta	α = 722, β = 864
Prevalence of LVSD in patients admitted for AHF	65%	Beta	α = 18628, β = 10030
Sensitivity of working diagnosis without NP	80%	Beta	α = 578, β = 144
Specificity of working diagnosis without NP	77%	Beta	α = 556, β = 166
Sensitivity of working diagnosis with NP	95.1%	Beta	α = 3560590, β = 182278
Specificity of working diagnosis with NP	62.7%	Beta	α = 299152, β = 177813
Probability of an FN being corrected	80%	Beta	α = 2.4, β = 0.6
Baseline mortality			
In-hospital mortality, with cardiologist input - LVSD	3.3%	Beta	α = 372, β = 10905
In-hospital mortality, with cardiologist input – Non-LVSD	5.3%	Beta	α = 205, β = 3667
Ratio of CV to all-cause deaths	0.796	Beta	α = 1253, β = 321
Ratio of worsening HF to all-cause readmissions	0.459	Beta	α = 294, β = 495
Treatment effect			
Hazard ratio in-hospital mortality, General medical vs cardiologist input: LVSD	1.94	Log Normal	Point estimate = 1.94, se(LnHR) = 0.09
Hazard ratio in-hospital mortality, General medical vs cardiologist input: Non-LVSD	1.95	Log Normal	Point estimate = 1.95, se(LnHR) = 0.11
Hazard ratio post-discharge CV mortality ACEi/ARA vs placebo	0.898	Log Normal	Point estimate = 0.848, se(LnHR) = 0.04
Hazard ratio post-discharge CV mortality BB vs placebo	0.767	Log Normal	Point estimate = 0.818, se(LnHR) = 0.12
Hazard ratio post-discharge CV mortality MRA vs placebo	0.788	Log Normal	Point estimate = 0.783, se(LnHR) = 0.04
Risk ratio post-discharge HF readmission ACEi/ARA vs placebo	0.800	Log Normal	Point estimate = 0.790, se(LnHR) = 0.03
Risk ratio post-discharge HF readmission BB vs placebo	0.770	Log Normal	Point estimate = 0.740, se(LnHR) = 0.06
Risk ratio post-discharge HF readmission MRA vs placebo	0.650	Log Normal	Point estimate = 0.710, se(LnHR) = 0.02
Probability of ACEi treatment: Cardiology team	78%	Beta	α =4285 , β = 1208
Probability of ACEi treatment: General medical team	61%	Beta	α = 887, β = 575
Probability of BB treatment: Cardiology team	87%	Beta	α = 4676, β = 723
Probability of BB treatment: General medical team	59%	Beta	α = 840, β = 593
Probability of MRA treatment: Cardiology team	38%	Beta	α = 2042, β = 3345
Probability of MRA treatment: General medical team	18%	Beta	α = 258, β = 1186
Resource parameters			
Mins/pt/wk Cardiologist on a cardiology ward	20	Gamma	Point estimate = 20, se = 2.92
Mins/pt/wk Cardiologist on a non-cardiology ward	20	Gamma	Point estimate = 20, se = 2.8
Mins/pt/wk Non-cardiologist on a cardiology ward	15	Gamma	Point estimate = 15, se = 4.15
Mins/pt/wk Non-cardiologist on a non-cardiology ward	23	Gamma	Point estimate = 23, se = 2.68
Mins/pt/wk HFSN on a cardiology ward	30	Gamma	Point estimate = 30, se = 7.53
Mins/pt/wk HFSN on a non-cardiology ward	30	Gamma	Point estimate = 30, se = 7.06
Proportion of cardiology ward pts seen by a non-cardiologist	0.2	Gamma	Point estimate = 0.2, se = 0.05
Median length of index stay (days)	8.0	Gamma	Point estimate = 8.0, se = 2
Length of stay penalty for false working diagnoses (days)	2.0	Gamma	Point estimate = 2.0, se = 0.5
Unit cost parameters			
Echocardiogram	63.60	Gamma	Point estimate = 63, se = 15.65
Bed day	232.09	Gamma	Point estimate = 232, se = 58.02
Natriuretic peptide test (BNP)	28.13	Gamma	Point estimate = 0.28, se = 7.03
Consultant hour	132	Gamma	Point estimate = 0.132, se = 33.00
Heart failure specialist nurse hour	52	Gamma	Point estimate = 0.52, se = 13.00
Utility parameters			
Dis-utility for 3-months in AHF	0.064	Gamma	Point estimate = 0.064, se = 0.016
Utility score for CHF	0.752	Beta	α = 966, β = 318

M.2.4 Computations

The model was constructed in Microsoft Excel 2010 and was evaluated by cohort simulation. Time dependency was built in by cross-referencing age as a respective risk factor for mortality.

Patients start in cycle 1 in the 'Suspected acute heart failure' state. Patients with true acute heart failure moved to either to the 'Chronic heart failure' state, the 'Readmitted acute heart failure' state, or the 'Dead' state at the end of each cycle as defined by the mortality and readmission transition probabilities. Patients with underlying conditions other than heart failure moved to the 'Usual health' state or the 'Dead' health state only.

Transition probabilities for mortality and readmission were derived from a review of the literature. A fixed hazard ratio was applied to baseline probabilities according to the characteristics of each of the eleven end cohorts defined by the decision tree. Hazard ratios were calculated from risk ratios.

Mortality and readmission rates were converted into transition probabilities for the respective cycle length (3 months). The probability of death over the follow-up period of the source data was necessary converted into a rate before being converted into a probability appropriate for the cycle length. The above conversions were done using the following formulae:

$Selected\ rate\ (r) = \frac{-\ln(1-P)}{t}$	Where *P*=probability of event over time *t* *t*=time over which probability occurs
$Transition\ Probability\ (P) = 1 - e^{-rt}$	Where *r*=selected rate *t*=cycle length (3 months)
$Hazard\ ratio\ (HR) = \frac{\ln(1-RR.p)}{\ln((1-p)}$	Where *p*=probability of event *in the control group* RR=risk ratio

Life years for the cohorts were computed each cycle. Quality-adjusted life years for the cohorts were computed for each cycle by multiplying the number of individuals in each health state at the end of the year by the respective utility. QALYs were then discounted to reflect time preference (discount rate = 3.5%). The total discounted QALYs were the sum of the discounted QALYs for each cycle.

Costs per cycle were summed in the same way as QALYs. Costs were discounted to reflect time preference (discount rate = 3.5%) in the same way as QALYs using the following formula:

Discount formula:

$\text{Discounted total} = \frac{\text{Total}}{(1+r)^n}$	Where: *r*=discount rate per annum *n*=time (years)

The total number of QALYs and resource costs accrued by each cohort was recorded. The total cost and QALYs accrued by the cohort was divided by the number of patients in the population to calculate a cost per patient and QALYs per patient.

The mean costs (and QALYS) for each strategy were then calculated as the product of the proportion of people in each of the 11 cohorts and the mean costs (and QALYs) of each of those cohorts.

M.2.5 Sensitivity analyses

One-way deterministic sensitivity analyses

A series of one-way sensitivity analyses were conducted, each time varying parameters which were identified by the guideline development group as being either uncertain, subject to significant variation in clinical practice, or thought to significantly influence the incremental results.

In addition, one-way sensitivity analyses were conducted on all sourced input parameters by varying the point estimate by +/- 10%. This assisted with the identification of parameters for univariate testing.

Threshold: the effect of varying the cost-effectiveness threshold from £20,000 per QALY gained to £30,000 per QALY gained was also assessed.

M.2.6 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 plausible results were generated for given inputs. The model was peer reviewed by an experienced health economist; this included systematic checking of the model calculations.

M.2.7 Estimation of cost effectiveness

The widely used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER). This is calculated by dividing the difference in costs associated with two alternatives by the difference in QALYs. The decision rule then applied is that if the ICER falls below a given cost per QALY threshold the result is considered to be cost effective. If both costs are lower and QALYs are higher the option is said to dominate and an ICER is not calculated.

$$ICER = \frac{Costs(B) - Costs(A)}{QALYs(B) - QALYs(A)}$$

Where: Costs(A) = total costs for option A; QALYs(A) = total QALYs for option A

Cost-effective if:
- ICER < Threshold

When there are more than two comparators, as in this analysis, options must be ranked in order of increasing cost then options ruled out by dominance or extended dominance before calculating ICERs excluding these options. An option is said to be dominated, and ruled out, if another intervention is less costly and more effective. An option is said to be extendedly dominated if a combination of two other options would prove to be less costly and more effective.

It is also possible, for a particular cost-effectiveness threshold, to re-express cost-effectiveness results in term of net monetary benefit (NMB). This is calculated by multiplying the total QALYs for a comparator by the threshold cost per QALY value (for example, £20,000) and then subtracting the total costs (formula 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.

$$Net\ Monetary\ Benefit(X) = \left(QALYs(X) \times \lambda\right) - Costs(X)$$

Where: λ = threshold (£20,000 per QALY gained)

Cost-effective if:
- Highest net benefit

Both methods of determining cost effectiveness will identify exactly the same optimal strategy. For ease of computation NMB is used in this analysis to identify the optimal strategy.

Results are also presented graphically where total costs and total QALYs for each diagnostic strategy are shown. Comparisons not ruled out by dominance or extended dominance are joined by a line on the graph where the slope represents the incremental cost-effectiveness ratio.

M.2.8 Interpreting Results

NICE's report 'Social value judgements: principles for the development of NICE guidance[117] sets out the principles that GDGs should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- The intervention costs less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

As we have several interventions, we use the NMB to rank the strategies on the basis of their relative cost-effectiveness. The highest NMB identifies the optimal strategy at a willingness to pay of £20,000 per QALY gained.

M.3 Results

M.3.1 Base case probabilistic results

M.3.1.1 Decision tree outputs

The proportional distribution of patients into the 11 cohorts is given in Table 118 for each strategy. The resultant requirement for echocardiography is shown in Table 119, along with the number of NP tests. The proportion of patients receiving care by each staff type is given in Table 120.

By definition there was no difference in the distribution of patients between strategies and 1 and 3, and 2 and 4 except for the strategy requirement to discriminate by cardiology team involvement.

Distributions in the NP strategies 2 and 4 differ from the standard work-up strategies 1 and 3. Redistribution with the NP test is present in all four outcomes.

Table 118: Proportional distribution of patients by strategy resultant from the decision tree (split by underlying condition, cause, diagnostic work-up, work-up correction and consequent type of care given)

Sub-group	Subgroup description	Strategy 1 STM	Strategy 2 STM-NP	Strategy 3 SPM	Strategy 4 SPM-NP
1	LVSD True positive, Cardiology team input	12.2	14.5	24.4	29.1
2	LVSD True positive, No cardiology team input	12.2	14.5	0	0
3	LVSD False negative, Corrected, No cardiology team input	4.9	1.2	4.9	1.2
4	LVSD False negative, Not corrected, No cardiology team input	1.2	0.3	1.2	0.3
5	Non-LVSD True positive, Cardiology team input	6.6	7.8	13.2	15.6
6	Non-LVSD True positive, No cardiology team input	6.6	7.8	0	0
7	Non-LVSD False negative, Corrected, No cardiology team input	2.6	0.6	2.6	0.6
8	Non-LVSD False negative, Not corrected, No cardiology team input	0.7	0.2	0.7	0.2
9	Not-HF False positive, Cardiology team input	6.1	9.9	12.2	19.8

Sub-group	Subgroup description	Strategy 1 STM	Strategy 2 STM-NP	Strategy 3 SPM	Strategy 4 SPM-NP
10	Not-HF False positive, No cardiology team input	6.1	9.9	0	0
11	Not-HF True negative, No cardiology team input	40.8	33.2	40.8	33.2

Table 119: Diagnostic test utilisation by strategy (1000 patients at index admission)

Strat	Strategy description	Number of NP tests	Number of Echocardiograms
1	Standard management	0	573
2	Standard management with NP	1000	663
3	Specialist management	0	573
4	Specialist management with NP	1000	663

Table 120: Proportion of patients receiving care by staff type at index admission

Strat	Strategy description	Cardiologist		HFSN		General physician	
		Cardio ward	General ward	Cardio ward	General ward	Cardio ward	General ward
1	Standard management	249	0	249	0	50	751
2	Standard management with NP	322	0	322	0	64	678
3	Specialist management	249	249	249	249	50	502
4	Specialist management with NP	322	322	322	322	64	355

M.3.1.2 Mortality

Survival curves are given below according to the underlying condition, cause, work-up, work-up correction and care received (Figure 211 and Figure 212).

Figure 211: 4-year survival curve for patients with LVSD cause AHF

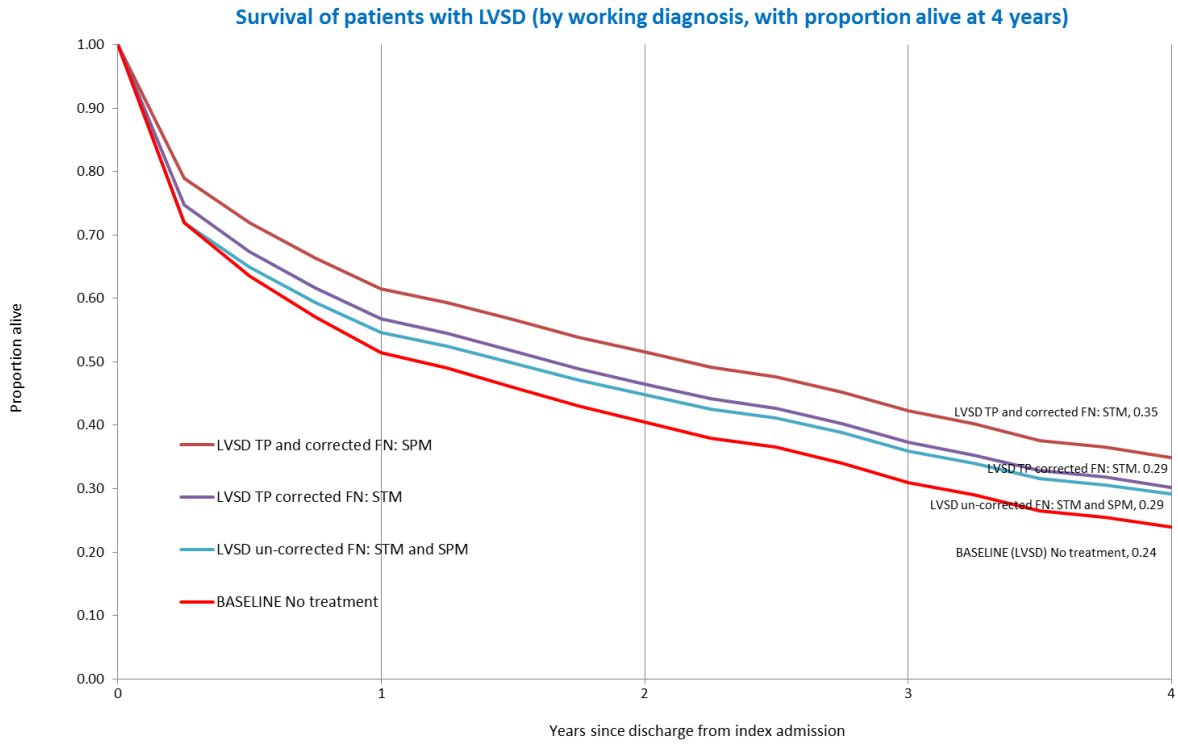
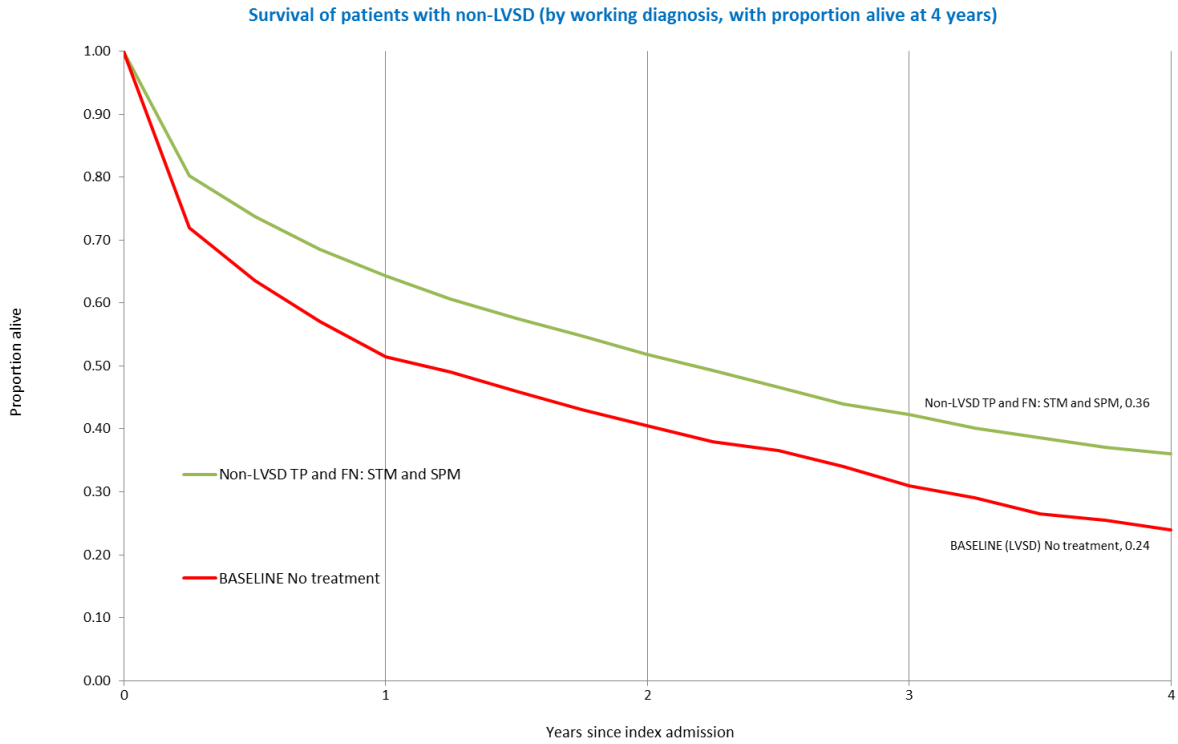


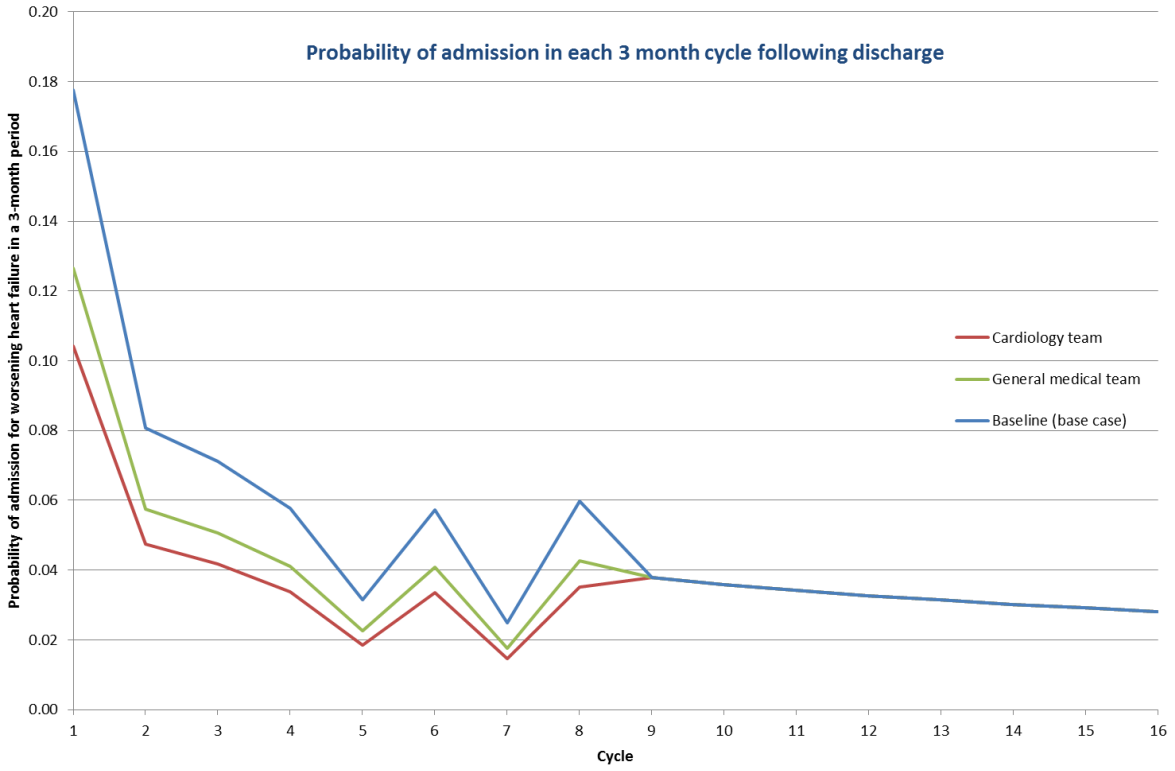
Figure 212: 4-year survival curve for patients with non-LVSD cause AHF



M.3.1.3 Readmissions for worsening heart failure

Figure 213 below shows the reduction in the probability of readmission for worsening heart failure in the 4 years post discharge from the index admission. The hazard ratio for patients with care input from the cardiology team is greater because of their higher likelihood of prescribing LVSD drugs. Note that patients with non-LVSD cause heart failure are given the same probability of readmission as patients with no cardiology team involvement.

Figure 213: Probability of readmission for cardiology team and general medical team, next to baseline probability which is assumed from year 3



M.3.1.4 Life-years and QALYs

The total life-years and total quality-adjusted life-years are shown in Table 121. The most QALYs are achieved in strategy 4 where the QALY increases from natriuretic peptide testing and specialist management are combined.

Table 121: Life-years and Quality-adjusted life years by strategy

Strat	Strategy description	Life years	QALYs
1	Standard management	3.146	2.206
2	Standard management with NP	3.151	2.210
3	Specialist management	3.169	2.222
4	Specialist management with NP	3.178	2.229

M.3.1.5 Disaggregated costs

Table 122 provides a break-down of costs for respective strategies.

Table 122: Cost of components of care by strategy (£ per patient)

Strategy		Work-up	Index admission	Re-admissions	Drugs and visits	Total
1	STM	£35	£2,011	£342	£272	£2,661
2	STM-NP	£69	£2,018	£336	£283	£2,706
3	SPM	£35	£2,031	£335	£312	£2,713
4	SPM-NP	£69	£2,044	£328	£331	£2,771

Strategies 2 and 4, which use thenatriuretic peptide test as part of diagnostic work-up, have the highest work-up cost. The cost of the index (initial) hospital admission is higher for specialist management strategies, but the total cost of subsequent readmissions is lower in specialist management strategies compared to their corresponding standard management strategy. The cost of LVSD drugs and consequent visits to other healthcare professionals is higher in specialist strategies.

M.3.1.6 Probabilistic incremental analysis

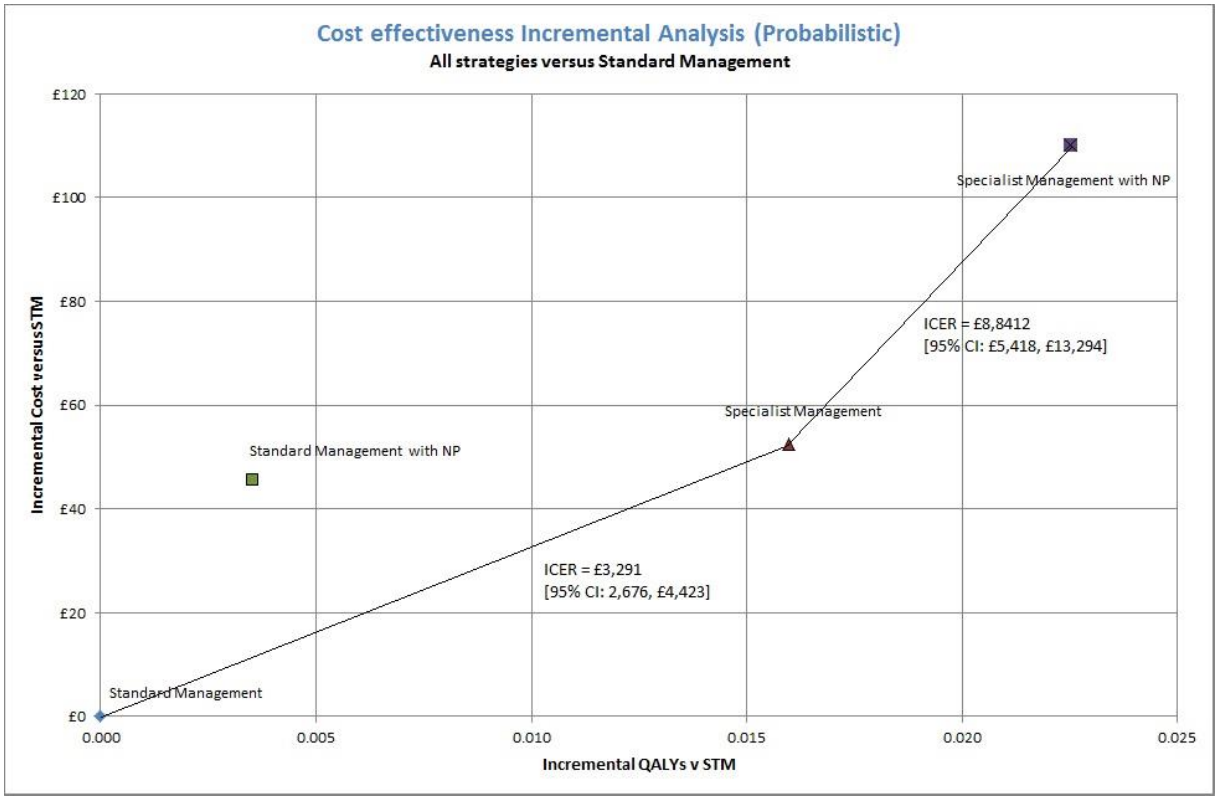
In the incremental analysis of the probabilistic model (Table 123) Standard management is found to be the least cost effective strategy.The most cost effective strategy is Specialist management with NP, which was found to be the optimal strategy in all 1000 model simulations.

Table 123: Net monetary benefit at £20,000 per QALY, with rank and probability of the strategy being the most cost effective

Strategy		Net monetary benefit	Rank	Probability the strategy is the most cost-effective at £20,000 per QALY
1	STM	£41,461	4	0%
2	STM-NP	£41,485	3	0%
3	SPM	£41,727	2	0%
4	SPM-NP	£41,801	1	100%

Figure 214 illustrates the results of the incremental analysis on the cost effectiveness plane, where for each strategy the difference in costs versus strategy 1 are plotted against the difference in QALYs. Specialist management is more cost-effective than standard management (£3,291 per QALY gained); and specialist management with NP is more cost-effective than specialist management (£8,812 per QALY gained). Standard management with NP is extendedly dominated by both specialist management and specialist management with NP.

Figure 214: Incremental costs plotted against incremental QALYs (the cost effectiveness plane)



Abbreviation: ICER = incremental cost effectiveness ratio (cost per QALY gained); NP = natriuretic peptide; QALY = Quality-adjusted life year; STM = Standard Management

M.3.1.7 Deterministic incremental analysis

The incremental analysis of the deterministic model is shown in Table 124. Rank order of most cost effective strategy was unchanged and incremental costs and QALYs showed 98.6% conformity with the deterministic model.

Table 124: Net monetary benefit at £20,000 per QALY, with rank

Strategy		Net monetary benefit at £20,000 per QALY	Rank
1	STM	£41,085	4
2	STM-NP	£41,114	3
3	SPM	£41,361	2
4	SPM-NP	£41,440	1

M.3.2 Sensitivity analyses

M.3.2.1 Fixed threshold analysis

The sensitivity of findings to fixed changes of +/-10% in the probabilistic input variables is shown below. Figure 215 shows the sensitivity in the comparison of standard management versus standard management with NP (an illustration of the variables sensitive in the NP analysis). Figure 216 shows the sensitivity in the comparison of specialist management versus standard management with NP (an illustration of the variables sensitive in the care management analysis).

Figure 215: Tornado diagram showing the tolerance the ICER to changes to a fixed +/-10% change in input variables: STM-NP versus STM (NP analysis)

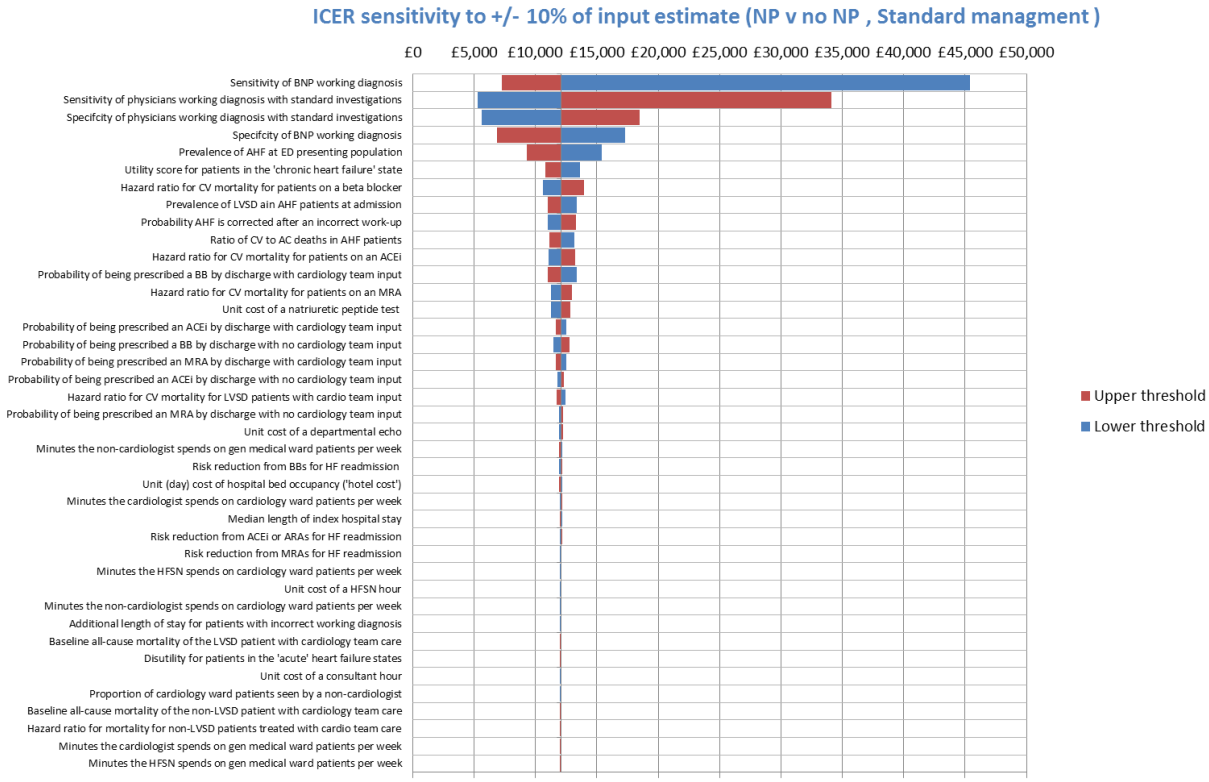
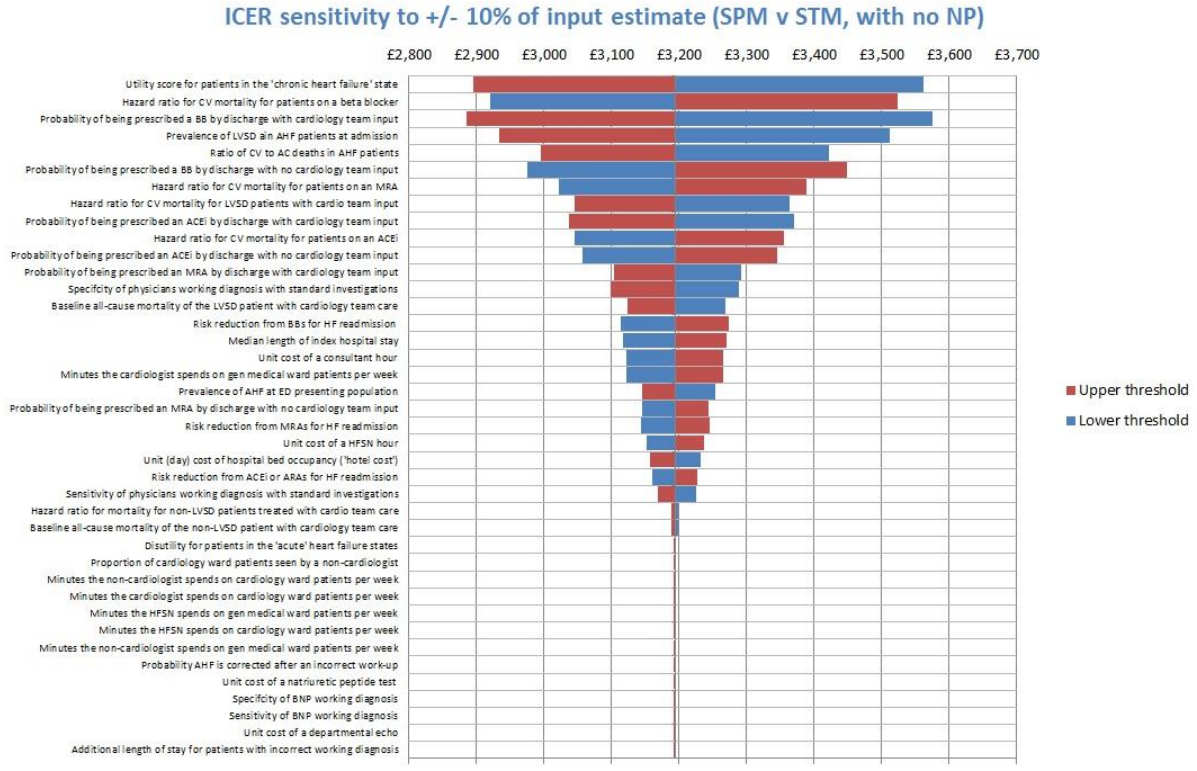


Figure 216: Tornado diagram showing the tolerance of the ICER to changes to a fixed +/-10% change in input variables: SPM versus STM (Specialist management analysis)



M.3.2.2 Univariate sensitivity analysis

The results of the univariate (one-way) sensitivity tests of the deterministic findings are detailed in Table 125. In each case the test examines a less conservative estimate for the input variable.

Table 125: Univariate deterministic analysis

Test No.	Test	Base case value(s)	Test value(s)	ICER 2 v 1 STM-NP v STM (Cost per QALY gained)	ICER 3 v 1 SPM v STM (Cost per QALY gained)	ICER 4 v 1 SPM-NP v STM (Cost per QALY gained)	Optimal strategy
0	**Base case (Probabilistic)**	-	**-**	**£12,942**	**£3,291**	**£4,895**	**SPM with NP**
0	**Base case (Deterministic)**	-	**-**	**£12,067**	**£3,277**	**£4,739**	**SPM with NP**
Natriuretic peptide testing analysis							
1	NT-proBNP test used instead of BNP test	BNP Sens: 95% Spec: 63%	NT-proBNP Sens: 99% Spec: 43%	£21,356	n/a	£6,800	SPM with NP
2	Physician work-up accuracy matched to BNP sensitivity	Sens: 80% Spec: 77%	Sens: 95% Spec: 30%	STM-NP dominates STM	n/a	SPM-NP dominates STM	SPM with NP
3	Physician work-up accuracy matched to BNP specificity	Sens: 80% Spec: 77%	Sens: 87% Spec: 63%	£405	n/a	£2,920	SPM with NP
4	Mortality and readmission penalty from incorrect work-up of patients with AHF: removed	3 month period of no LVSD treatment and 33% readmission risk	As for true work-up	£15,737	n/a	£5,080	SPM with NP
5	Length of stay penalty for incorrect work-ups: decreased/increased	2 days	0 days	£11,512	n/a	£4,652	SPM with NP
			4 days	£12,622	n/a	£4,825	SPM with NP
6	Proportion of patients with AHF with incorrect work-up who are corrected during the hospital stay	80%	100%	£15,413	n/a	£5,035	SPM with NP
Specialist management analysis							
7	In-hospital mortality benefit from Cardiology team input: 15 day benefit removed	Cardiology team to general medical team hazard ratio: 1.9 Survival of LVSD patients with correct work-up (STM/SPM) at: 1 year: 57/62% 2 years: 47/52% 4 years: 30/35%	Cardiology team to general medical team hazard ratio: 1.0 Survival of LVSD patients with correct work-up (STM/SPM) at: 1 year: 57/58% 2 years:47/49% 4 years: 30/33%	£23,061	£6,686	£9,838	SPM with NP
8	Difference in probability of being prescribed LVSD drugs (between cardiology team and general medical team): halved	Difference: ACEi: 17% BB: 28% MRA: 20% Survival of LVSD patients with correct work-up (STM/SPM) at: 1 year: 57/62% 2 years: 47/53% 4 years: 30/35%	Difference: ACEi: 9% BB: 14% MRA: 10% Survival of LVSD patients with correct work-up (STM/SPM) at: 1 year:57/60% 2 years: 47/50% 4 years: 31/33%	£16,956	£4,844	£6,982	SPM with NP
9	Post discharge survival informed by the national audit estimates instead of probability of LVSD drug (arguably includes a broader range of effects as well as including non-LVSD patients. E.g. effect of cardiology follow-up, community nursing, cardiac rehabilitation)	Survival of LVSD patients with correct work-up (STM/SPM) at: 1 year: 57/62% 2 years: 47/53% 4 years: 30/35%	Survival of LVSD patients with correct work-up (STM/SPM) at: 1 year: 60/68% 2 years: 47/58% 4 years: 31/44%	£6,056	£1,772	£2,437	SPM with NP

10	Time spent on patient related activities per patient per week by the Cardiology team: doubled	Mins/pt/week (cardiology ward/general ward) Cardiologist: 20/20 HFSN: 30/30 Gen physician: 15/23	Mins/pt/week (cardiology ward/general ward) Cardiologist: 40/40 HFSN: 60/60 Gen physician: 15/23	£,12,431	£4,209	£5,891	SPM with NP
11	Post discharge survival advantage of Specialist management: applied for only 1 year	Survival of LVSD patients with correct work-up (STM/SPM) at: 1 year: 57/62% 2 years: 47/53% 4 years: 30/35%	Survival of LVSD patients with correct work-up (STM/SPM) at: 1 year: 57/62% 2 years: 47/52% 4 years: 32/35%	£14,291	£3,931	£5,706	SPM with NP
12	Baseline events and treatment effect from all-cause risk instead of cardiovascular specific mortality and heart failure specific readmission	CV mortality and HF readmission 1 year: 57/62% 2 years: 47/53% 4 years: 30/35%	All-cause mortality and all-cause readmission 1 year: 57/62% 2 years: 47/52% 4 years: 30/35%	£12,150	£2,832	£4,379	SPM with NP
13	Proportion of patients with a positive work-up who are admitted to a cardiology ward bed in *standard* management: reduced	50%	25%	£18,036	£3,415	£4,464	SPM with NP
14	Proportion of patients with a positive work-up who are admitted to a cardiology ward bed in *specialist* management: increased	50%	75%	£12,067	£3,070	£4,577	SPM with NP
15	Proportion of patients in general ward beds who receive input into care from the cardiology team (i.e. extent of outreach service)	100%	75%	£12,067	£3,277	£5,101	SPM with NP
			50%	£12,067	£3,277	£5,727	SPM with NP
			25%	£12,067	£3,277	£7,074	SPM with NP
16	Cost of follow-on services: GP visits removed for patients not seen by a HFSN team	7 visits	0 visits	£12,918	£4,339	£5,768	SPM with NP
17	Cost of ITU transfers: included	0%	Cardiology team care: 3.6% General medical team care: 1.4%	£12,333	£3,586	£5,041	SPM with NP

M.3.2.3 Analyses of specific scenario

Use of the NT-pro-BNP test

When the deterministic univariate analysis was run for NT-proBNP all 17 tests maintained *specialist management with NP* testing as the optimal strategy.

Extended time horizon

A 10 year time horizon was assessed whereby baseline mortality and readmission rates were extrapolated. The readmission treatment effect was limited to two years as in the base case but the effect of treatment on mortality was applied continuously. The net monetary benefit and associated rank of most cost-effectice startegy over a 10 year horizon is shown in Table 114.

Table 126: 10 year time horizon: Net Monetary Benefit and Rank (deterministic)

Strategy		Net Monetary Benefit at £20,000 per QALY	Rank
1	STM	£74,639	4
2	STM-NP	£74,732	3
3	SPM	£75,237	2

4	SPM-NP	£75,441	1

M.4 Discussion

M.4.1 Summary of results

An original economic model with conservative assumptions found both specialist heart failure management and NP testing to be effective but more costly than standard management. The health gain was large enough to be considered cost effective for the NHS. In the probabilistic model the cost per QALY gained was £4,895 for specialist management plus NP testing compared with standard management.

Univariate sensitivity analysis of the deterministic model, in which the key variables (mortality, risk of re-admission, resource use, time-horizon, and proportion of patients receiving care in the specialist ward) were significantly inflated or deflated individually, all found specialist management to be cost effective versus standard management. For example, when the benefits of treatment were assumed to last only for one year, specialist management was still highly cost-effective. The only sensitivity analyses in which the cost per QALY gained was above a threshold of £20,000 were in the context of standard management in the NP analysis. Specifically when the in-hospital mortality benefit of the cardiology team was removed; and when test sensitivity and specificity was used from the guideline's meta-analysis of NT-proBNP studies. In both cases, the cost per QALY was less that £30,000. In the context of specialist management none of the sensitivity tests raised the cost per QALY above £20,000.

Probabilistic sensitivity analysis in which all input base case variables were simultaneously varied confirmed this stability: in all 1000 simulations specialist management with NP testing was the optimal strategy. i.e. there is a 100% probability that specialist management with NP is the most cost-effective of the four strategies.

M.4.2 Limitations and interpretation

M.4.2.1 Specialist management

The base case model was conservative, in particular:

- No benefits from specialist care were assumed for patients with acute heart failure of non-LVSD cause (even though costs of specialist management were attributed to these patients)
- The time horizon was only 4 years (not a lifetime) and therefore the QALY gain is likely to be under-estimated.
- Follow-up post-discharge was assumed to be substantially higher for patients seen by the specialist team, for which costs were attributed but not benefits.

Differences in mortality and heart failure readmission were predicated on differences in the number of patients on effective LVSD drug therapy (beta blockers, ace inhibitors and mineralocorticoid receptor antagonists) at discharge.

The proportion of patients prescribed drugs in cardiology ward and non-cardiology ward settings was taken from a non-randomised source - the national heart failure audit - but controlling for 13 different patient characteristics including NYHA score. 97% of Trusts (n=147) and 92% of hospitals (n=198) participated in the audit. Overall, NICOR estimate that 60% of English heart failure admissions are captured in the 2012/13 analyses, which is a reasonable coverage.

The relative treatment effects (hazard ratios for cardiovascular mortality and heart failure readmission) were obtained from RCT evidence in chronic heart failure populations.

In addition to this drug treatment effect (post-discharge) a mortality effect during the hospital stay for cardiologist versus non-cardiologist teams was also estimated, this too was calculated by NICOR from the National Heart Failure Audit. The variable rate of implementation of effective LVSD therapeutics, and the specialist nursing care offered by the HF team must play a major role in creating the striking effect observed. However, the data is not from a randomised controlled trial and one major con-founder is that, the type of patient triaged/selected to be admitted under a cardiologist will tend to be less likely to have significant other co-morbidities that may hinder therapy, besides potentially being older. The NICOR analysis has attempted to eliminate this bias in this treatment effect by controlling for various confounders but this is unlikely to be as unbiased as randomised evidence. In a sensitivity analysis, we remove the within-hospital mortality effect but specialist management is still cost-effective based on the post-discharge drug treatment effect alone.

Cardiology ward versus outreach

Both the 'specialist' and 'standard' arrangements of care that were modelled, assumed half of patients admitted for heart failure were admitted to cardiology wards – but the specialist arrangement operated an 'outreach' specialist team for other wards. In doing so, access to specialists is increased from half to all patients admitted for acute heart failure.

The model describes a specialist heart failure service which comprises of a cardiologist specialising in heart failure and a specialist nurse, both of whom operating on the cardiology ward and outreaching across the hospital. For most patients, it will be less costly and optimal for their management to be cared for on the cardiology ward. However, for some patients, other medical needs will mean that they are best cared for in another specialty ward but with outreach from the heart failure team.

In sensitivity analyses the cost of specialist management was varied by changing the ratio of patients on cardiology wards to those being seen by outreach. Regardless of the ratio assumed, specialist management was always cost-effective compared to standard management. Thus, if patients can be admitted to a cardiology ward then it is likely to be less costly than outreach. But in situations where access to a cardiology ward bed is not possible, then access to a specialist heart failure team through outreach across the hospital is still cost-effective.

M.4.2.2 NP testing

The consequences (mortality and risk of readmission from heart failure causes) of false positive and false negative diagnostic work-ups were based on expert clinical opinion:

- A 2 day length of stay penalty for patients who are falsely assessed as being likely/unlikely to have AHF work-up
- Of the few people who have AHF but are missed by the physician/NP test at work-up, 80% will be identified during the admission (a conservative assumption with regard to the benefits of NP testing). For the 20% that are not identified, it is assumed that they are correctly diagnosed at 3 months and only at that point those with LVSD are put on to appropriate drugs (beta blockers, ace inhibitors and mineralocorticoid receptor antagonists). These 20% were also assumed to have a 1/3 probability of re-admission during those 3 months.

A point estimate of the diagnostic accuracy was not found for the physician in the absence of NP testing. Instead there was a ROC curve (a set of alternative pairs of sensitivities and specificities) from the Breathing Not Properly Trial. The point on the curve closest to the point of perfect accuracy was taken as the base case and other points on the curve were looked at in sensitivity analyses. In the

development of the model the GDG noted the difficulty of estimating the sensitivity and specificity of the physician using standard clinical investigations but sensitivity analyses found that the optimal strategy was satisfactorily robust, except when physician sensitivity is greater than that 84%.

In the base case, where NP testing is assumed to be less specific (but more sensitive) than the physician not using NP testing, the model predicts an increase in the number of echocardiograms performed by NP testing, but this cost is justified by the QALY gains as represented by the low incremental cost effectiveness ratio. In a sensitivity analysis where a different point is taken from the ROC curve and the physician diagnosis is assumed to have greater sensitivity than in the base case, here NP testing reduces the number of echocardiograms ordered and is still the most cost-effective option.

The consequences of a false positive

In the base case analysis there were more false positives during work-up with NP testing than with no testing. There was no health loss associated with a false positive in the model. However, all positive work-ups (true and false) were assumed to lead to echocardiography for diagnosis, so any negative impact may be limited. If echocardiography is conducted quickly, then any health risk will be minimised.

But as noted above, if we are on a the sensitive end of the ROC curve for physician diagnosis then the number of false positives would be reduced instead of increased - sensitivity analysis 2.

M.4.3 Generalisability to other populations

The model population was assumed to be an **incident AHF population**, that is, it excludes patients presenting whose chronic heart failure has been well established. However, since the data on the proportion of patients receiving LVSD treating drugs and the effectiveness of those drugs was not specific to incident cases, the conclusions with regard to specialist management are likely to hold for the prevalent population. With regard to NP testing, the value of testing may be less for prevalent cases than for incident ones, since the diagnostic uncertainty is less. However, one may postulate, in the absence of evidence, that there may be some value in testing, e.g. to assess the urgency of the need for echocardiography.

It was conservatively assumed that only patients with LVSD would benefit; this meant that the results of the model were based on the results of randomised trials of drug treatment. However, the observational mortality evidence from the NHFA suggested that after controlling for potential confounders, there was a significant reduction in mortality (almost half) for **non-LVSD HF patients** seen on a cardiology ward. In a sensitivity analysis, it was shown how including this survival benefit makes specialist management even more cost-effective.

M.4.4 Comparisons with published studies

M.4.4.1 NP testing

The model was similar to the 6 published economic evaluations in finding NP testing to be cost-effective. However these studies based on cohort studies found NP testing to be cost saving, whereas the model base case suggested an increase in cost. This might be explained by the point on the ROC curve that was chosen for the physician accuracy – see M.4.2.2 for further discussion. Perhaps in those studies the physicians (in the absence of NP testing) were more sensitive but less specific than what was assumed in the base case analysis here and therefore sensitivity analysis 2 is more comparable to them than the base case analysis. In hospitals where echocardiography is easily accessed one might expect the physician to err on the side of caution and order an echocardiogram

and therefore in these hospitals the physicians will (prior to echocardiography) be more sensitive and less specific in the work-up than those in hospitals where echocardiography is more restricted.

M.4.4.2 Specialist management

There were no economic evaluations found assessing specialist management.

The resultant four-year survival in the model for patients with LVSD seen by specialists was 35%, compared to 30% for those not receiving specialist input. This was derived by combining drug treatment effects with the incidence of drug prescribing from the National Heart Failure Audit. There were 2 other sources of mortality evidence in the clinical evidence review for specialist versus non-specialist management, both cohort studies. Of these the Auerbach[12] study had a somewhat greater survival benefit (0.8) but the Lowe study recorded higher mortality with specialist management (RR=1.6). But both these studies were older, in less relevant contexts and with smaller sample sizes than the National Heart Failure Audit.[31]

M.4.5 Conclusions

- One original cost-utility analysis found that a specialist management service was cost-effective compared with standard management for patients presenting to the emergency department with acute dyspnoea and suspected to have an incident acute heart failure. This analysis was assessed as directly applicable with minor limitations.
  - In a context of NP testing: £3,403 per QALY gained
  - In a context of no NP testing: £3,291 per QALY gained
- One original cost-utility analysis found that NP was cost-effective compared with no NP testing for patients presenting to the emergency department with acute dyspnoea and suspected to have an incident acute heart failure. This analysis was assessed as directly applicable with minor limitations.
  - In a context of specialist management: £8,812 per QALY gained
  - In a context of non-specialist management: £12,942 per QALY gained

Appendix N: Unit costs

N.1 Invasive Monitoring

Device type	Product name	Unit cost*
Pulmonary arterial catheter	Catheter arterial pulmonary thermo-dilution Pentacath	£48.27

**Cost was sourced from the NHS supply chain catalogue, accessed April 2013.*

N.2 Opiates

Intervention; with assumed dose/duration of treatment for typical AHF patient [a]	Unit cost of pharmacological intervention [b]	Additional Costs; Administration/monitoring/prevention of complications
Morphine Injection: one 10mg unit daily	Cost per day= £15.00 Cost per 15-day course = £225	Administration by injection

(a) Doses were sourced from the BNF (March 2013

(b) Unit costs were sourced from the NHS drug tariff (March 2013) unless otherwise stated. VAT is not included in these unit costs.

N.3 Vasodilators

Intervention; with assumed dose/duration of treatment for typical AHF patient [a]	Unit cost of pharmacological intervention [b][c]	Additional Costs; Administration/monitoring/prevention of complications [d]	Notes
Glyceryl trinitrate (GTN) Tablet: Two 300 mcg doses; first day only IV: Up to 48 hours infusion at 200 mcg/min	Cost per tablet = £0.03 Cost per tablet course = £0.05 Cost per infusion day = £95.40 Cost per infusion course = £190.80	Administered as a sublingual tablet or by intravenous infusion	Tablet cost sourced from the NHS drug tariff (March 2013). IV unit cost sourced from the BNF (March 2013).
Isosorbide dinitrate (ISDN) Tablets: 160 mcg daily IV: 10 mg/hour for up to 48 hours	Cost per tablet = £0.18 Cost per tablet day = £1.41 Cost per tablet course = £2.82 Cost per infusion day= £64.63 Cost per infusion course = £129.26	Administered as a tablet or by intravenous infusion	Tablet cost sourced from the NHS drug tariff (March 2013). IV unit cost sourced from MIMS (March 2013).
Sodium nitroprusside 92.3 mcg/min mean dose (Cohn1982) for 24 hours	Cost per 1 day course = £27.06	Administered by intravenous infusion	Sodium nitroprusside is an unlicensed product produced as a 'special' for hospital use. The cost presented is that provided by Royal Sussex County Hospital pharmacy

(a) Doses were sourced from the BNF (March 2013).
(b) Unit costs were sourced from the NHS drug tariff (March 2013) unless otherwise stated. VAT is not included in these unit costs.
(c) Dose estimates assume the dose at the top end of the BNF dose range (where given) unless stated otherwise.
(d) Additional Costs: These are intravenously infused drugs whose administration will incur additional cost. There may be common or severe side effects which impact on health/resource utilisation.

N.4 Inotropes and Vasopressor

N.4.1 Vasopressor drug costs

Intervention: with assumed dose/duration of treatment for typical AHF patient (a)	Unit cost of pharmacological intervention (b)	Additional costs: Administration / monitoring / prevention of complications(c)
Norepinephrine 0.2-1.0mcg/kg/min (d)	Cost per 20 ml ampoule (1 mg/ml base) = £6.35 Cost per day = £31.75 Cost per 7 day course = £222.25	Administered by intravenous infusion via central venous catheter

N.4.2 Inotrope drug costs

Intervention: with assumed dose/duration of treatment for typical AHF patient (a)	Unit cost of pharmacological intervention (b)	Additional costs: Administration / monitoring/ prevention of complications(c)	Notes
Milrinone lactate 50 mcg/kg followed by IV infusion at 0.375–0.75 mcg/kg/min for 48–72 hrs	Cost per 10 ml ampoule (1 mg/mL) = £19.91 Cost per day = £159.25 Cost per 3 day course = £457.84	Administered by intravenous infusion	Drug unit cost sourced from MIMS (March 2013)
Dobutamine 2.5–10 mcg/kg/min, adjusted according to response	Cost per 50 ml vial (5 mg/ml) = £7.50 Cost per day = £37.50 Cost per 7 day course = £217.50	Administered by intravenous infusion	
Dopamine hydrochloride 2–5 mcg/kg/min initially	Cost per 5 ml ampoule; 40 mg/ml = £0.90; 160 mg/ml = £3.40 Cost per day = £3.40 Cost per 7 day course = £17.00	Administered by intravenous infusion	

(a) Pharmacological Intervention: Information informing dose is sourced from the BNF unless stated otherwise. Duration of treatment for these interventions may be variable so they are presented as single day and one week costs. Costs are calculated for a 70kg patient.

(b) Source of unit costs: In this instance they are sourced from the BNF (March 2013) unless otherwise stated in the notes. Where dose ranges are given, the upper range limit is selected for cost calculation.

(c) Additional Costs: These are intravenously infused drugs whose administration will incur additional cost. There may be common or severe side effects which impact on health/resource utilisation.

(d) Dose taken from the European Society of Cardiology guideline.2012

N.5 Mechanical Ventilation: Cost of Adult Critical Care

Level of critical care (number of supported organs)	National Average Unit Cost per Day (£) (a)
ICU 6 or more	570
ICU 5	279
ICU 4	264
ICU 3	280
ICU 2	333
ICU 1	312

(a) Calculated from the NHS National Schedule of Reference Costs 2011-2012 by the NCGC (National average unit cost for period of care divided by the average days per period)

N.6 Ultrafiltration (Diuretics) unit costs

Drug	Preparation	Cost/day (a)	Cost/year	Indication
Furosemide	Tablets	£0.02 (b)	£8	Oedema
	Tablet	£0.02 (b)	£8	Oedema
	Ampoule (d)	£0.27 (c)	£99	Oedema
	Ampoule (d)	£3.00 (c)	£1,095	Oedema
Bumetanide	Tablets	£0.10 (b)	£35	Oedema
	Tablets	£0.45 (b)	£163	Oedema
	Injection	£0.45 (c)	£163	Oedema
Torasemide	Tablets	£0.49 (b)	£179	Oedema
	Tablets	£1.22 (b)	£443	Oedema

Drug	Preparation	Cost/day (a)	Cost/year	Indication
Amiloride	Tablets	£0.07 (b)	£24	Congestive heart failure
Bendroflumethiazide	Tablets	£0.05 (b)	£17	Oedema
Indapamide	Tablets	£0.04 (b)	£14	Essential hypertension

(a) Maintenance doses are used
(b) Sourced from the National drug tariff database, December 2012
(c) Sourced from the British National Formulary (BNF), November 2012
(d) By intramuscular injection or slow intravenous injection (rate of administration, see Cautions above), initially 20–50 mg, increased if necessary in steps of 20 mg not less than every 2 hours; doses greater than 50 mg by intravenous infusion only; max. 1.5 g daily.

N.7 Beta-blocker drug costs

Intervention with assumed dose [a]	Unit cost of pharmacological intervention [b]	Additional Costs considerations Administration/monitoring/prevention of complications [c]
Bisoprolol fumarate 10mg once daily	Cost per 14 day course = £0.62	None
Carvedilol 25mg twice daily	Cost per 14 day course = £1.57	None

(a) The maximum indicated dose for an 80kg patient. Based on licensed information described in BNF65.
(b) Unit costs are sourced from the NHS electronic drug tariff, NHS Business Services Authority (Accessed August 2013)
(c) These are orally administered drugs whose administration is not anticipated to incur costs additional to that of routine staff time. There may be common and/or severe side effects which impact on health/resource utilisation which are not considered here

N.8 ACE inhibitor drug unit costs

Intervention; with assumed dose [a]	Unit cost of pharmacological intervention [b]	Additional Costs considerations; Administration/monitoring/prevention of complications [c]
Captopril Maximum 150mg daily	Cost per 28 day course = £2.91	None
Cilazapril Maximum 5mg daily	Cost per 28 day course = £12.51	None
Enalapril maleate Maximum 40mg daily	Cost per 28 day course = £2.34	None
Lisinopril hydrochloride Maximum 35mg daily	Cost per 28 day course = £1.79	None
Ramipril Maximum 10mg daily	Cost per 28 day course = £1.62	None

(a) The maximum indicated dose for an 80kg patient. Based on licensed information described in BNF65.
(b) Unit costs are sourced from the NHS electronic drug tariff, NHS Business Services Authority (Accessed August 2013)
(c) These are orally administered drugs whose administration is not anticipated to incur costs additional to that of routine staff time. There may be common and/or severe side effects which impact on health/resource utilisation which are not considered here

N.9 Aldosterone antagonist drug unit costs

Intervention; with assumed dose [a]	Unit cost of pharmacological intervention [b]	Additional Costs considerations; Administration/monitoring/prevention of complications [c]
Spironolactone Maximum 50mg daily	Cost per 28 day course = £1.98	None

Intervention; with assumed dose [a]	Unit cost of pharmacological intervention [b]	Additional Costs considerations; Administration/monitoring/prevention of complications [c]
Eplenerone Maximum 50mg daily	Cost per 28 day course = £42.72	None

(a) The maximum indicated dose for an 80kg patient. Based on licensed information described in BNF65.
(b) Unit costs are sourced from the NHS electronic drug tariff, NHS Business Services Authority (Accessed August 2013)
(c) These are orally administered drugs whose administration is not anticipated to incur costs additional to that of routine staff time. There may be common and/or severe side effects which impact on health/resource utilisation which are not considered here

N.10 Mechanical assist device unit costs

Device class	Make and model	Unit cost of device (£)	Other
Ambulatory LVAD (a)	Thoratec HeartMate II (second generation device)	£94,200	Implant procedure = £19,628
Intra-aortic balloon counter pulsation device (IABP) (b)	Not stated	£603 (c)	Less invasive procedure compared to ambulatory LVAD
Percutaneous LVAD (pVAD) (b)	Abiomed Impella	£8,222 (c)	Less invasive procedure compared to ambulatory LVAD, but requires console rental at approximately £565/day for e.g. 7 days

(a) Unit costs taken from Mereno2012[108]
(b) Unit costs taken from Cochran2002[32]
(c) Converted from 2002 US dollars to UK pounds using 2012 purchasing power parities[128]

Appendix O: Research recommendations

O.1 In patients with acute heart failure, congestion and worsening renal function, does the addition of low-dose dopamine to standard therapy lead to greater diuresis and renal protection compared with adding placebo to standard therapy?

A randomised trial should be conducted to investigate whether the addition of low-dose dopamine to standard therapy leads to more clinically and cost effective decongestion in people admitted to hospital for treatment of decompensated heart failure. The study should aim to investigate the diuretic effect of dopamine as well as effects on renal function.

One of the most common and difficult to manage problems arising during the initial treatment of patients with acute heart failure is an inadequate response to iv diuretic therapy (i.e. failure to relieve congestion), often associated with worsening renal function. This combination frequently leads to a prolonged in-patient stay and is associated with higher in-patient mortality and higher post-discharge mortality and readmission rates. The best treatment for this combination of problems is unknown although there is theoretical and experimental evidence that low-dose dopamine is may improve renal blood flow, as well as enhance sodium and water excretion. Clinical trials to date have not yet resolved whether in some patients, the use of low-dose dopamine actually results in improved decongestion and shorter hospital stays.

Table 127: Dopamine PICO

Criteria for selecting high-priority research recommendations PICO question	
Population	Patients with acute heart failure and reduced LVEF, congestion, despite at least 24 hours of intravenous diuretic therapy and worsening renal function. co-morbidities and risk factors: **include systemic hypertension, diabetes mellitus, COPD, atrial fibrillation** gender: **Males and Females** age: **All age groups** ethnic group: **All ethnic groups** specific inclusion criteria: **LVEF less than or equal to 40%; congestion defined as at least 2 of: peripheral oedema, ascites, hepatic enlargement, elevated JVP; worsening renal function defined as a rise in creatinine of greater than or equal to 26.5 µmol/l [0.3 mg/dl].** specific exclusion criteria: **Acute myocardial infarction; inability to give informed consent e.g. due to cognitive impairment** health status or setting **in-patient** (**secondary care**)
Intervention	Dopamine infusion at a rate or 2.5 µg/Kg/min for a period of 48-72 hours.
Comparator(s)	Matching placebo infusion. Patients in both treatment groups will need a bladder catheter in situ for the duration of the infusion
Outcome	1. Urine volume 2. Body weight (as a measure of fluid loss) 3. Relief of congestion (measured using a standard score) 4. Change in creatinine 5. Change in cystatin C 6. Change in BNP (as a measure of left ventricular wall stress) 7. Days from randomisation to discharge 8. Thirty day mortality rate 9. Thirty day re-admission rate length of follow-up required: **30 days**
Study Design	Randomised, double-blind, placebo controlled, parallel group.
Timeframe	No timeframe

Dopamine: Table 2 Criteria to support prioritisation of key research recommendations

Potential Criterion	Explanation
Importance to patients or the population	One of the most common and difficult to manage problems arising during the initial treatment of patients with acute heart failure is an inadequate response to iv diuretic therapy (i.e. failure to relieve congestion), often associated with worsening renal function. This combination frequently leads to a prolonged in-patient stay and is associated with higher in-patient mortality and higher post-discharge mortality and readmission rates. The best treatment for this combination of problems is unknown although there is theoretical and experimental evidence that low-dose dopamine is "reno-protective" and may improve renal blood flow, as well as enhance sodium and water excretion. There is also some inconsistent and non-robust clinical evidence that low-dose dopamine might be beneficial in patients.
Relevance to NICE guidance	If low-dose dopamine were to enhance diuresis, relieve congestion while at the same time preserving or improving renal function it would be recommended in future guidelines and widely used in practice.
Relevance to the NHS	As stated above the combination of inadequate relief of congestion and worsening renal function is common in acute heart failure and is associated with longer hospital stays and greater morbidity and mortality. As heart failure hospitalisation is one of the most common and costly problems the NHS has to deal with, any shortening of in-patient stay or reduction in mortality and morbidity would be of great importance.
National priorities	Not at the moment.
Current evidence base	1. A recent trial (ROSE) in patients with acute heart failure and either reduced or preserved LVEF suggested that low-dose dopamine enhanced diuresis in the sub-group of patients with a reduced LVEF. **2.** Prior smaller studies varied in the types of patients enrolled, doses of dopamine used and study design/comparator and collectively failed to give a consistent or robust finding regarding the efficacy of dopamine although suggested it may improve renal blood flow and enhance sodium and water excretion.
Equality	No.
Feasibility	Can the proposed research be carried out within a realistic timescale?

	Yes Would the sample size required to resolve the question be feasible? **Yes – two recent trials on which to base a power calculation on (CARRESS, ROSE) suggest that a total of 250 patients is sufficient.** Would the expense needed to resolve the question be warranted? **Yes** Are there any ethical or technical issues? **No.**
Other comments	Previous attempt: see above – ROSE trial. Other potential funders: BHF, NIHR.

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O.2 In patients with acute heart failure and persistent congestion, does the addition of a thiazide diuretic to standard therapy lead to greater diuresis compared with adding placebo to standard therapy?

A randomised trial should be conducted to investigate whether the addition of a thiazide diuretic to standard therapy leads to more clinically and cost effective decongestion in people admitted to hospital for treatment of decompensation heart failure.

One of the most common and difficult to manage problems arising during the initial treatment of patients with acute heart failure is an inadequate response to IV diuretic therapy. This problem frequently leads to a prolonged in-patient stay and is associated with higher in-patient mortality and higher post-discharge mortality and readmission rates. The best treatment for this problem is unknown, although there is some inconsistent and non-robust evidence that addition of a thiazide or thiazide-like diuretic (metolazone) may be beneficial. The proposed study would aim to resolve this uncertainty and guide the management of a difficult clinical problem.

Table 128: PICO

Criteria for selecting high-priority research recommendations PICO question	
Population	Patients with acute heart failure and reduced LVEF and persisting congestion, despite at least 48 hours of adequate intravenous diuretic therapy. co-morbidities and risk factors: **include systemic hypertension, diabetes mellitus, COPD, atrial fibrillation** gender: **Males and Females** age: **All age groups** ethnic group: **All ethnic groups** specific inclusion criteria: **LVEF less than or equal to 40%; congestion defined as at least 2 of: peripheral oedema, ascites, hepatic enlargement, elevated JVP; adequate intravenous diuretic therapy means at least 48 hours treatment with at least two-and-a-half times the patients pre-existing daily oral diuretic dose (furosemide equivalents).** specific exclusion criteria: **Acute myocardial infarction; inability to give informed consent e.g. due to cognitive impairment** health status or setting **in-patient** (**secondary care**)
Intervention	Bendroflumethiazide 10mg once daily in the morning for period of at least 2 days

Comparator(s)	Matching placebo tablets. Patients in both treatment groups will need a bladder catheter in situ for the duration of the infusion
Outcome	1. Urine volume 2. Body weight (as a measure of fluid loss) 3. Relief of congestion (measured using a standard score) 4. Change in creatinine 5. Change in cystatin C 6. Change in BNP (as a measure of left ventricular wall stress) 7. Days from randomisation to discharge 8. Thirty day mortality rate 9. Thirty day re-admission rate length of follow-up required: **30 days**
Study Design	Randomised, double-blind, placebo controlled, parallel group.
Timeframe	No timeframe.

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1 **Table 129: Criteria to support prioritisation of key research recommendations**

2

Potential Criterion	Explanation
Importance to patients or the population	One of the most common and difficult to manage problems arising during the initial treatment of patients with acute heart failure is an inadequate response to iv diuretic therapy (i.e. failure to relieve congestion). This problem frequently leads to a prolonged in-patient stay and is associated with higher in-patient mortality and higher post-discharge mortality and readmission rates. The best treatment for this problem is unknown, although there is some inconsistent and non-robust evidence that addition of a thiazide or thiazide-like diuretic (metolazone) be beneficial.
Relevance to NICE guidance	If the addition of a thiazide diuretic were to enhance diuresis and relieve congestion (without causing renal dysfunction or hyponatraemia) it would be recommended in future guidelines and widely used in practice.
Relevance to the NHS	As stated above, inadequate relief of congestion is common in acute heart failure and is associated with longer hospital stays and greater morbidity and mortality. As heart failure hospitalisation is one of the most common and costly problems the NHS has to deal with, any shortening of in-patient stay or reduction in mortality and morbidity would be of great importance.
National priorities	Not at the moment.
Current evidence base	1. Several prior trials in patients with acute heart failure suggested that a thiazide or thiazide-like diuretic can greatly enhance diuresis and relieve congestion. 2. However, there is no randomised placebo-controlled trial providing reliable evidence on which to base a guideline recommendation.
Equality	No.
Feasibility	Can the proposed research be carried out within a realistic timescale? **Yes** Would the sample size required to resolve the question be feasible? **Yes – two recent trials on which to base a power calculation on (CARRESS, ROSE) suggest that a total of 250 patients is sufficient.**

	Would the expense needed to resolve the question be warranted? **Yes** Are there any ethical or technical issues? **No.**
Other comments	Previous attempt: see above. Other potential funders: BHF, NIHR.

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O.3 In patients with acute heart failure and hypo-perfusion syndrome, is the use of intra-aortic balloon counter-pulsation pump (IABP) better than the use of intravenous inotropes?

A randomised trial should be conducted in people with decompensated heart failure due to left ventricular systolic dysfunction and systemic hypo-perfusion comparing the use of intra-aortic balloon counter pulsation (IABP) to the use of inotropes/vasopressors. This would determine which strategy is more clinically and cost-effective in this cohort.

IABP is used in the hospital setting as an adjuvant in patients with critical coronary ischaemia, patients with mechanical complications of acute myocardial infarction and had been used in people who develop cardiogenic shock following acute myocardial infarction. It is uncertain whether it may be able to provide clinical benefit in the critically unwell patients with acute heart failure due to left ventricular systolic dysfunction and systemic hypoperfusion

Table 130:PICO

Criteria for selecting high-priority research recommendations PICO question	
Population	Patients with acute heart failure caused by severe left ventricular systolic dysfunction and associated with symptomatic arterial hypotension with evidence of tissue hypoperfusion (mental obtundation/confusion, cold peripheries, oliguria). Acute Heart Failure not caused by acute myocardial infarction NYHA class IV co-morbidities and risk factors: **include systemic hypertension, diabetes mellitus, COPD, atrial fibrillation** gender: **Males and Females** age: **All age groups <80 years** ethnic group: **All ethnic groups** specific inclusion criteria: **Acute heart failure due to severe left ventricular systolic dysfunction, not caused by acute myocardial infarction** specific exclusion criteria: **Acute myocardial infarction, the presence of abdominal aortic aneurysm, peripheral vascular disease, established cognitive impairment** health status or setting (**secondary care**)

Intervention	Insertion of intra-aortic balloon counter-pulsation pump in patients with acute heart failure associated with no evidence of myocardial infarction, but with hypoperfusion syndrome. This is to be compared with treatment of a similar group of patients with intravenous inotropic agents. The interventions should ideally be for a period of 2-7 days. The dose of inotropes should be determined by the patient's response. All patients should have had myocardial infarction excluded by the ECG and cardiac enzyme criteria. This is due to the fact that we wish to exclude patients with cardiogenic shock due to acute myocardial infarction, in whom it is established that IABP alone may not be effective.
Comparator(s)	Intravenous inotropic agents via a central venous line at a level III environment.
Outcome	1. Improve the mortality rate 2. Shorten the hospitalisations 3. Reduce the re-hospitalisation rate 4. Improve the renal function as measured by the change in eGFR compared to the eGFR on admission 5. Improve the NYHA class at discharge 6. Improve the 6 minute walk test result at 6 weeks after discharge 7. Reduce the risk of sudden cardiac death during the admission. length of follow-up required: 1 year
Study Design	Randomised clinical trial (open label), as blinding to the patient and the physician is impossible.
Timeframe	No timeframe.

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1 **Table 131:Criteria to support prioritisation of key research recommendations**

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Potential Criterion	Explanation
Importance to patients or the population	We know that there is evidence that inotropic support might buy us time and improve the condition of the patient in shock (hypoperfusion state), but observations have documented that the inevitable demise of the patients cannot be avoided in the short to medium term. One may hope that by avoiding the use of inotropes myocardial injury is minimised by off-loading the heart using the theoretically beneficial mechanism of action of the IABP. One would hope that the IABP might save the patient from the detrimental effects of shock on the vital organs without subjecting the myocardium to the toxic effects of inotropic agents.
Relevance to NICE guidance	It is of high importance, as the success of the hypothesis may turn out to be very helpful to the relatively small number of patients who would fulfil the criteria. Although their numbers are small, they are critically ill with very high mortality rate and thus any attempt to reduce their mortality and improve their poor outlook would be worth supporting. If successful it would certainly inform future guidance by NICE**.**
Relevance to the NHS	Whether using inotropes or IABP, these patients would be cared for in high-dependency units (Level III beds). However, it is possible that reducing the cost of drugs that these patients need to have, and reducing the chance of re-hospitalisation could reduce the budgetary burden of caring for these patients.
National priorities	Is the question relevant to a national priority area (such as a National Service Framework or White Paper)? Not at the moment.
Current evidence base	• The IABP was used in cardiogenic shock in the context of acute myocardial infarction. • Mechanical support devices are restricted to being a bridge to transplant. Many acute heart failure patients are not candidates for transplantation. IABP can offer a type of short term mechanical support that is available in all cardiac interventional laboratories and can be safely applied. • There is no data to support the use of IABP outside the acute phase of myocardial infarction complicated by cardiogenic shock.
Equality	No. The reason I proposed excluding patients over the age of 80 years is simply because the myriad of co-morbidities they have would make the analysis of the results difficult, and because evidence form the Shock trial and registry did point towards

	tapered benefits in octogenarians.
Feasibility	Can the proposed research be carried out within a realistic timescale? **Yes** Would the sample size required to resolve the question be feasible? **Yes** Would the expense needed to resolve the question be warranted? **Yes** Are there any ethical or technical issues? **The only issue that needs to be resolved by agreement with the REC is how to resolve the issue of withdrawal of support after a set time-frame, beyond which improvement can not be expected to occur.**
Other comments	Potential funders- BHF, NIHR.

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O.4 In people with decompensated heart failure, fluid congestion and diuretic resistance, does ultrafiltration lead to more rapid and effective decongestion when compared to continuing diuretic treatment?

A randomised-controlled trial should be undertaken to determine whether ultrafiltration is more clinically and cost-effective than conventional diuretic therapy for patients admitted to hospital with decompensated heart failure. The study should investigate a number of clinical outcomes but also consider the impact of treatments on quality of life and provide data on safety.

Patients with fluid retention, resistant to conventional diuretic therapy, with or without renal dysfunction, are responsible for a high proportion of hospital admissions due to heart failure, and such admissions are often prolonged and thus have important budgetary implications for the NHS. The few, relatively small scale, randomised trials of ultrafiltration performed so far have been conducted in health care settings very different from the UK, with less fluid retention than is usually seen in UK practice, and where length of stay is usually much shorter than in UK (and European) practice. Although technically feasible, the evidence for benefit on heart failure outcomes is inconsistent and difficult to generalise to UK practice. Therefore a UK based study of sufficient quality is required to resolve the clinical equipoise.

1 **Table 132: Ultrafiltratlion PICO**

Criteria for selecting high-priority research recommendations PICO question	
Population	People hospitalised for treatment of fluid congestion due to heart failure who have received escalating doses of intravenous loop diuretic with the addition of a thiazide but remain inadequately decongested, or alternatively patients who present to hospital with massive fluid retention (e.g. weight >5kg above usual 'dry' weight). **co-morbidities and risk factors**: include systemic hypertension, diabetes mellitus, COPD, atrial fibrillation **gender:** Males and Females **age:** All age groups **ethnic group:** All ethnic groups **specific inclusion criteria:** congestion defined as at least 2 of: peripheral oedema, ascites, hepatic enlargement, elevated JVP. Considered resistant to IV loop diuretic and thiazide combination, or who present with considerable (>5kg) fluid retention. **specific exclusion criteria:** Trials to date have excluded the following patient groups: Acute coronary syndrome within 3 months; severe renal impairment (eGFR <20 ml/min or requirement for renal replacement therapy); inability to give informed consent; systolic blood pressure < 90 mmHg at time of enrolment; Pulmonary Arterial Hypertension not secondary to left heart disease; contraindications to systemic anticoagulation; Hematocrit > 45%; Inability to obtain venous access; haemodynamic instability severe enough to require IV positive inotropic agents, IV vasodilators or both; use of iodinated radiocontrast material within the previous 72 hours or planned study requiring IV contrast during the current hospitalisation; severe concomitant disease expected to prolong hospitalization; severe concomitant disease expected to cause death in ≤ 90 days; sepsis or ongoing systemic infection; severe uncorrected valvular stenosis; active myocarditis; hypertrophic obstructive cardiomyopathy; constrictive pericarditis or restrictive cardiomyopathy; liver cirrhosis; previous solid organ transplant; requirement for mechanical ventilatory support; presence of a mechanical circulatory support device; unwillingness or inability to complete follow up; active drug or alcohol substance abuse; participating in another interventional clinical trial **health status or setting:** hospitalised people
Intervention	Ultrafiltration with patient dependent filtration rates using newer technology allowing smaller venous cannulae for as long as required for effective decongestion.
Comparator(s)	Continued IV diuretic regime

Outcome	Time to first event (rehospitalisation, mortality); total fluid removed during the index hospitalisation; urine output; weight loss; time to freedom from congestion; freedom from congestion (defined as jugular venous distention of < or equal to 8 cm, with no orthopnoea, and with trace peripheral oedema or no oedema); change in B-type natriuretic peptide (BNP) levels over time; length of stay (LOS) during the index hospitalisation; total bed days over follow up period; number of days patient is in hospital for HF treatment; total number of cardiovascular (CV) rehospitalisations; total number of all cause rehospitalisations; all-cause mortality; cardiovascular mortality; quality of life (Minnesota living with heart failure questionnaire); changes in renal function; total follow up 1 year.
Study Design	Randomised,
Timeframe	Follow up 1 year.

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1 **Table 133: Ultrafiltration criteria to support prioritisation of key research recommendations**

Potential Criterion	Explanation
Importance to patients or the population	Recurrent hospitalisations are common for people with heart failure and often difficult to manage. Diuretic resistance frequently becomes a problem along with complications from high dose diuretic therapy leading to long in-hospital stays. There have been a few small to medium sized randomised trials of ultrafiltration, conducted in health care settings very different from the UK, with less fluid retention than is usually seen in UK practice, and where length of stay is usually much shorter than in UK (and European) practice. Although technically feasible, the evidence for benefit of ultrafiltration on heart failure outcomes is inconsistent and difficult to generalise to UK practice.
Relevance to NICE guidance	If ultrafiltration was able, within the UK healthcare setting, to provide more rapid congestion relief with reduced rehospitalisation rates, without significantly increased adverse events, then it may well become cost effective and would be recommended in future guidelines.
Relevance to the NHS	If ultrafiltration were found to be more clinically and cost effective than current practice this may well provide financial advantage but would require initial investment in equipment and specialist training for more wide spread provision. The benefit may be a reduced number of bed days nationally required for the treatment of diuretic resistant fluid retention in heart failure.
National priorities	No
Current evidence base	The current studies available have demonstrated mixed results and so clinical uncertainty still exists. The study settings and design have not been immediately applicable to the envisaged role of UF in the UK healthcare setting. The ongoing AVOID-HF study may well address the question of whether there is any benefit of using UF acutely for patients with heart failure hospitalisations but will not address its use following failure of medical therapy.
Equality	No.
Feasibility	Can the proposed research be carried out within a realistic timescale? **Yes** Would the sample size required to resolve the question be feasible? **Yes** Would the expense needed to resolve the question be warranted? **Yes** Are there any ethical or technical issues?

	No
Other comments	Potential funders- BHF (currently considering such a trial), NIHR

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