National Clinical Guideline Centre

.

Myocardial infarction with ST-segment elevation

The acute management of myocardial infarction with ST-segment elevation

Clinical guideline 167

Methods, evidence and recommendations

July 2013

November 2020: NICE's original guidance on myocardial infarction with ST-segment elevation was published in 2013. See the NICE website for the guideline recommendations and the evidence reviews for the 2020 Acute coronary syndromes update. This document preserves evidence reviews and committee discussions from the 2013 guideline.

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Contents

Guideline development group members

Name	Role
Huon Gray (Chair)	Consultant Cardiologist, Wessex Cardiac Unit, University of Southampton Hospital NHS Foundation Trust, Southampton
Robert Henderson (Deputy Chair)	Consultant Cardiologist, Nottingham University Hospitals NHS Trust
Sotiris Antoniou	Consultant Pharmacist, Cardiovascular Medicine, Barts Health NHS Trust
Charles Deakin	Hon Professor of Resuscitation & Prehospital Emergency Medicine, University of Southampton. Consultant in Cardiac Anaesthesia and Intensive Care, University Hospital Southampton.
Jason Kendall	Consultant in Emergency Medicine, Frenchay Hospital, North Bristol NHS Trust
Hugh McIntyre	Consultant Physician, East Sussex Hospitals Trust
Jim McLenachan	Consultant Cardiologist, Leeds General Infirmary
Francesco Palma	Patient and carer member
Gerald Robinson	Patient and carer member
Fiona Sayers	Head of Nursing, Cardiology & Acute Services, Frimley Park Hospital NHS Foundation Trust
Dave Smith	Consultant Interventional Cardiologist, Regional Cardiac Centre, Morriston Hospital, ABM University Health Board
L David R Smith	Consultant cardiologist, Royal Devon and Exeter NHS Hospital Trust
Mark Vaughan	General Practitioner, Avenue Villa Surgery, Llanelli
Mark Whitbread	Senior Paramedic, London Ambulance Service, East Area Headquarters, Ilford Ambulance Station, Essex
Technical team	
Daria Bilan	Information Scientist (Guideline Information Scientist from October 2011 until February 2012)
Serena Carville	Senior Research Fellow / Project Manager (Guideline Project Manager from October 2012)
Jill Cobb	Information Scientist (guideline information scientist until September 2011)
Angela Cooper	Senior Research Fellow, NCGC, (Guideline Research Fellow, from December 2011)
Martin Harker	Health Economist, NCGC (Guideline Health Economist from April 2012)
Taryn Krause	Senior Project Manager and Research Fellow, NCGC (Guideline Project Manager, Guideline Research Fellow until October 2012)
Kate Lovibond	Senior Health Economist, NCGC (Guideline Health Economist until April 2012, Senior Health Economist until August 2012)
Jill Parnham	Guidelines Operation Director, NCGC (Guideline Lead)
Robert Pitcher	Research Fellow, NCGC (Guideline Research Fellow until January 2012)
Carlos Sharpin	Joint Head of Information Science and Research Fellow, NCGC (Guideline Information Scientist from February 2012)
David Wonderling	Head of Health Economics, NCGC (Senior Health Economist from August 2012)
Invited experts	**Role**
Tony Gershlick	Professor of Interventional Cardiology, University of Leicester
Keith Fox	Professor of Cardiology, University of Edinburgh

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Peter Ludman, Consultant cardiologist, University Hospitals Birmingham NHS Foundation Trust, Queen Elizabeth Hospital, Queen Elizabeth Medical Centre, Birmingham.

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1 Introduction

1.1 Cardiovascular disease

The process by which arteries become stiff and thickened is termed arteriosclerosis, and is the most common form of cardiovascular disease (CVD). It is the consequence of a number of predisposing risk factors, such as advancing age, smoking, hypertension, diabetes, raised cholesterol, impaired renal function, obesity, inactivity and family history. A number of individual and population-based interventions are known to be capable of reducing the prevalence of CVD.[233] Mortality from CVD in the UK has been falling for a number of years.[281] Nevertheless CVD still remains the commonest cause of death and disability. When coronary arteriosclerosis impairs blood supply to heart muscle (myocardium), the person affected may suffer exertional chest pain relieved by rest, a condition known as stable angina. NICE has offered guidance on the approach to managing this,[239] and on the diagnosis of chest pain suspected to be cardiac in origin.[230]

1.2 Myocardial ischaemia and infarction

When myocardial blood flow is acutely impaired (ischaemia), and often not provoked by exertion, a person will commonly suffer more prolonged pain; this is referred to as acute coronary syndrome (ACS). The underlying common pathophysiology of ACS involves the erosion or sudden rupture of an atherosclerotic plaque within the wall of a coronary artery. Exposure of the circulating blood to the cholesterol-rich material within the plaque stimulates blood clotting (thrombosis), which obstructs blood flow within the affected coronary artery.[65] This coronary obstruction may be of short duration, and may not result in myocardial cell damage (necrosis), in which case the clinical syndrome is termed unstable angina. Unstable angina may result in reversible changes on the electrocardiogram (ECG) but does not cause a rise in troponin, a protein released by infarcting myocardial cells. Ischaemia which causes myocardial necrosis (infarction) will result in elevated troponin. When the ischaemia-causing infarction is either short-lived or affects only a small territory of myocardium the ECG will often show either no abnormality or subtle changes. This syndrome is termed non-ST-segment elevation myocardial infarction (NSTEMI). The diagnosis and immediate management of STEMI and the management of unstable angina and NSTEMI is addressed in other NICE Clinical Guidelines (CG95[230] and CG94[229]).

When the ischaemia-causing myocardial infarction (MI) is prolonged the affected person will usually experience more severe and sustained chest pain, often together with breathlessness, nausea and sweating. Symptoms can be atypical, particularly in women, the elderly, and people with diabetes. Not only will cardiac troponin be released, but the ECG will usually show ST-segment elevation, resulting in this more severe type of heart attack being termed ST-segment elevation myocardial infarction (STEMI).

1.3 Pathophysiology of STEMI

STEMI is most often caused by complete and persistent occlusion of a coronary artery by blood clot (thrombus). As soon as the coronary blood supply is interrupted, myocardial damage begins and the longer the blood supply is occluded the greater the amount of heart muscle lost. In animal models of experimental coronary artery occlusion a ‘wave-front’ of myocardial injury spreads from the inner layer of heart muscle (sub-endocardial myocardium) to the outermost layer (sub-epicardial myocardium), whereupon the infarction is then said to be ‘full thickness’. In those who survive STEMI, the infarcted muscle is gradually replaced by scar tissue (fibrosis), and the extent of damage will determine the overall pumping ability of the heart, and is a determinant of ‘heart failure’[231] and

longer-term survival. Because there are also some less common pathophysiological explanations for myocardial infarction an international definition of MI has been agreed.[304]

1.4 Epidemiology of STEMI

The incidence of STEMI has been declining over the past 20 years.[243,267] Its incidence varies between regions[250] and averages around 500 hospitalised episodes per million people each year in the UK.[331] Ventricular arrhythmias may occur early after the onset of an acute coronary syndrome and may cause sudden cardiac death before the person is able to access emergency medical care. Studies conducted around 2 decades ago reported that around one-third of people with an acute coronary syndrome died before arrival in hospital.[181,244] The London Ambulance Service attended 9,657 cardiac arrests in 2011–12 for a population of around 8.2 million (1,177 per million),[332] most of which will be have been due to acute coronary syndromes, so the overall population prevalence of STEMI is likely to be in the region of 750–1250 per million. Delay in calling the emergency services for help results in a higher risk of cardiac arrest and greater myocardial damage, and certain groups (such as women and those from ethnic minorities) may be slow to call for medical help. Over the past 30 years in-hospital mortality following acute coronary syndromes has fallen from around 20% to nearer 5%. This has been attributed to various factors, including improved drug therapy and speed of access to effective treatments.[245] In a Swedish registry study, an increase in the prevalence of evidence-based treatments for STEMI was associated with a decrease in mortality that was sustained over 12 years.[145]

1.5 The importance of 'time' and reperfusion therapy

Nearly half of potentially salvageable myocardium is lost within 1 hour of the coronary artery being occluded, and two-thirds is lost within 3 hours.[258] The extent of myocardial damage may be modulated by the presence of any collateral supply to the ischaemic territory from other coronary arteries. It was demonstrated that complete coronary occlusion was the cause of STEMI more than 30 years ago using coronary angiography[84] and this quickly resulted in clinical trials of 'clot-busting' (thrombolytic, fibrinolytic) and other drugs[259] being undertaken in an attempt to reopen thrombosed coronary arteries and thereby limit myocardial damage.

Apart from resuscitation from any cardiac arrest, the highest priority in the management of STEMI is to restore an adequate coronary blood flow as quickly as possible. During the 1980s and 1990s the best means of achieving restoration of flow was to administer a fibrinolytic drug. These were initially given by direct intracoronary injection, but later administration intravenously was shown to be at least as effective and had the advantage of being much more easily administered, offering the possibility of being given by trained ambulance crews. The UK introduced a comprehensive system for delivering fibrinolysis following publication of the National Service Framework (NSF) for Coronary Heart Disease in 2000.[78] However, whilst shown to be much more effective than placebo,[210] fibrinolysis was not without its imperfections: some people were unsuitable for its use (for instance because of bleeding complications), in around 20%–30% it failed to result in coronary reperfusion, and in a few (1.0%) it caused haemorrhagic stroke. In an attempt to improve outcomes attention turned to mechanical techniques as a means of restoring coronary flow (coronary angioplasty, thrombus extraction catheters, stenting), that are grouped under the overarching term 'primary percutaneous coronary intervention' (PPCI).

1.5.1 Primary percutaneous coronary intervention (PPCI)

To investigate the potential for PPCI to be delivered in England the Department of Health undertook a feasibility study (National Infarct Angioplasty Project), which reported in 2008 and concluded that PPCI is both feasible and cost effective, and that it should become the treatment of choice for STEMI,

provided it could be delivered 'in a timely fashion'.[80] This PPCI strategy requires emergency access to specialist cardiac catheter laboratories and staff at all times.

The issue of 'timeliness' forms a key part of this guideline. Broadly speaking, if too much time elapses between the moment when fibrinolysis could be given and PPCI is actually delivered, then the outcome benefits of PPCI may be lost. In other words, if some people live far enough away from a PPCI centre, or their travel times would be expected to be long because of road conditions, then a strategy of PPCI might not be the best one for them. As part of the NIAP, an analysis of expected ambulance travel times was undertaken and estimated that approximately 95% of the population live close enough to a PPCI centre for this to be their routine reperfusion treatment, and that therefore around 5% may still require fibrinolysis. This issue of time to PPCI has been re-analysed as part of this guideline and forms an important part of its recommendations.

The roll-out of PPCI and the reduction in the use of fibrinolysis has been dramatic, with fibrinolysis being used in only 5% of STEMI cases in 2011/12.[204] With such a marked reduction in need for fibrinolysis many ambulance services have stopped carrying fibrinolytic drugs. The number of people receiving 'no reperfusion' therapy has remained largely unchanged at around 30% of all STEMI cases; some will present too late to benefit from reperfusion therapy, some may have comorbidity or bleeding risks that makes it inappropriate, and others may undergo angiography with a view to PPCI but are found not to need that.

1.6 PPCI pathways

Given the complexity of delivering PPCI, optimal service configuration requires a single reperfusion pathway for people with STEMI in each locality. The pathway should work consistently and be reproducible for all people, both within and outside normal working hours. It is not appropriate to provide the 'preferred' reperfusion treatment for some, but a potentially sub-optimal treatment for others simply on the basis of the time of presentation, or availability of staff or facilities at the admitting hospital. People may develop symptoms of STEMI and call the emergency services, or they may self-present to an emergency department. STEMI may also occur in someone already in hospital for a different reason, such as a surgical operation. Whatever the circumstances, care pathways should exist to ensure that PPCI is offered in a timely and efficient manner to all who may benefit. The prime determinant of clinical benefit following reperfusion therapy for STEMI is the degree of myocardial salvage (a function of timeliness, effectiveness and maintenance of coronary reperfusion). Bleeding complications also play an important part in both morbidity and mortality if combinations of potent antiplatelet and antithrombin agents are used. Multi-professional team working is an important aspects of care. After successful acute treatment, secondary prevention therapy, lifestyle modification and cardiac rehabilitation recommendations (including rehabilitation beginning in the hospital period) parallel those for non-STEMI acute coronary syndromes, on which NICE has also produced guidance.[214,219,235]

1.7 Which issues does this guideline address?

As detailed above, much is known about the management of STEMI and many advances have been made over the last 30 years. The recommendations in this guideline relate only to people with a diagnosis of STEMI. Chest pain of recent onset (NICE clinical guideline 95), covers the diagnosis of STEMI and should be read in conjunction with this guideline.

A number of questions have been addressed within this guideline:

- It is accepted that PPCI is the preferred reperfusion strategy, but 'timeliness' of its delivery is fundamental to producing better outcomes. This is addressed in great detail so commissioners and those delivering services for people with STEMI can plan their configuration in such a way that outcomes are optimal.

- The use of drug therapy immediately after a diagnosis of STEMI has been the subject of much research, and this guideline addresses the use of antiplatelet and antithrombin agents.
- When someone with STEMI activates the PPCI pathway the first intervention is to undertake coronary angiography, to determine the extent and severity of the person's coronary disease. If PPCI is indicated a number of procedural issues arise:
  - Is it better to undertake a PPCI procedure via a femoral or radial arterial approach?
  - Should the culprit (occluded) artery alone be treated, or is there benefit in undertaking PCI to other diseased vessels at the same time?
  - When treating the culprit vessel is there benefit in using devices that allow the extraction of blood clot (thrombus) from the coronary artery before inserting a stent?
- When someone with STEMI suffers a cardiac arrest, and after a cardiac rhythm is restored, is it more important to admit the person to the closest hospital that can provide intensive neurological support, or is it better to activate the PPCI pathway and attempt to achieve coronary reperfusion whilst neurological support (such as therapeutic hypothermia[240]) is also being given?
- When someone with STEMI develops cardiogenic shock, is there evidence for benefit of revascularisation?
- For centres undertaking PPCI is there a relationship between the number of procedures undertaken each year and the outcomes for patients?
- For the minority of people still receiving fibrinolysis as their reperfusion treatment:
  - How can outcomes be improved if the person fails to reperfuse?
  - Should coronary angiography be undertaken following evidence of successful reperfusion, and if so, when should this be performed?

2 Development of the guideline

2.1 What is a NICE clinical guideline?

NICE clinical guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances within the NHS – from prevention and self-care through primary and secondary care to more specialised services. We base our clinical guidelines on the best available research evidence, with the aim of improving the quality of healthcare. We use predetermined and systematic methods to identify and evaluate the evidence relating to specific review questions.

NICE clinical guidelines can:

- provide recommendations for the treatment and care of people by health professionals
- be used to develop standards to assess the clinical practice of individual health professionals
- be used in the education and training of health professionals
- help patients to make informed decisions
- improve communication between patient and health professional.

While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

We produce our guidelines using the following steps:

- Guideline topic is referred to NICE from the Department of Health.
- Stakeholders register an interest in the guideline and are consulted throughout the development process.
- The scope is prepared by the National Clinical Guideline Centre (NCGC).
- The NCGC establishes a guideline development group.
- A draft guideline is produced after the group assesses the available evidence and makes recommendations.
- There is a consultation on the draft guideline.
- The final guideline is produced.

The NCGC and NICE produce a number of versions of this guideline:

- the full guideline contains all the recommendations, plus details of the methods used and the underpinning evidence
- the NICE guideline lists the recommendations
- the information for the public is written using suitable language for people without specialist medical knowledge
- the NICE pathway links all recommendations and includes links to other relevant guidance..

This version is the full version. The other versions can be downloaded from NICE at www.nice.org.uk.

2.2 Remit

NICE received the remit for this guideline from the Department of Health. They commissioned the NCGC to produce the guideline.

The remit for this guideline is: To produce a clinical guideline on the management of myocardial infarction with ST-segment elevation.

2.3 Who developed this guideline?

A multidisciplinary Guideline Development Group (GDG) comprising professional group members and consumer representatives of the main stakeholders developed this guideline (see section on Guideline Development Group Membership and acknowledgements).

The National Institute for Health and Care Excellence funds the National Clinical Guideline Centre (NCGC) and thus supported the development of this guideline. The GDG was convened by the NCGC and chaired by Huon Gray in accordance with guidance from the National Institute for Health and Care Excellence (NICE).

The group met every 6 weeks during the development of the guideline. At the start of the guideline development process all GDG members declared interests including consultancies, fee-paid work, shareholdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared arising conflicts of interest. Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in Appendix B.

Staff from the NCGC provided methodological support and guidance for the development process. The team working on the guideline included a project manager, systematic reviewers, health economists and information scientists. They undertook systematic searches of the literature, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate and drafted the guideline in collaboration with the GDG.

2.4 What this guideline covers

This guideline covers the following populations:

- Adults (18 years or older) believed to be having spontaneous onset of STEMI (types 1 and 3 of the 'universal definition of myocardial infarction' categories).
- Adults with suggestive symptoms of spontaneous onset of STEMI, but whose electrocardiogram may be difficult to interpret because of the presence of left bundle branch block or permanent pacing.
- Where data exist, guidance will address differences between specific populations, such as older adults, women and people from ethnic minorities.
- Particular attention will be paid to people with STEMI who remain unconscious following resuscitation.

The following clinical issues are covered:

The diagnosis of STEMI will be considered to have been made once a patient is identified as having a suggestive clinical presentation and either ST-segment elevation on the electrocardiograph or an electrocardiograph where interpretation is complicated by the presence of left bundle branch block or permanent pacing. The acute aspects of the following will be addressed, from symptom onset to the point of hospital discharge:

- Adjunctive pharmacotherapy (for example, antiplatelet and antithrombin agents).
- Time factors in relation to acute coronary reperfusion.
- The time interval from onset of STEMI beyond which fibrinolysis may be preferable to PPCI.
- Drug combinations administered before PPCI (facilitated PPCI).
- Timing and effectiveness of angiography or PCI following fibrinolytic therapy.
- Timing and effectiveness of PCI following failed fibrinolysis (rescue PCI).
- Procedural aspects of PPCI (for example, thrombus extraction).

- For further details please refer to the scope in Appendix A and review questions in section 3.1.

2.5 What this guideline does not cover

- Management of suspected brain injury in those with STEMI who have suffered cardiac arrest.
- Management of STEMI after hospital discharge, including post-myocardial infarction treatments (we will cross-refer to existing NICE guidance, as detailed in section 2.6).

2.6 Relationships between the guideline and other NICE guidance

Health Technology Appraisals to be incorporated in this guidance:

Ticagrelor for the treatment of acute coronary syndromes. NICE technology appraisal guidance 236 (2011).[226]

Bivalirudin for the treatment of ST-segment-elevation myocardial infarction. NICE technology appraisal guidance 230 (2011).[234]

Related NICE Health Technology Appraisals:

Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events. NICE technology appraisal guidance 210 (2010).[232]

Cardiac resynchronisation therapy for the treatment of heart failure. NICE technology appraisal guidance 120 (2010).[218]

Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention. NICE technology appraisal 182 (2009).

Drug-eluting stents for the treatment of coronary artery disease. NICE technology appraisal 152 (2008).[220]

Implantable cardioverter defibrillators (ICDs) for arrhythmias. NICE technology appraisal 95 (2006).[216]

Statins for the prevention of cardiovascular events. NICE technology appraisal guidance 94 (2006).[217]

Myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction. NICE technology appraisal guidance 73 (2003).[213]

Guidance on the use of coronary artery stents. NICE technology appraisal guidance 71 (2003).[212]

Guidance on the use of drugs for early thrombolysis in the treatment of acute myocardial infarction. NICE technology appraisal guidance 52 (2002).[210]

Guidance on the use of glycoprotein IIb/IIIa inhibitors in the treatment of acute coronary syndromes. NICE technology appraisal guidance 47 (2002).[211]

Related NICE Interventional Procedures:

Off-pump coronary artery bypass (OPCAB). NICE interventional procedure guidance 377 (2011).[238]

Related NICE Clinical Guidelines:

General:

Patient experience in adult NHS services. NICE clinical guidance 138 (2012).[241]

Medicines adherence. NICE clinical guidance 76 (2011).[227]

Condition-specific:

Hyperglycaemia in acute coronary syndromes. NICE clinical guideline 130 (2011).[237]

Hypertension (update). NICE clinical guideline 127 (2011).[236]

Stable angina. NICE clinical guideline 126 (2011).[239]

Chest pain of recent onset. NICE clinical guideline 95 (2010).[230]

Unstable angina and NSTEMI. NICE clinical guideline 94 (2010).[229]

Familial hypercholesterolaemia. NICE clinical guideline 71 (2008).[222]

Related NICE Public Health Guidance:

Prevention of cardiovascular disease. NICE public health guidance 25 (2010).[233]

Smoking cessation services in primary care, pharmacies, local authorities and workplaces, particularly for manual working groups, pregnant women and hard to reach communities. NICE public health guidance 10 (2008).[224]

Brief interventions and referral for smoking cessation in primary care and other settings. NICE public health guidance 1 (2006).[215]

NICE Related Guidance currently in development:

Acute coronary syndrome – rivaroxaban. Publication date to be confirmed.

Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention. NICE technology appraisal guidance (update). Publication expected August 2014.

MI - secondary prevention (update). NICE clinical guideline. Publication expected November 2013.

Lipid modification (update). NICE clinical guideline. Publication expected July 2014.

3 Methods

This guidance was developed in accordance with the methods outlined in the NICE guidelines manual (2009).[228]

3.1 Developing the review questions and outcomes

Review questions were developed in a PICO framework (patient, intervention, comparison and outcome) for intervention reviews, and with a framework of population, index tests, reference standard and target condition for reviews of diagnostic test accuracy. This was to guide the literature searching process and to facilitate the development of recommendations by the guideline development group (GDG). They were drafted by the NCGC technical team and refined and validated by the GDG. The questions were based on the key clinical areas identified in the scope (Appendix A). Further information on the outcome measures examined follows this section.

A total of 12 review questions were identified. Full literature searches, critical appraisals and evidence reviews were completed for all the specified clinical questions.

Chapter	Review questions	Outcomes
5. Time to reperfusion (delay between fibrinolysis and primary percutaneous coronary intervention)	What is the duration of PPCI-related time delay at which fibrinolysis becomes more clinically and cost effective compared to PPCI in people with STEMI and how is this modulated by patient presentation delay and patient risk profile?	• Mortality (all-cause and cardiovascular specific) • Non-fatal and all (non-fatal and fatal) stroke • Intracranial bleeding • Non-fatal and all (non-fatal and fatal) myocardial reinfarction • Heart failure • Major bleeding • Minor bleeding • Unplanned revascularisation • Length of hospital stay • Quality of life • Time to equipoise between the treatments for outcomes listed above
6. Facilitated primary percutaneous coronary intervention (fPPCI)	What is the clinical and cost effectiveness of facilitated primary PCI (fPPCI) compared to primary PCI (PPCI) in people with STEMI?	• Mortality (all-cause and cardiovascular specific) • Non-fatal and all (non-fatal and fatal) stroke • Intracranial bleeding • Non-fatal and all (non-fatal and fatal) myocardial reinfarction • Major bleeding • Minor bleeding • Heart failure • Repeat revascularisation • Length of hospital stay • Quality of life
7. Femoral versus radial approach for primary percutaneous coronary intervention	What is the clinical and cost effectiveness of radial access compared to femoral access for coronary angiography and, if appropriate, follow-on PPCI in people with STEMI managed by PPCI?	• Mortality (all-cause and cardiovascular specific) • Non-fatal and all (fatal and non-fatal) stroke • Intracranial bleeding • Non-fatal and all (fatal and non-fatal) myocardial reinfarction • Heart failure • Repeat revascularisation

Chapter	Review questions	Outcomes
		• Access site crossover • Inability to cross the lesion with a wire, balloon or stent during PCI • Radiation exposure (X-ray time/fluoroscopic exposure/total radiographic contrast media used/fluoroscopy time) • Vascular access site complications • Procedure time • PPCI procedural success • Major bleeding • Minor bleeding • Length of hospital stay • Patient experience (pain) • Quality of life
8. Thrombus extraction during primary percutaneous coronary intervention	What is the clinical and cost effectiveness of using thrombus extraction devices (catheter aspiration devices, mechanical thrombus extraction devices) during PPCI compared with PPCI alone for the treatment of STEMI in adults?	• Mortality (all-cause and cardiovascular specific) • Non-fatal and all (fatal and non-fatal) stroke • Intracranial bleeding • Non-fatal and all (fatal and non-fatal) myocardial reinfarction • Heart failure • Target vessel revascularisation • Major bleeding • Minor bleeding • Length of hospital stay • Quality of life
9. Culprit versus multivessel revascularisation	What is the clinical and cost effectiveness of multivessel PCI compared to culprit-only PPCI in people with STEMI and multivessel coronary disease undergoing primary PCI (PPCI)?	• Mortality (all-cause and cardiovascular specific) • Non-fatal and all (fatal and non-fatal) stroke • Intracranial bleeding • Non-fatal and all (fatal and non-fatal) myocardial reinfarction • Heart failure • Repeat revascularisation • Target vessel revascularisation • Major bleeding • Minor bleeding • Contrast-induced nephropathy • Length of hospital stay • Radiation exposure (fluoroscopic time/X-ray time) • Procedural time • PCI procedural success • Quality of life
10. Cardiogenic shock	In people with cardiogenic shock due to STEMI what is the clinical and cost effectiveness of early revascularisation compared with medical stabilisation?	• Mortality (all-cause and cardiovascular specific) • Non-fatal and all (fatal and non-fatal) stroke • Intracranial bleeding • Non-fatal and all (fatal and non-fatal) myocardial reinfarction • Heart failure

Chapter	Review questions	Outcomes
		• Unplanned revascularisation • Major bleeding • Minor bleeding • Renal failure (use of dialysis) • Length of hospital stay • Use of intra-aortic balloon pump • Quality of life
11. Unconscious patients	Does immediate angiography followed by PPCI where indicated improve outcomes of people with presumed STEMI who are resuscitated but remain unconscious after a cardiac arrest?	• Mortality (all-cause and cardiovascular specific) • Non-fatal and all (fatal and non-fatal) stroke • Intracranial bleeding • Non-fatal and all (fatal and non-fatal) myocardial reinfarction • Heart failure • Unplanned revascularisation • Major bleeding • Minor bleeding • Length of hospital stay • Use of intra-aortic balloon pump • Quality of life • Neurologically intact survival (CPC score) or other measures of neurological disability
12. Hospital volumes of primary percutaneous coronary intervention	What is the impact of high volume versus low volume PPCI services on patient outcomes?	• Mortality (all-cause and cardiovascular specific) • Non-fatal and all (non-fatal and fatal) stroke • Non-fatal and all (non-fatal and fatal) myocardial reinfarction • Heart failure • Unplanned revascularisation • Major bleeding • Minor bleeding • Length of hospital stay • Quality of life
13. Pre-hospital versus in-hospital fibrinolysis	What is the clinical and cost effectiveness of pre-hospital versus in-hospital fibrinolysis?	• Mortality (all-cause and cardiovascular specific) • All-cause stroke (non-fatal and fatal) • Intracranial bleeding • Myocardial reinfarction (non-fatal and fatal) • Heart failure • Major bleeding • Minor bleeding • Unplanned revascularisation • Length of hospital stay • Quality of life
14. Use of antithrombin as an adjunct to fibrinolysis	Does administration of antithrombin treatment at the same time as pre-hospital fibrinolysis improve outcomes compared to administration of pre-hospital fibrinolysis alone?	• Mortality (all-cause and cardiovascular specific) • Non-fatal and all (fatal and non-fatal) stroke • Intracranial bleeding • Non-fatal and all (fatal and non-fatal) myocardial reinfarction • Heart failure

Chapter	Review questions	Outcomes
		• Unplanned revascularisation • Major and minor bleeding • Length of hospital stay • Quality of life
15. Rescue percutaneous coronary intervention	What is the clinical and cost effectiveness of rescue PCI, repeated fibrinolysis or conservative management compared to each other in people with STEMI who fail to reperfuse after fibrinolytic therapy?	• Mortality (all-cause and cardiovascular specific) • Non-fatal and all (non-fatal and fatal) stroke • Non-fatal and all (non-fatal and fatal) myocardial reinfarction • Heart failure • Major bleeding • Minor bleeding • Length of hospital stay • Quality of life
16. Routine early angiography	What is the clinical and cost effectiveness of routine early angiography following STEMI successfully treated by fibrinolysis compared to routine deferred or selective angiography?	• Mortality (all-cause and cardiovascular specific) • Non-fatal and all (non-fatal and fatal) fatal stroke • Intracranial bleeding • Non-fatal and all (non-fatal and fatal) myocardial reinfarction • Unplanned revascularisation • Major bleeding • Minor bleeding • Length of hospital stay • Refractory ischaemia • Heart failure • Quality of life

3.2 Searching for evidence

3.2.1 Clinical literature search

Systematic literature searches were undertaken to identify evidence within published literature in order to answer the review questions as per the guidelines manual (2009).[228] Clinical databases were searched using relevant medical subject headings, free-text terms and study type filters where appropriate. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English language. All searches were conducted on core databases, MEDLINE, Embase, Cinahl and The Cochrane Library.

Search strategies were checked by looking at reference lists of relevant key papers, checking search strategies in other systematic reviews and asking the GDG for known studies. The questions, the study types applied, the databases searched and the years covered can be found in Appendix F. All searches were updated on 29 November 2012. No papers published after this date were considered.

During the scoping stage, a search was conducted for guidelines and reports on the websites listed below and on organisations relevant to the topic. Searching for grey literature or unpublished literature was not undertaken. All references sent by stakeholders were considered.

- Guidelines International Network database (www.g-i-n.net)
- National Guideline Clearing House (www.guideline.gov/)
- National Institute for Health and Care Excellence (NICE) (www.nice.org.uk)

- National Institutes of Health Consensus Development Program (consensus.nih.gov/)
- National Library for Health (www.library.nhs.uk/).

3.2.2 Health economic literature search

Systematic literature searches were also undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to a STEMI population or terms relating to PCI or angioplasty in the NHS Economic Evaluation Database (NHS EED), the Health Technology Assessment database (HTA) and the Health Economic Evaluations Database (HEED) with no date restrictions. Additionally, the search was run on MEDLINE and Embase, with a specific economic filter, from 2010, to ensure recent publications that had not yet been indexed by these databases were identified. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English language.

The search strategies for health economics are included in Appendix F. All searches were updated on 29 November 2012. No papers published after this date were considered.

3.3 Evidence of effectiveness

The Research Fellow:

- Identified potentially relevant studies for each review question from the relevant search results by reviewing titles and abstracts – full papers were then obtained.
- Reviewed full papers against pre-specified inclusion and exclusion criteria to identify studies that addressed the review question in the appropriate population and reported on outcomes of interest (review protocols are included in Appendix C).
- Critically appraised relevant studies using the appropriate checklist as specified in the guidelines manual.[228]
- Extracted key information about the study's methods and results into evidence tables (evidence tables are included in Appendix G).
- Generated summaries of the evidence by outcome (included in the relevant chapter write-ups):
  - Randomised studies: meta-analysed, where appropriate and reported in GRADE profiles (for clinical studies) – see below for details.
  - Observational studies: data presented as a range of values in GRADE profiles.

3.3.1 Inclusion and exclusion

See the review protocols in Appendix C for full details.

The inclusion and exclusion of studies was based on the review protocols. The GDG were consulted about any uncertainty regarding the inclusion or exclusion of selected studies. The proportion of people with STEMI was among the criteria used for the inclusion of studies in the evidence reviews. Indirect populations were not considered, unless otherwise stated in the evidence reviews. The evidence reviews recorded where there was uncertainty in the definition of the STEMI population.

3.3.1.1 Review questions that include PPCI as a comparator

Studies published after 1990 were considered for the majority of the guideline questions in order to ensure that the extracted evidence is reflective of current practice, especially with regard to the widespread adoption of stenting in place of balloon angioplasty for PPCI procedures over the last 15 years. There was no cut-off date for included studies in the following 2 evidence reviews; use of

antithrombin as an adjunct to fibrinolysis (chapter 14) and pre-hospital versus in-hospital fibrinolysis (chapter 13) as literature published before 1990 was still considered to be relevant by the GDG. . The following criteria were also applied for the majority of evidence reviews:

- Where ≥ 3 RCTs (with a combined population of ≥ 500) deploy stents in ≥ 50% of PPCI procedures (in which stenting is feasible) we excluded studies where stents are deployed in < 50% of PCI procedures.
- Where < 3 RCTs deploy stents in ≥ 50% of PPCI procedures (or the total population of RCTs deploying stents is < 500) we included all studies that began enrolling participants after 1996.
- If < 3 RCTs began enrolling participants after 1996 (or the total population is < 500), we considered all studies published after 1990.
- Studies were excluded if < 50% of participants had PPCI (that is, population included people who had rescue PCI or facilitated PPCI).

The following exclusion criteria were applied for the facilitated primary percutaneous coronary intervention evidence review:

- RCTs that did not use stents or < 50% people received stents.
- RCTs that did not mention the percentage of stent usage.

3.3.1.2 Review questions that include fibrinolytic agents as a comparator

Our search strategy reflected NICE technology appraisal 52, which recommends alteplase, reteplase, streptokinase and tenecteplase for in-hospital fibrinolysis and reteplase and tenecteplase for pre-hospital fibrinolysis.

3.3.1.3 Review questions and number of participants in studies

No limits were applied for study sample size except for the evidence reviews of culprit versus complete revascularisation, hospital volumes of primary percutaneous coronary intervention, time to reperfusion and facilitated primary percutaneous coronary intervention. For the evidence review of culprit versus complete revascularisation, cohort studies ≥ 500 participants were included. For the evidence review of hospital volumes of primary percutaneous coronary intervention, prospective and retrospective observational studies with > 1000 participants were included. The time to reperfusion review only included registry studies if there were > 100,000 participants unless they were conducted in the UK. Studies that performed meta-regression analyses of RCT evidence were only selected if ≥ 10 RCTs were included in the analyses, as per standard review methodology that for meta-regression studies there should be at least 10 trials per covariate. For the evidence review of facilitated primary percutaneous coronary intervention, studies with < 60 participants were excluded if there were larger RCTs.

3.3.2 Methods of combining clinical studies

Data synthesis for intervention reviews

Where possible, meta-analyses were conducted to combine the results of studies for each review question using Cochrane Review Manager (RevMan5) software. Fixed-effects (Mantel-Haenszel) techniques were used to calculate risk ratios (relative risk) for the binary outcomes: mortality (all-cause and cardiovascular specific), non-fatal and all (fatal and non-fatal) stroke, intracranial bleeding, non-fatal and all (fatal and non-fatal) myocardial reinfarction, heart failure, repeat revascularisation, major bleeding, minor bleeding, PPCI vascular access site complications, renal failure, refractory ischaemia, and neurologically intact survival (CPC score). Repeat revascularisation was assumed to be target vessel revascularisation and definitions were reported in the evidence reviews where given. The continuous outcomes of hospital stay, total fluoroscopy contrast media used during PPCI, PPCI

fluoroscopy time, PPCI access site crossover, PPCI procedure length, use of intra-aortic balloon pump and quality of life were analysed using an inverse variance method for pooling weighted mean differences and where the studies had different scales, standardised mean differences were used. Where reported, time-to-event data was presented as a hazard ratio.

3.3.2.1 Data synthesis of outcomes and study follow-up

Each outcome was analysed at short-term and longer-term follow-up. The majority of questions used a short-term follow-up defined as intervals ≤ 30 days (the included studies table for each evidence review specifies the exact time point). The reported outcome interval closest to 30 days was analysed where more than 1 interval was reported. The rescue percutaneous coronary intervention and the routine early angiography evidence reviews analysed short-term outcomes at multiple time intervals, namely in-hospital, 30 days and 6 weeks. Longer-term follow-up was defined as intervals > 6 weeks. When multiple time intervals > 6 weeks were reported, we used the value as close to 6 months as possible (the exact duration is specified in the included studies table for each review and the forest plots). Six months was chosen for consistency and because outcome rates were substantially reduced and largely constant by this stage, while our confidence in the accuracy of outcomes recorded at longer follow-up intervals may be unduly affected by large numbers of participants lost to follow-up.

Where possible, follow-up data (recorded after > 6 weeks) was also analysed as 'time-to-event' using the longest available follow-up data. This analysis replaced longer-term follow-up data analysed as relative risk, but only when this did not result in the exclusion of data from studies that could only be analysed as relative risk, in which case data was analysed as both relative risk and time-to-event.

In terms of decision-making, the GDG gave greater weighting to longer-term data because it demonstrated whether effects were sustained or not. Short-term data was also reviewed because many studies only recorded follow-up at 30 days and short-term data provides results that can be more readily attributed to the investigated interventions.

3.3.2.2 Data synthesis and population subgroups

The following groups were considered separately if data were present:

- People with diabetes
- People from ethnic minorities
- People with renal dysfunction
- Females
- People aged over 70 years (if data was available, a cut off of those aged over 65 years was considered instead).

Sub-analyses based on these groups were conducted where there was sufficient data available and if the subgroup was defined a priori. If there was insufficient data for analyses relevant data was reported in the evidence tables or in summary table in the evidence reviews.

Statistical heterogeneity was assessed by considering the chi-squared test for significance at $p < 0.1$ or an I-squared inconsistency statistic of > 50% to indicate significant heterogeneity. Sensitivity analysis based on the quality of studies was also carried out if there were differences, with particular attention paid to allocation concealment, blinding and loss to follow-up (missing data). In cases where there was inadequate allocation concealment, unclear blinding, more than 50% missing data or differential missing data, this was examined in a sensitivity analysis. For the latter, the duration of follow-up was also taken into consideration prior to including in a sensitivity analysis. The following were predefined subgroups for sensitivity analysis for all evidence reviews: ethnic minorities, people with diabetes, people with renal dysfunction, females, and people aged over 70 years. For the

evidence reviews of facilitated primary percutaneous coronary intervention, rescue percutaneous coronary intervention, hospital volumes of primary percutaneous coronary intervention and unconscious people, the following were additional predefined subgroups; people receiving balloon angioplasty versus stenting, and people receiving glycoprotein IIb/IIIa inhibitors (GPIs) with PCI versus no GPI with PCI. The routine angiography evidence review had the following additional predefined subgroups: high risk versus low risk people, mean time interval to angiography after fibrinolysis, and people receiving balloon angioplasty versus stenting. The femoral versus radial approach for primary percutaneous coronary intervention evidence review had the following additional predefined subgroups: operator expertise, people receiving GPIs versus people not receiving GPIs, and people receiving GPIs with PCI versus no GPIs with PCI, and stent usage. The culprit versus complete revascularisation evidence review had the following additional predefined subgroups: stent usage and GPI therapy.

Assessments of potential differences in effect between subgroups were based on the chi-squared tests for heterogeneity statistics between subgroups. If no sensitivity analysis was found to completely resolve statistical heterogeneity then a random-effects (DerSimonian and Laird) model was employed to provide a more conservative estimate of the effect.

The means and standard deviations of continuous outcomes were required for meta-analysis. However, in cases where standard deviations were not reported, the standard error was calculated if the p values or 95% confidence intervals were reported and meta-analysis was undertaken with the mean and standard error using the generic inverse variance method in Cochrane Review Manager (RevMan5) software (http://ims.cochrane.org/revman). Where p values were reported as 'less than', a conservative approach was undertaken. For example, if p value was reported as '$p \leq 0.001$', the calculations for standard deviations will be based on a p value of 0.001. If these statistical measures were not available then the methods described in section 16.1.3 of the Cochrane Handbook (September 2009) 'Missing standard deviations' were applied as the last resort.

For binary outcomes, absolute event rates were also calculated using the GRADEpro software using event rate in the control arm of the pooled results.

3.3.3 Appraising the quality of evidence by outcomes

The evidence for outcomes from the included RCTs and observational studies were evaluated and presented using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software (GRADEpro) developed by the GRADE working group was used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The 'Clinical evidence profile' table, reported in this guideline, includes details of the quality assessment pooled outcome data, where appropriate, an absolute measure of intervention effect and the summary of quality of evidence for that outcome. In this table, the columns for intervention and control indicate the sum of the sample size for continuous outcomes. For binary outcomes such as number of people with an adverse event, the event rates (n/N: number of people with events divided by sum of number of people) are shown with percentages. Reporting or publication bias was only taken into consideration in the quality assessment and included in the clinical evidence profile table if it was apparent. Each outcome was examined separately for the quality elements listed and each graded using the quality levels listed in Table 2. The main criteria considered in the rating of these elements are discussed below (see Grading of Evidence). Footnotes were used to describe reasons for grading a quality element as having serious or very serious problems. The ratings for each component were summed to obtain an overall assessment for each outcome listed in Table 3.

Table 1: Description of quality elements in GRADE for intervention studies

Quality element	Description
Limitations	Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of the effect.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of results.
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question, or recommendation made.
Imprecision	Results are imprecise when studies include relatively few participants and few events and thus have wide confidence intervals around the estimate of the effect relative to the clinically important threshold.
Publication bias	Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies.

Table 2: Levels of quality elements in GRADE

Level	Description
None	There are no serious issues with the evidence.
Serious	The issues are serious enough to downgrade the outcome evidence by 1 level.
Very serious	The issues are serious enough to downgrade the outcome evidence by 2 levels.

Table 3: Overall quality of outcome evidence in GRADE

Level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

3.3.4 Grading the quality of clinical evidence for RCTs and observational studies

After results were pooled, the overall quality of evidence for each outcome was considered. The following procedure was adopted when using GRADE:

1. A quality rating was assigned, based on the study design. RCTs start HIGH and observational studies as LOW, uncontrolled case series as LOW or VERY LOW.
2. The rating was then downgraded for the specified criteria: Study limitations, inconsistency, indirectness, imprecision and reporting bias. These criteria are detailed below. Observational studies were upgraded if there was: a large magnitude of effect, dose-response gradient, and if all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results showed no effect. Each quality element considered to have 'serious' or 'very serious' risk of bias was rated down −1 or −2 points respectively.
3. The downgraded and upgraded marks were then summed and the overall quality rating was revised. For example, all RCTs started as HIGH and the overall quality became MODERATE, LOW or VERY LOW if 1, 2 or 3 points were deducted respectively.
4. The reasons or criteria used for downgrading were specified in the footnotes.

The details of criteria used for each of the main quality elements are discussed further in the following sections 3.3.5 to 3.3.8.

3.3.5 Study limitations

The main limitations for randomised controlled trials are listed in Table 4. Outcomes from studies were only downgraded where:

- > 50% of the pooled population contributed towards any risk of bias
- > 50% of the pooled population were derived from studies with unclear allocation concealment or unclear randomisation process or both
- > 50% of the pooled population were derived from studies that used end point definitions which differed between comparators from the same study (the threshold for defining reinfarction was higher in group allocated to revascularisation compared to comparator)
- > 50% of the pooled population were derived from studies that were open label, outcome wasn't defined and outcome assessors weren't blinded
- Comparison groups did not receive the same care
- > 20% dropout in either arm.

Table 4: Study limitations of randomised controlled trials

Limitation	Explanation
Allocation concealment	Those enrolling participants are aware of the group to which the next enrolled patient will be allocated (major problem in 'pseudo' or 'quasi' randomised trials with allocation by day of week, birth date or chart number)
Lack of blinding	Patient, caregivers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which participants are allocated
Incomplete accounting of participants and outcome events	Loss to follow-up not accounted and failure to adhere to the intention to treat principle when indicated
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results
Other limitations	For example: • Stopping early for benefit observed in randomised trials, in particular in the absence of adequate stopping rules. • Use of unvalidated patient-reported outcomes. • Carry-over effects in cross-over trials. • Recruitment bias in cluster randomised trials.

3.3.6 Inconsistency

Inconsistency refers to an unexplained heterogeneity of results. When estimates of the treatment effect across studies differ widely (that is, there is heterogeneity or variability in results), this suggests true differences in underlying treatment effect. When heterogeneity exists (chi-squared $p < 0.1$ or I-squared inconsistency statistic of > 50%), but no plausible explanation can be found, the quality of evidence was downgraded by 1 or 2 levels, depending on the extent of uncertainty to the results contributed by the inconsistency in the results. The quality of evidence was downgraded by −1 for I-squared inconsistency statistic of > 50%, and downgraded by −2 for I-squared inconsistency statistic of > 75%. If inconsistency could be explained based on pre-specified subgroup analysis, the GDG took this into account and considered whether to make separate recommendations based on the identified explanatory factors (population and intervention). Where subgroup analysis gives a plausible explanation of heterogeneity, the quality of evidence would not be downgraded.

3.3.7 Indirectness

Directness refers to the extent to which the populations, intervention, comparisons and outcome measures are similar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention. In deciding what evidence should be downgraded the GDG took into account the availability of information on populations, interventions or comparators, and directness was considered on an individual evidence reviews basis. Outcomes were downgraded as appropriate and the information was noted in the LETR. Further details are detailed in the review protocols, see Appendix C.

3.3.8 Imprecision

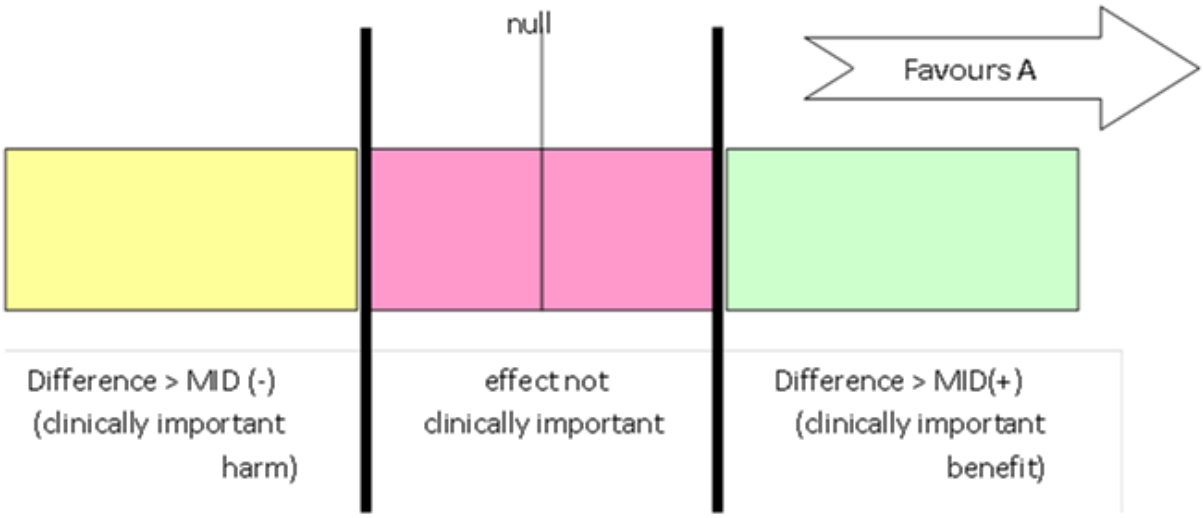
The sample size, event rates and the resulting width of confidence intervals were the main criteria considered. Where the minimal important difference (MID) of an outcome is known, the optimal information size (OIS), that is the sample size required to detect the difference with 80% power and $p \leq 0.05$, was calculated and used as the criteria. The criteria applied for imprecision are based on the confidence intervals for pooled or the best estimate of effect, outlined in Table 5. For the purposes of this guideline, the default MIDs of risk ratios of < 0.75 and > 1.25 were used for dichotomous outcomes.

Table 5: Criteria applied to determine precision

Dichotomous outcomes
Confidence interval crosses one default MID and line of no effect: downgrade by −1.
Confidence interval crosses both default MIDs and line of no effect: downgrade by −2.
Continuous outcomes
Hospital duration: MID of mean difference of > 2 days (based on consensus) (downgrade by −1 or −2)
Health-related quality of life (HRQoL) measured using 15D instrument: MID of mean difference of > 0.03 (downgrade by −1 or −2)
Other continuous outcomes: a standard mean difference (SMD) of 0.05 (downgrade by −1 or −2)

Figure 1 considers a positive outcome for the comparison of treatment A versus B. Three decision-making zones can be identified, bounded by the thresholds for clinical importance (MID) for benefit and for harm (the MID for harm for a positive outcome means the threshold at which drug A is less effective than drug B and this difference is clinically important to patients (favours B).

Figure 1: Imprecision illustration



When the confidence interval of the effect estimate is wholly contained in 1 of the 3 zones (for example, clinically important benefit), we are not uncertain about the size and direction of effect (whether there is a clinically important benefit or the effect is not clinically important or there is a clinically important harm), so there is no imprecision.

When a wide confidence interval lies partly in each of 2 zones, it is uncertain in which zone the true value of effect estimate lies, and therefore there is uncertainty over which decision to make (based on this outcome alone); the confidence interval is consistent with 2 decisions and so this is considered to be imprecise in the GRADE analysis and the evidence is downgraded by 1 ('serious imprecision').

If the confidence interval of the effect estimate crosses into 3 zones, this is considered to be very imprecise evidence because the confidence interval is consistent with 3 clinical decisions and there is a considerable lack of confidence in the results. The evidence is therefore downgraded by 2 in the GRADE analysis ('very serious imprecision').

3.3.9 Grading the quality of clinical evidence of studies for meta-regression analyses of RCTs evidence

The time to reperfusion (delay between fibrinolysis and primary percutaneous coronary intervention) evidence review used meta-regression analyses of data from RCTs or registries. The quality of evidence for these types of studies is largely dependent upon the following: the models used to analyse the data (simple linear regression versus more complex modelling) and the type and number of studies included in the model (RCT evidence from individual patient data (IPD) or study-level and registry data).

The GDG considered that IPD was the most robust quality evidence versus study-level data and registry data. The original data for each participant in an included study is used in meta-analysis or in this evidence review in meta-regression analysis. IPD reduces the risk of outcome reporting bias and the reasons for missing outcome data can be identified. We downgraded outcomes in meta-regression analyses that used study-level data which is subject to ecological fallacy. Ecological fallacy assumes that individual members of a group have the average characteristics of the group as a whole. Statistics that use group characteristics do not necessarily apply to individuals within the group, and do not account for the fact that individuals have a greater variability than the variability

of their mean. We also downgraded outcomes that were derived from fewer than 10 RCTs and from older RCTs where included RCT evidence may not reflect current clinical practice (for example stent usage and GPI IIb/IIIa inhibitor therapy). Outcomes from registry studies were downgraded because the data was derived from non-randomised participants. Outcomes data from simple linear regression models were also considered to less robust evidence compared to models that performed sensitivity analyses.

3.3.10 Evidence statements

Evidence statements were formed for each outcome indicating the quantity and quality of evidence available, and the outcome and population to which they relate. Below are some examples to illustrate how the wording indicates the imprecision (uncertainty) and clinical importance:

- Precise, both the point estimate and confidence intervals are outside the MID:

[GRADE quality] evidence showed that intervention a is more clinically effective when compared to intervention b at reducing/improving* [outcome] at xx months/years [xx studies, n =].

- Precise, both the point estimate and confidence intervals are between the MID and no difference:

[GRADE quality] evidence showed that intervention a is more effective when compared to intervention b at reducing/improving* [outcome] at xx months/years, but the effect size is too small to be clinically important [xx studies, n =].

- Serious imprecision, point estimate outside the MID, and the confidence interval crosses the MID:

[GRADE quality] evidence suggested that intervention a is potentially more clinically effective when compared to intervention b at reducing/improving* [outcome] at xx months/years [xx studies, n =].

- Serious imprecision, point estimate between the MID and no difference, and the confidence interval crosses the MID:

[GRADE quality] evidence suggested that there may be no clinical difference between intervention a when compared to intervention b at reducing/improving* [outcome] at xx months/years, but the direction of the estimate of effect favoured intervention a [xx studies, n =].

- Very serious imprecision, point estimate outside the MID, and the confidence interval crosses the MID in both directions:

[GRADE quality] evidence suggested that intervention a is potentially more clinically effective when compared to intervention b at reducing/improving* [outcome] at xx months/years, but the direction of the estimate of effect could favour either intervention [xx studies, n =].

- Very serious imprecision, point estimate between the MID and no difference, and the confidence interval crosses the MID in both directions:

[GRADE quality] evidence suggested that there may be no clinical difference between intervention a and intervention b at reducing/improving* [outcome] at xx months/years, but the direction of the estimate of effect could favour either intervention [xx studies, n =].

- Precise, point estimate close to line of no difference, confidence intervals just cross line of no difference:

[GRADE quality] evidence showed that there is no clinical difference between intervention a and intervention b at reducing/improving* [outcome] at xx months/years [xx studies, n =].

* As appropriate according to outcome

When imprecision could not be assessed, the following statement will be used: ‘the difference is uncertain as no comparative analysis could be carried out’.

3.4 Evidence of cost effectiveness

The GDG is required to make decisions based on the best available evidence of both clinical and cost effectiveness. Guideline recommendations should be based on the estimated costs of the treatment options in relation to their expected health benefits (that is, their 'cost effectiveness'), rather than on the total implementation cost.[228] Thus, if the evidence suggests that a strategy provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population.

Evidence on cost effectiveness related to the key clinical issues being addressed in the guideline was sought. The health economist undertook:

- A systematic review of the published economic literature.
- New cost-effectiveness analysis in priority areas.

3.4.1 Literature review

The health economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts – full papers were then obtained.
- Reviewed full papers against pre-specified inclusion and exclusion criteria to identify relevant studies (see below for details).
- Critically appraised relevant studies using the economic evaluations checklist as specified in the guidelines manual.[228]
- Extracted key information about the studies' methods and results into evidence tables (evidence tables are included in Appendix H).
- Generated summaries of the evidence in NICE economic evidence profiles (included in the relevant chapter for each review question) – see below for details.

3.4.1.1 Inclusion and exclusion

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost–utility, cost-effectiveness, cost–benefit and cost–consequence analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially includable as economic evidence.

Studies that only reported cost per hospital (not per patient), or only reported average cost effectiveness without disaggregated costs and effects, were excluded. Abstracts, posters, reviews, letters, editorials, comment articles, publications not in English and unpublished studies were excluded. Studies judged to have an applicability rating of 'not applicable' were excluded (this included studies that took the perspective of a non-OECD country).

The remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high-quality, directly applicable UK analysis was available other less relevant studies may not have been included. Where exclusions occurred on this basis, this is noted in the relevant section.

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist (the guidelines manual[228]) and the health economics research protocol in Appendix C.

3.4.1.2 NICE economic evidence profiles

The NICE economic evidence profile has been used to summarise cost and cost-effectiveness estimates. The economic evidence profile shows an assessment of applicability and methodological quality for each economic study, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from the guidelines manual.[228] It also shows incremental costs, incremental effects (for example, quality-adjusted life-years [QALYs]) and the incremental cost-effectiveness ratio from the primary analysis, as well as information about the assessment of uncertainty in the analysis.

If a non-UK study was included in the profile, the results were converted into pounds sterling using the appropriate purchasing power parity.[249]

Table 6: Content of NICE economic evidence profile

Item	Description
Study	First author name, reference, date of study publication and country perspective.
Applicability	An assessment of applicability of the study to the clinical guideline, the current NHS situation and NICE decision-making*: • Directly applicable – the applicability criteria are met, or one or more criteria are not met but this is not likely to change the conclusions about cost effectiveness. • Partially applicable – one or more of the applicability criteria are not met, and this could change the conclusions about cost effectiveness. • Not applicable – one or more of the applicability criteria are not met, and this is likely to change the conclusions about cost effectiveness. Studies which are not applicable would be excluded from the economic profile table.
Limitations	An assessment of methodological quality of the study*: • Minor limitations – the study meets all quality criteria, or the study fails to meet one or more quality criteria, but this is unlikely to change the conclusions about cost effectiveness. • Potentially serious limitations – the study fails to meet one or more quality criteria, and this could change the conclusion about cost effectiveness • Very serious limitations – the study fails to meet one or more quality criteria and this is very likely to change the conclusions about cost effectiveness. Studies with very serious limitations would usually be excluded from the economic profile table.
Other comments	Particular issues that should be considered when interpreting the study.
Incremental cost	The mean cost associated with one strategy minus the mean cost of a comparator strategy.
Incremental effects	The mean QALYs (or other selected measure of health outcome) associated with one strategy minus the mean QALYs of a comparator strategy.
Cost effectiveness	Incremental cost-effectiveness ratio (ICER): the incremental cost divided by the respective QALYs gained.
Uncertainty	A summary of the extent of uncertainty about the ICER reflecting the results of deterministic or probabilistic sensitivity analyses, or stochastic analyses of trial data, as appropriate.

*Limitations and applicability were assessed using the economic evaluation checklist from Appendix H of the guidelines manual[228]

3.4.2 Undertaking new health economic analysis

As well as reviewing the published economic literature for each review question, as described above, new economic analysis was undertaken by the health economist in selected areas. Priority areas for

new health economic analysis were agreed by the GDG after formation of the review questions and consideration of the available health economic evidence.

The GDG did not identify any priority areas which were suitable for original economic modelling. The GDG identified radial versus femoral access PPCI and the use of thrombus extraction devices as the 2 highest priority areas for original comparative cost analysis. These were chosen as in each case both options (PPCI via radial access or femoral access; PPCI with and without the use of thrombus extraction devices) are in common use, their relative cost effectiveness was uncertain, and their relative costs were not known but thought to be similar.

The following general principles were adhered to in developing the comparative cost analyses:

- Methods were consistent with the NICE reference case.[221]
- The GDG was consulted during the research and interpretation of the analyses.
- Data inputs were based on the systematic review of the clinical literature supplemented with other published data sources where possible.
- When published data was not available GDG expert opinion was used.
- Data inputs and assumptions were reported fully and transparently.
- The results were subject to sensitivity analysis where appropriate and limitations were discussed.
- The analyses were peer-reviewed by an independent external health economist.

Full methods for the comparative cost analyses are described in Appendices L and M.

3.4.3 Cost-effectiveness criteria

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that GDGs should consider when judging whether an intervention offers good value for money.[225] In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

a. 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
b. The intervention cost less than £20,000 per quality-adjusted life year (QALY) gained compared with the next best strategy.

If the GDG recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'Recommendations and link to evidence' section of the relevant chapter with reference to issues regarding the plausibility of the estimate or to the factors set out in 'Social value judgements: principles for the development of NICE guidance'.[225]

3.4.4 In the absence of cost-effectiveness evidence

When no relevant published studies were found, and a new analysis was not prioritised, the GDG made a qualitative judgement about cost effectiveness by considering expected differences in resource use between options and relevant UK NHS unit costs alongside the results of the clinical review of effectiveness evidence.

3.5 Developing recommendations

Over the course of the guideline development process, the GDG was presented with:

- Evidence tables of the clinical and economic evidence reviewed from the literature. All evidence tables are in Appendices G and H.
- Summary of clinical and economic evidence and quality (as presented in chapters 5-17).
- Forest plots (Appendix I).
- A description of the methods and results of the comparative cost analyses undertaken for the guideline (Appendices L and M).

Recommendations were drafted on the basis of the GDG interpretation of the available evidence, taking into account the balance of benefits, harms and costs. When clinical and economic evidence was of poor quality, conflicting or absent, the GDG drafted recommendations based on their expert opinion. The considerations for making consensus-based recommendations include the balance between potential harms and benefits, economic costs or implications compared to the benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The consensus recommendations were agreed through discussions in the GDG. The GDG also considered whether the uncertainty was sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation (see section 3.5.1 below).

The main considerations specific to each recommendation are outlined in the 'Recommendations and link to evidence' sections.

3.5.1 Research recommendations

When areas were identified for which good evidence was lacking, the GDG considered making recommendations for future research. Decisions about inclusion were based on factors such as:

- the importance to patients or the population
- national priorities
- potential impact on the NHS and future NICE guidance
- ethical and technical feasibility.

3.5.2 Validation process

This guidance is subject to a 6-week public consultation and feedback as part of the quality assurance and peer review of the document. All comments received from registered stakeholders are responded to in turn and posted on the NICE website when the pre-publication check of the full guideline occurs.

3.5.3 Updating the guideline

A formal review of the need to update a guideline is usually undertaken by NICE after its publication. NICE will conduct a review to determine whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

3.5.4 Disclaimer

Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited

here must be made by practitioners in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The National Clinical Guideline Centre disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

3.5.5 Funding

The National Clinical Guideline Centre was commissioned by the National Institute for Health and Care Excellence to undertake the work on this guideline.

4 Guideline summary

4.1 Algorithm

The current visual summaries can be found at: www.nice.org.uk/guidance/ng185

4.2 Key priorities for implementation

This content has been removed. The current recommendations can be found at: www.nice.org.uk/guidance/ng185

4.3 Full list of recommendations

The current recommendations can be found at: www.nice.org.uk/guidance/ng185

4.3.1 Recommendations incorporated from NICE technology appraisal guidance:

The current recommendations can be found at: www.nice.org.uk/guidance/ng185

4.4 Key research recommendations

The current research recommendations can be found at: www.nice.org.uk/guidance/ng185

5 Time to reperfusion (delay between fibrinolysis and primary percutaneous coronary intervention)

5.1 Introduction

STEMI is most often caused by complete occlusion of a coronary artery by a blood clot (thrombus). As soon as the coronary blood supply is interrupted, heart muscle (myocardium) starts to be lost, and the longer the blood supply is occluded the greater the heart muscle damage. In animal models nearly half of potentially salvageable myocardium is lost within 1 hour, and two-thirds lost within 3 hours, of experimental coronary artery occlusion.[258]

The objectives of treatment are to restore coronary blood supply (reperfusion) as soon as possible after the onset of symptoms of acute STEMI. Reperfusion can be achieved by mechanical techniques (coronary angioplasty, thrombus extraction catheters, stenting) that are grouped under the overarching term 'primary percutaneous coronary intervention' (PPCI), or by the use of fibrinolytic drugs that lyse the coronary thrombus ('clot-busting' agents).

Fibrinolytic drugs are administered intravenously and can be initiated out of hospital by an ambulance crew or in the emergency department of a hospital. PPCI, on the other hand, requires transfer to an interventional cardiology service, which inevitably delays initiation of reperfusion treatment and incurs additional costs (for access to a specialist cardiac catheter laboratory and an on-call multidisciplinary clinical team). Regardless of the reperfusion method used, delays to treatment are associated with an increased risk of impaired left ventricular systolic function and death.[7,25,32,41,42,48,75,77,184,191,206]

Meta-analyses of randomised clinical trials have shown that PPCI is superior to fibrinolysis, with lower rates of mortality, reinfarction and stroke, but only when the additional time taken to deliver PPCI relative to fibrinolysis is not excessive.[14,127,158] The effects of reperfusion therapy are also believed to be influenced by various factors, such as:

- Age – mortality and adverse events (such as stroke and renal impairment) increase with age.
- Site of infarction – large anterior myocardial infarcts may result in greater loss of heart muscle than infarcts in other coronary artery territories.
- 'Patient presentation delay' – this is the time interval between the onset of symptoms of STEMI and the 'call for help' (either a call to the ambulance service or arrival at hospital if the patient self-presents to the emergency department). The longer the patient presentation delay, the greater the potential for heart muscle damage, and if the patient presentation delay exceeds 12 hours there is consensus that little benefit is gained by either reperfusion technique.[32,285]
- 'PPCI-related time delay' – this is the estimated time interval between when fibrinolysis could be offered, and the later time when PPCI could be undertaken. The PPCI-related time delay is a consequence of the additional time taken to transfer the patient to a PPCI centre.

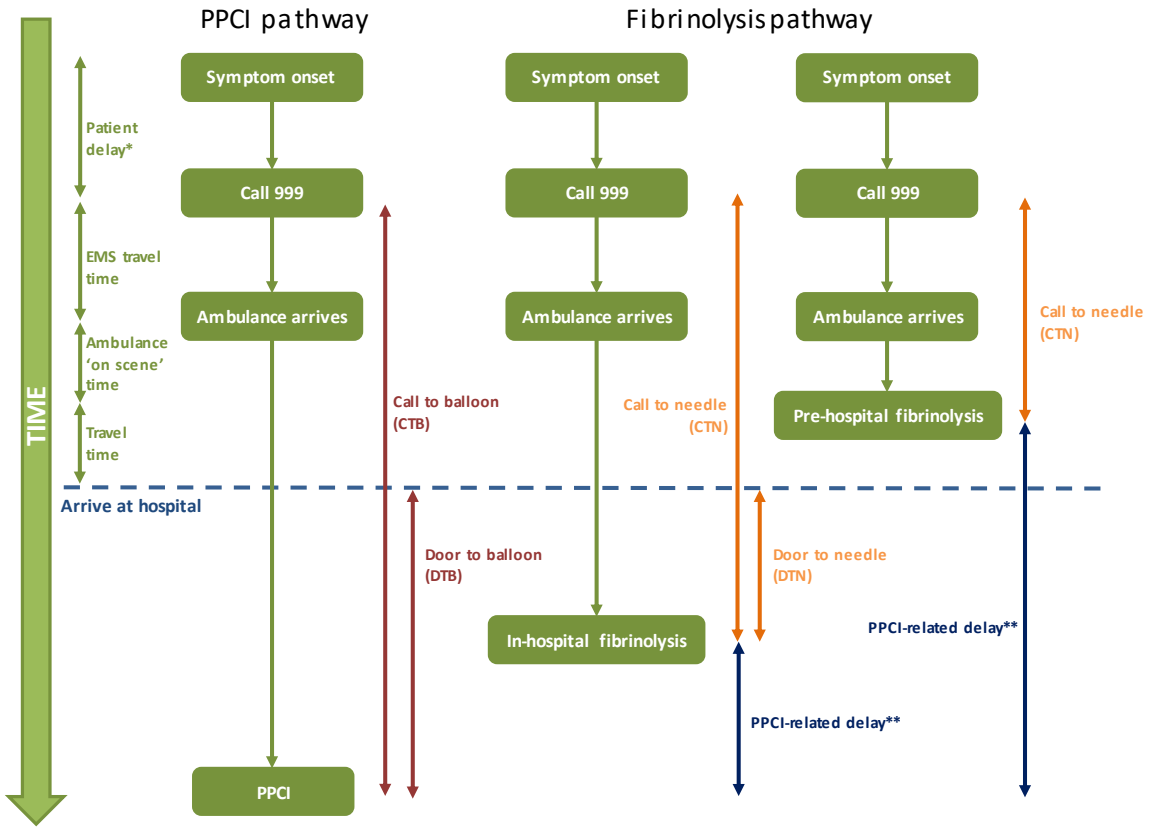
When assessing the potential 'timeliness' of PPCI and deciding which method of reperfusion therapy to use for an individual patient, certain time intervals are considered, and these are shown in Figure 2. Given that clinical outcomes are related to the rapidity with which coronary reperfusion can be achieved, the most clinically-relevant time interval is the time from the onset of symptoms of acute STEMI to the time of reperfusion of the occluded coronary artery. In the case of PPCI this is the 'symptom-to-balloon' time (the difference between the time of symptom onset and the time of inflation of an angioplasty balloon in the occluded coronary artery) and for fibrinolysis this is the

'symptom-to-needle' time (the difference between the time of symptom onset and the time of insertion of an intravenous cannula for delivery of the fibrinolytic agent). However, the component of this clinically most relevant time interval that can be influenced by health services begins when the patient calls for help and activates the emergency services. Hence, the performance of reperfusion services is assessed, at least in part, by achievement of satisfactory 'call-to-balloon' (CTB) and 'call-to-needle' (CTN) times. In addition, the hospital component of the reperfusion pathway can be assessed by the 'door-to-balloon' (DTB) and 'door-to-needle' (DTN) times (defined as the time difference between arrival at the hospital and inflation on an angioplasty balloon or in-hospital administration of the fibrinolytic agent). The PPCI-related time delay is defined in clinical trials of reperfusion therapy as the difference between the CTB and CTN times (or DTB and DTN times) and represents the additional delay required to deliver PPCI relative to fibrinolysis.

In 2008 PPCI became the preferred coronary reperfusion therapy in the UK, provided that it can be delivered in a 'similar timeframe' to fibrinolysis.[80] Since then the Department of Health has been implementing PPCI across the NHS,[80] and it is estimated that it should be feasible to provide PPCI with acceptable treatment times to approximately 95% of the STEMI population.[79] In England and Wales in 2011/12, 92.5% (19,907) of people with STEMI who received reperfusion were treated by PPCI and 7.5% were given fibrinolysis.[204] In the UK in 2011 median call-to-balloon times for PPCI were 111 minutes across all hospitals, 105 minutes for direct admissions to PPCI hospitals, and 150 minutes for inter-hospital transfer.[183] In England in 2011/12, 92% of eligible people with STEMI were treated with PPCI within 90 minutes of arrival at the PPCI centre and fibrinolysis was administered to 54% of eligible people within 60 minutes of calling for professional help.[204]

This chapter reviews evidence from trials of reperfusion therapy to assess the impact of delays to treatment on the relative outcomes of PPCI and fibrinolysis. In particular the data were reviewed to determine whether there is a PPCI-related time delay at which fibrinolysis becomes more clinically and cost effective than PPCI in people with STEMI and whether this time delay is modulated by patient presentation delay and patient risk profile.

Figure 2: Time intervals related to each reperfusion strategy



**Patient delay (or patient presentation delay) is the delay between symptom onset and the call to the ambulance service or arrival at hospital if the patient self-presents to the emergency department.*
***PPCI-related time delay is the delay between the time at which fibrinolysis would have been given and the time at which PPCI was provided.*
EMS = emergency medical service
CTB = call-to-balloon
CTN = call-to-needle
DTB = door-to-balloon
DTN = door-to-needle

5.2 Review question: what is the duration of PPCI-related time delay at which fibrinolysis becomes more clinically and cost effective compared to PPCI in people with STEMI and how is this modulated by patient presentation delay and patient risk profile?

For full details see review protocol in Appendix C.

5.3 Clinical evidence

The primary aim of the clinical review was to determine the relationship between the PPCI-related time delay and the incremental benefit of PPCI over fibrinolysis. We were also interested in the impact of patient presentation delay and patient risk factors on the relative benefit of PPCI. The definition of PPCI-related time delay in this review is the difference between time to balloon (for PPCI) and time to needle for fibrinolysis (as detailed in Figure 2). PPCI-related time delay cannot be derived from individual patient data. In the studies included in this review PPCI-related time delay was calculated as the difference between the median time to PPCI and median time to fibrinolysis

within individual trials (trial-specific PPCI-related time delay) or at individual hospitals (hospital-specific PPCI-related time delay). The definition of patient presentation delay in this review is the time from symptom onset to the 'first medical contact' (either the call to the ambulance service or arrival at hospital for people self-presenting to the emergency department). In the randomised trials of PPCI versus fibrinolysis the patient presentation delay was the time from symptom onset to randomisation or hospitalisation (Table 7).

We found no RCTs that were specifically designed to determine the impact of the PPCI-related time delay on the relative efficacy of PPCI and fibrinolysis. Consequently, we undertook a literature review of meta-regression studies that examined the association between clinical outcomes and PPCI-related time delay or patient presentation delay. The studies either used study-level data from RCTs, individual patient data (IPD), or registry data.

Twelve studies matched our inclusion criteria.[14,30,33,74,159,205,206,251,295,296,306,339] Eight studies were post-hoc analyses of pooled study-level data from RCTs.[14,30,74,159,205,206,295,296] Two studies used IPD from RCTs.[33,339] Two studies used registry data.[251,306]

We assessed the inclusion and exclusion criteria of the 10 meta-regression studies of RCTs to ensure that they included only RCTs of PPCI versus fibrinolysis. In addition we conducted an independent literature review to identify all RCTs comparing PPCI to fibrinolysis and thus check whether all relevant RCTs were included in the meta-regression studies. Details of all of the RCTs that were identified in our literature search or included in the 10 meta-regression studies are given in Table 7. The footnotes record any RCTs that were identified by our search but not included in the individual meta-regression studies**.**

Table 7: RCTs identified in our literature search and RCTs included in each meta-regression study*

RCT	This review#	Tarantini 2010	DeLuca 2009	Asseburg 2007	Boersma 2006	Betriu 2005	Nallamothu 2004	Tarantini 2004	Nallamothu 2003	Zijlstra 2002	Kent 2001
Akhras 1997[2]	✓	L	B	B	✓	B	B	B	B	✓	F
Andersen 2002¥; Andersen2003[4]	✓	✓	✓	✓	✓	✓	✓	✓	✓	F	F
Aoki 1997[9]	K	F	F	G	✓	G	G	G	G	F	F
Armstrong 2013[11]	✓	F	F	F	F	F	F	F	F	F	F
Aversano 2002[15]	✓	✓	✓	✓	✓	✓	✓	✓	✓	F	F
Bonnefoy 2002[37]	✓	✓	✓	✓	I	✓	✓	✓	✓	F	F
Bueno 2011[44]	✓	F	F	F	F	F	F	F	F	F	F
de Boer 1994[67]	✓	L	F	✓	G	G	G	G	G	G	G
de Boer 2002[68]	✓	L	✓	✓	✓	✓	✓	✓	✓	F	F
DeWood 1989¤; DeWood 1990¤; DeWood 1992[81-83]	✓	✓	✓	✓	H	✓	✓	✓	✓	H	✓
Dobrzycki 2006[86]	D	G	✓	F	F	F	F	F	F	F	F
Garcia 1999; Garcia 1997§[110,111]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	F
Gao 2010[109]	✓	F	F	F	F	F	F	F	F	F	F
Gibbons 1993[114]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Grines 1993[123]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Grines 2002[124]	✓	✓	✓	✓	✓	✓	C	✓	✓	F	F
Grines 2005[122]	K	✓	B	F	F	F	F	F	F	F	F
Grinfeld 1996†; Berrocal 2003[28]	✓	L	✓	✓	✓	✓	✓	✓	✓	✓	✓
GUSTO IIb 1997[299]	✓	✓	✓	✓	✓	✓	✓	√	✓	✓	✓
Hochman 1999[134]	✓	J	J	E	G	A	A	J	A	F	F
Kastrati 2002[154]	✓	✓	✓	✓	✓	✓	✓	✓	✓	F	F

RCT	This review#	Tarantini 2010	DeLuca 2009	Asseburg 2007	Boersma 2006	Betriu 2005	Nallamothu 2004	Tarantini 2004	Nallamothu 2003	Zijlstra 2002	Kent 2001
Kedev 1997[155]	✓	L	F	G	✓	G	G	G	G	F	F
Le May 2001[167]	✓	✓	✓	✓	✓	✓	✓	✓	✓	F	F
Morais 1997[201]	K	F	F	G	H	G	G	G	G	F	F
Ribeiro 1993[260]	✓	L	✓	✓	✓	✓	✓	✓	✓	✓	✓
Ribichini 1996€; Ribichini 1998[261]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Schomig 2000[270]	✓	✓	✓	✓	✓	✓	✓	✓	✓	F	F
Svensson 2006[292]	D	G	✓	F	F	F	F	F	F	F	F
Vermeer 1999[318]	✓	✓	✓	✓	✓	✓	✓	✓	✓	F	F
WEST 2006[12]	✓	✓	✓	F	F	F	F	F	F	F	F
Widimsky 2000[330]	✓	L	✓	✓	✓	✓	✓	✓	✓	F	F
Widimsky 2002¶;Widimsky 2003[329]	✓	L	✓	✓	✓	✓	✓	✓	✓	F	F
Zijlstra 1993[338]	✓	L	✓	✓	✓	✓	✓	✓	✓	✓	✓
Zijlstra 1997[337]	✓	L	✓	✓	✓	✓	✓	✓	✓	✓	✓

**This table includes meta-regression studies using RCT evidence; studies using registry data are detailed in Table 8*
 # Literature review conducted by NCGC to identify all RCTs assessing PPCI compared to fibrinolysis in people with STEMI (January 1990–October 2011). We also scanned the reference lists of all included meta-analyses for relevant articles
§ Abstract subsequently published as Garcia 1999
¥ Abstract subsequently published as Andersen 2003, unable to source abstract
¶ Abstract subsequently published as Widimsky 2003, unable to source abstract
€ Abstract subsequently published as Ribichini 1998, unable to source abstract
† Abstract subsequently published as Berrocal 2003, unable to source abstract
¤ Abstracts subsequently published as DeWood 1992
A Excluded because study performed exclusively in participants with cardiogenic shock
B Excluded because study did not report time to treatment
C Excluded because study used streptokinase and rt-PA
D Excluded because the study compared facilitated PPCI to fibrinolysis
E Excluded because emergency revascularisation arm did not differentiate results by type of intervention (angioplasty 64%, surgery 36%)
F RCT published after the meta-regression's literature search was run
G Not identified/included by meta-analyses
H Excluded from primary analysis because of non-availability of individual patient data

I Excluded from primary analysis because CAPTIM investigators judged that their protocol (which included pre-hospital fibrinolysis) was incompatible with the other trials included in the pooled analysis; included in sensitivity analysis
J Excluded because it did not directly compare PPCI to fibrinolysis
K Excluded - conference abstract with insufficient information to include in review
L Excluded because the study used streptokinase

Final selection of meta-regression studies together with the reasons for exclusion of some studies are given in Table 8. We excluded 5 out of 10 meta-regression studies using pooled RCT evidence after our initial assessment.[30,74,205,206,295] Four studies were excluded because they only reported absolute risk reductions for the outcome measures.[30,205,206,295] Absolute risk reductions do not take account of the underlying baseline risk of events occurring in the population. One study was excluded because it included 2 RCTs that assessed facilitated PPCI versus fibrinolysis.[74] One study that used registry data was included.[251] A second study using registry data was excluded because it did not report the relative benefit of either PPCI or fibrinolysis according to PPCI-related time delay.[306]

Table 8: Final selection of meta-regression studies and reasons for exclusions

Meta-regression study	Included (yes / no)	Reason for exclusion
Kent 2001[159]	Yes	NA
Zijlstra 2002[339]	Yes	NA
Nallamothu 2003[206]	No	Only reported absolute risk reduction
Nallamothu 2004[205]	No	Only reported absolute risk reduction
Tarantini 2004[295]	No	Only reported absolute risk reduction
Betriu 2005[30]	No	Only reported absolute risk reduction
Boersma 2006[33]	Yes	NA
Pinto 2006[251]	Yes	NA
Asseburg 2007[14]	Yes	NA
Ting 2008[306]	No	Benefit of either PPCI or fibrinolysis according to PPCI-related time delay not reported
Deluca 2009A[74]	No	Meta-regression analysis included 2 RCTs of facilitated PPCI versus fibrinolysis
Tarantini 2010[296]	Yes	NA

NA = not applicable

Details of the 6 meta-regression studies included in this review are given are given in **Table 9**. Three meta-regression studies used study-level RCT data.[14,159,296], 2 meta-regression studies used individual patient data from RCTs[33,339], and 1 meta-regression study used registry data.[251] The methodology, quality assessment and results of the individual studies are discussed in Section 5.3.1. Comparisons of the evidence and quality of the meta-regressions studies are discussed in Section 5.3.2.

Table 9: Summary of the included meta-regression studies, their analysis methods and data

Study	Assessed PPCI-related time delay (Yes / No)	Assessed Patient presentation delay (Yes / No)	Subgroup analysis based on patient risk profile (Yes / No)	Data source	Analysis	Outcome
Kent 2001[159]	Yes	No	No	10 RCTs (n = 2628) 5 RCTs used streptokinase 0 RCTs used stents 0 RCTs used GPIs	• Study-level data • Linear regression using weighted mean squares regression • No adjustment for confounders • Sensitivity analysis of the regression to outliers (longest or shortest delays)	30-day all-cause mortality
Zijlstra 2002[339]	No	Yes	No	10 RCTs (n = 2635) 5 RCTs used streptokinase 0 RCTs used stents 0 RCTs used GPIs	• Patient-level data • Categorised into early, intermediate time to presentation	1-month and 6-month all-cause mortality, reinfarction, stroke
Pinto 2006[251]	Yes	Yes	Yes	NRMI registry (n = 192,509)	• Patient-level data • GENMOD linear regression; multivariable • Covariate adjusted; treatment type (PPCI or fibrinolysis), age, gender, race, diabetes mellitus, hypertension, angina, Killip class 2/3, Killip class 4, previous MI, current smoking, stroke, pulse, systolic blood pressure, payer, pre-hospital delay, and discharge year. Hospital covariates included STEMI volume, PPCI volume, transfer-in rate, rural location, and status as a teaching hospital • Subgroup analysis; time from symptom onset to hospital presentation (≤ 120 minutes versus > 120 minutes), < 65 years versus ≥ 65 years, anterior versus non-anterior MI	In-hospital all-cause mortality
Boersma 2006[33]	Yes	Yes	Yes	22 RCTs (n = 6763) 9 RCTs used	• Patient-level data • Single and multilevel logistic regression (fixed and random	30-day all-cause mortality

Study	Assessed PPCI-related time delay (Yes / No)	Assessed Patient presentation delay (Yes / No)	Subgroup analysis based on patient risk profile (Yes / No)	Data source	Analysis	Outcome
				streptokinase 10 RCTs used stents 6 RCTs used GPIs	effects) • Covariate adjustment • Patient level; age, gender, weight, diabetes mellitus, previous MI, prior revascularisation (PCI or CABG), anterior MI at presentation, heart rate, systolic blood pressure, patient presentation delay, and study treatment (PPCI or fibrinolysis). Hospital level: the average annual PPCI volume, PPCI-related time delay. • Study level: annual PPCI volume, likelihood of PPCI within 30 days after initial fibrinolysis, use of stents, use of GPIs, type of fibrinolytic agent used (streptokinase, t-PA, or accelerated t-PA), single-centre versus multi-centre RCT, and the year of publication. • Subgroup analysis (specified in advance): < 65 years versus ≥ 65 years, male / female, diabetes, prior MI, anterior versus non-anterior MI, systolic blood pressure (< 130 versus ≥ 130 mmHg), heart rate (70 versus ≥ 70 BPM), hospital-level annual PCI volume and study-level type of fibrinolytic agent used • Single-level logistic regression for (i) impact of exclusion of 3 RCTs without IPD, (ii) type of fibrinolytic agent used	OR (95% CI) for outcome: patient presentation delay in quintiles: 0–1, > 1–2, > 2–3, > 3–6, > 6 hours OR (95% CI) for outcome: PPCI-related time delay in quintiles: 0–35, > 35–50, > 50–62, > 62–79, > 79–120 minutes
Asseburg 2007[14]	Yes	No	No	22 RCTs (n = 7518) 8 RCTs used streptokinase 13 RCTs used stents 8 RCTs used GPIs	• Study-level data • Bayesian linear regression • No adjustment for confounders • Sensitivity analysis streptokinase versus tissue plasminogen activator trials	1- and 6-month all-cause mortality, non-fatal reinfarction, non-fatal stroke

Study	Assessed PPCI-related time delay (Yes / No)	Assessed Patient presentation delay (Yes / No)	Subgroup analysis based on patient risk profile (Yes / No)	Data source	Analysis	Outcome
Tarantini 2010[296]	Yes	No	No	16 RCTs (n = 6281) 0 RCTs used streptokinase 0 RCTs used stents 7 RCTs used GPIs	• Study-level data • Multiple linear regression analysis • No adjustment for confounders • Assessed association between baseline patient risk and PPCI-related time delay according to 30-day all-cause mortality outcome • Sensitivity analysis excluding the RCT reporting the smallest effect size and RCT reporting the greatest effect size	30-day all-cause mortality

GPIs; glycoprotein IIb/IIIa, OR; odds ratio, stents used during PPCI procedure

The search strategies for the 5 meta-regression studies using RCT data are given in Appendix N.

Our literature search identified 3 additional RCTs that published after the meta-regression analyses were completed[11,12,44] (Appendix N). The GDG considered the data from these additional RCTs would be unlikely to have a significant impact on the effect estimates or imprecision due to the consistency in the direction of effect and the relatively large pooled sample size in the meta-regression studies.

We performed a meta-analysis of the RCT data in the meta-regression studies and in the additional studies we identified (see Appendix I1). We excluded 5 studies in table 7 from the meta-analysis: 2 studies were published as abstracts and insufficient information was available[9,201], 2 RCTs were excluded as facilitated PPCI was compared with fibrinolysis[86,292], and 1 RCT was excluded because we were unable to source the abstract[122]. The meta-analysis demonstrates the benefit of PPCI versus fibrinolysis for the outcome of short-term all-cause mortality. The forest plot shows that the point estimate of effect varies across the RCTs but overall PPCI was associated with an 18% reduction in the risk of 30-day mortality relative to fibrinolysis.

The outcome of all-cause mortality at 30 days was examined in 3 meta-regression studies[33,159,296]. Two meta-regression study examined all-cause mortality, non-fatal reinfarction and stroke at 1 and 6 months[14,339], and 1 study examined all-cause mortality occurring in hospital before discharge [251].

5.3.1 Method, quality assessment and results of included meta-regression studies

This section discusses the methodology and findings of the 6 included meta-regression studies. The methods used to analyse the data, outcomes and length of follow-up, differed by study. Four studies calculated the PPCI-related time delay associated with equipoise.[14,159,251,296]. In this review equipoise is defined as the PPCI-related time delay at which there is no survival advantage of PPCI over fibrinolysis. One meta-regression study reported covariate adjusted ORs at 5 different patient presentation delays and PPCI-related time delays.[33] Two meta-regression studies assessed patient presentation delay.[33,339] Three meta-regression studies examined the relationship between the risk profile of the participants and patient presentation delay or PPCI-related time delay.[33,251,296] A summary of the methods used in the meta-regression studies, and where applicable RCT data sources including stent usage and relevant concomitant therapy is given in Table 9.

5.3.1.1 Kent 2001[159]

Methods

The Kent 2001 meta-regression study used study-level data from a previously published meta-analysis [325] of 10 RCTs (search date 1996, outcome of 30-day all-cause mortality).[159] The relationship between PPCI-related time delay and treatment effect was examined using linear regression. Weighted least squares regression was used to assess the magnitude and statistical significance of the relationship. The result from each RCT was weighted by the square root of the number of participants in the RCT. Sensitivity analysis was performed by excluding the RCTs that had the shortest or longest PPCI-related time delay.

Quality assessment

The meta-regression study included fewer RCTs (n = 10) than other analyses included in this systematic review.[14,33] Meta-regressions with small numbers of RCTs are more likely to have measurement errors which affect precision and result in a greater likelihood of chance findings. None of the included RCTs used stents, which is not reflective of current practice. Furthermore there was little information given on how the model was developed, and there was no assessment of potential confounders. There was no rationale given for the sensitivity analysis removing outliers and it was not defined in advance, which decreases confidence in the results.

A summary of the quality assessment using an adapted GRADE system is presented in Table 10.

Results

Linear regression analysis showed that when the PPCI-related time delay reached 50.1 minutes, the 30-day all-cause mortality rates were likely to be equivalent for PPCI versus fibrinolysis. Sensitivity analysis found that the result was essentially the same when the RCT with the longest PPCI-related time delay (defined in the study as 59 minutes) was excluded from the analysis (PPCI-related time delay at equipoise excluding the RCT with the longest PPCI-related time delay was 50.0 minutes). Similarly, excluding the RCT with the shortest PPCI-related time delay (defined in the study as 7 minutes) did not substantially alter the PPCI-related time delay at which PPCI was equivalent to fibrinolysis (PPCI-related time delay at equipoise excluding the RCT with the shortest PPCI-related time delay was 49.4 minutes) . Exclusion of both outliers did not alter the equipoise (total for 10 RCTs = 50.1 minutes versus 8 RCTs excluding outliers = 50.1 minutes).

Table 10: Clinical evidence profile: Kent 2001[159]

Quality assessment							Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Equipoise	Quality	Importance
Short-term all-cause mortality									
10	Study level of randomised trials	Very serious (a),(b)	No serious inconsistency	Serious (b)	No serious imprecision	No covariate adjustment	Equipoise: 50 minutes	VERY LOW	CRITICAL

(a) Study-level data that is subject to ecological fallacy. Ecological fallacy assumes that individual members of a group have the average characteristics of the group as a whole. Statistics that use group characteristics do not necessarily apply to individuals within the group, and do not account for the fact that individuals have a greater variability than the variability of their mean.
(b) None of studies used stents in PPCI arm, older RCTs less reflective of current practice.

5.3.1.2 Zijlstra 2002[339]

Methods

This meta-regression study used individual patient data from 10 RCTs to examine patient outcomes according to patient presentation delay (PPCI; n = 1302 versus fibrinolysis; n = 1333, search date 2004, outcomes of all-cause mortality, composite of all-cause mortality and reinfarction, composite of all-cause mortality, reinfarction and stroke).[339] The study used individual patient-level data that was based on a previously published meta-analysis [325] with the addition of 1 further RCT.[2]Time-to-presentation was measured from the onset of symptoms to randomisation in 6 RCTs and from symptom onset to hospital admission in 3 RCTs, while information was unavailable for 1 RCT. People were categorised as early (< 2 hours), intermediate (2–4 hours) or late (> 4 hours) presenters. The following risk factors were assessed using univariate and mutivariate logistic regression: time-to-presentation, age, gender, diabetes, infarct location, prior MI, heart rate on admission and systolic blood pressure.

Quality assessment

The meta-regression examined outcomes after PPCI and fibrinolysis as a function of time. IPD was used but only 10 RCTs were included in the analysis. There was no analysis of the correlation between the 2 interventions with respect to PPCI-related time delay.

A summary of the quality assessment using an adapted GRADE system is presented in Table 11.

Table 11: Clinical evidence profile: Zijlstra 2002[339]

Quality assessment							Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Event (%)	Quality	Importance
Short-term all-cause mortality									
10	IPD of randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Unable to estimate	No covariate adjustment, did not report confidence intervals around event rates	Fibrinolysis all-cause mortality (%) < 2 hours: 5.0 2–4 hours: 6.3 > 4 hours: 12.1 PPCI all-cause mortality < 2 hours: 3.9 2–4 hours: 4.1 > 4 hours: 4.7	LOW	CRITICAL
Longer-term all-cause mortality									
10	IPD of randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision	No covariate adjustment, did not report confidence intervals around event rates	Fibrinolysis all-cause mortality (%) < 2 hours: 5.4 2–4 hours: 7.3 > 4 hours: 14.6 PPCI all-cause mortality < 2 hours: 5.1 2–4 hours: 6.1 > 4 hours: 6.7	LOW	CRITICAL

(a) < 20 RCTs (10).

Results

The meta-regression study found that at both 30-day and 6-month follow-up, PPCI had lower major adverse event rates compared with fibrinolysis irrespective of the time to presentation category (Table 12 and Table 13).

Table 12: Death, reinfarction and stroke at 30 days follow-up

		Time to presentation			p value for trend	Test for interaction*
		< 2 hours (n = 414)	2–4 hours (n = 512)	> 4 hours (n = 297)		
Death (%)	**PPCI**	3.9	4.1	4.7	0.9	0.16
	Fibrinolysis	5.0	6.3	12.1	0.0005	
Death and non-fatal reinfarction	**PPCI**	5.6	8.2	7.1	0.5	0.09
	Fibrinolysis	11.6	12.6	18.1	0.02	
Death, non-fatal reinfarction and stroke	**PPCI**	5.8	8.6	7.7	0.4	0.09
	Fibrinolysis	12.5	14.2	19.4	0.01	

**The test for interaction compares whether the trend in event rates according to presentation time differs significantly between the PPCI and fibrinolysis groups.*
Source: Zijlstra, F et al. Eur Heart J. 2002;23:550-557[339]

Table 13: Death and reinfarction at 6-month follow-up

		Time to presentation			p value for trend	Test for interaction*
		< 2 hours (n = 414)	2–4 hours (n = 512)	> 4 hours (n = 297)		
Death (%)	**PPCI**	5.1	6.1	6.7	0.6	0.10
	Fibrinolysis	5.4	7.3	14.6	0.0001	
Death and non-fatal reinfarction	**PPCI**	8.2	11.7	9.8	0.6	0.06
	Fibrinolysis	15.1	14.9	21.6	0.04	
Death, non-fatal reinfarction and stroke	**PPCI**	8.2	11.7	9.8	0.6	0.06
	Fibrinolysis	15.1	14.9	21.6	0.04	

**The test for interaction compares whether the trend in event rates according to presentation time differs significantly between the PPCI and fibrinolysis groups.*
Source: Zijlstra, F et al. Eur Heart J. 2002;23:550-557[339]

Univariate analysis for 30-day all-cause mortality in all participants was significant for the following risk factors; increasing age, increasing time to presentation, increasing heart rate, increasing blood pressure, gender, diabetes, anterior infarction, prior MI. However after adjustment for the other important factors, time to presentation, diabetes and female gender were no longer significant.

5.3.1.3 Pinto 2006[251]

Methods

This meta-regression study examined PPCI-related time delay and patient risk factors using participants enrolled in the National Registry of Myocardial Infarction (NRMI), a voluntary, prospective registry of people with acute MI in the USA.[251] During a study period from June 1994 to August 2003, 192,509 eligible people were identified from 645 hospitals. All people received either PPCI or fibrinolysis < 12 hours after the onset of pain. Analysis was based on 4 time periods, and the hospitals were divided into 4 categories of increasing PPCI-related time delay (< 60 minutes, 60–89

minutes, 90–120 minutes, and > 120 minutes). The mean time delay within these time periods was calculated using the median PPCI-related time delay at each hospital, giving a mean-of-median door-to-balloon or door-needle times for each of the 4 time-delay categories.

The meta-regression study applied generalised estimating equations that used the GENMOD procedure (linear model) to assess the relationship between median door-to-balloon time / door-to-needle time (a hospital-level variable), the administered reperfusion strategy, and in-hospital all-cause mortality, with adjustment for both patient and hospital-level characteristics. The following patient covariates were used: treatment type (PPCI or fibrinolysis), age, gender, race, diabetes mellitus, hypertension, angina, Killip class 2/3, Killip class 4, previous MI, current smoking, stroke, pulse, systolic blood pressure, payer, pre-hospital delay, and discharge year. Hospital covariates included STEMI volume, PPCI volume, transfer-in (inter-hospital transfer) rate, rural location, and status as a teaching hospital. This modelling approach also allowed for adjustment for clustering both within hospitals and within reporting study periods.

The meta-regression study also used the GENMOD procedure to examine the relationship between PPCI-related time delay and the all-cause mortality difference in the following subgroups: age (< 65 years versus ≥ 65 years), infarct location (anterior versus other), and time from symptom onset to hospital presentation (≤ 120 or > 120 minutes).

Quality assessment

The meta-regression study was based on data from a very large 'real world' patient registry. This type of data might be considered more generalisable than data from RCTs, which is often obtained from a highly selected population (for example low risk people). However, the data is non-randomised and therefore at risk of bias arising from factors such as treatment allocation, reliability of data entry and loss to follow-up. The meta-regression adjusted for a number of covariates that were not adjusted for in other meta-regressions of study-level data. In contrast to the other meta-regressions included in this review, this meta-regression analysis considered a wide range of PPCI-related time delays. This makes it easier to interpret the data with respect to the linear association as the uncertainty of fit is reduced when the number of data points increases, in this case longer PPCI-related time delay.

A summary of the quality assessment using an adapted GRADE system is presented in Table 14.

Table 14: Clinical evidence profile: Pinto 2006[251]

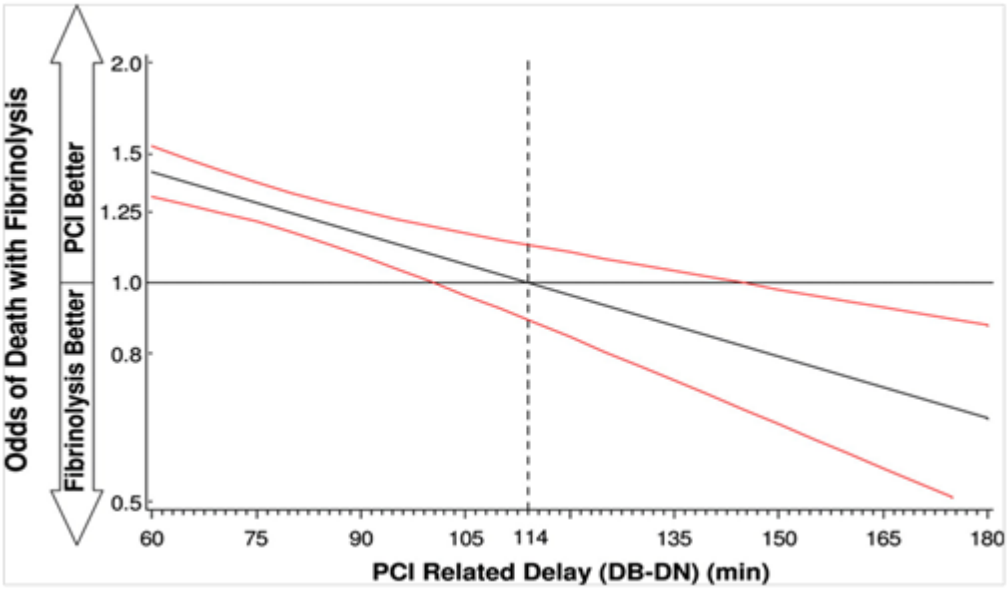
Quality assessment							Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Equipoise	Quality	Importance
Short-term all-cause mortality									
1	Registry cohort	Very serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision	None	114 minutes (95% CI 96, 132)	VERY LOW	CRITICAL

(a) Registry data.

Results

The meta-regression study found that increasing PPCI-related time delay correlated with increasing all-cause mortality ($p < 0.001$), and there was an approximate 10% increase in relative risk of in-hospital all-cause mortality for every 30 minute increase in PPCI-related time delay (OR 1.095, 95% CI 1.065–1.126, $p < 0.001$). The multivariate adjusted model found that the adjusted odds of in-hospital all-cause mortality were identical with either PPCI or fibrinolysis when the PPCI-related time delay was 114 minutes (95% CI 96–132 minutes, $p < 0.001$) (Figure 3).

Figure 3: Pinto 2006.[251] Multivariable analysis estimating the treatment effect of reperfusion therapy with PPCI or fibrinolysis based on increasing PPCI-related time delay.

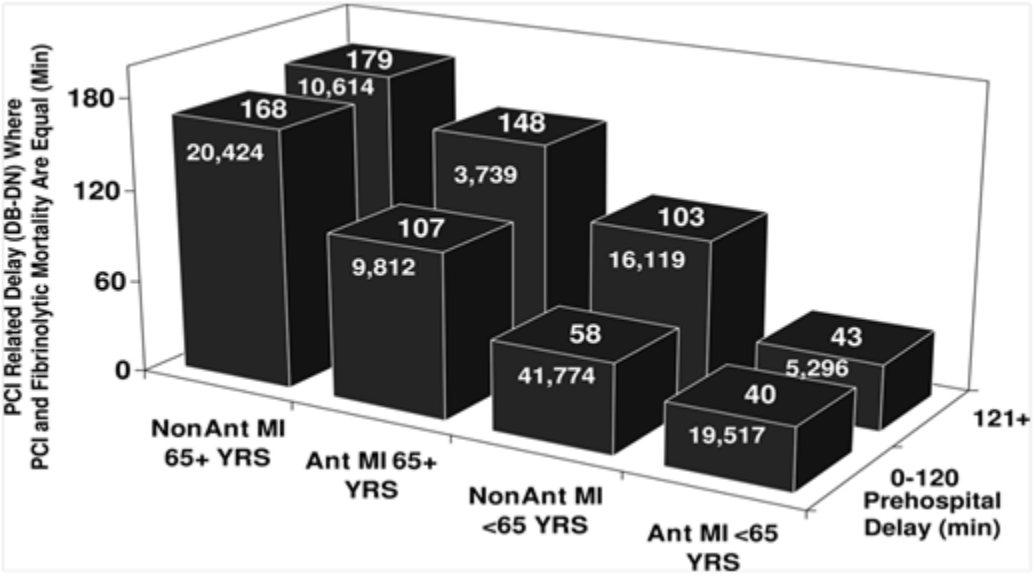


Source: Pinto D S et al. Circulation 2006;114:2019-25 Reproduced with permission of LIPPINCOTT WILLIAMS & WILKINS in the format reused in government report via Copyright Clearance Centre.

After correction for patient and hospital-based factors, the time at which odds of in-hospital death with PPCI were equal to those for fibrinolysis occurred when the PPCI-related time delay (DB-DN time) was ≈ 114 minutes. Variables included in the model were treatment type (PPCI or fibrinolysis), age, gender, race, diabetes mellitus, hypertension, angina, Killip class 2/3, Killip class 4, previous infarction, current smoking, stroke, pulse, systolic blood pressure, payer, symptom duration, infarct location, and discharge year. Hospital covariates included STEMI volume, PPCI volume, transfer-in rate, rural location and status as a teaching hospital.

The meta-regression study also found that there was significant heterogeneity in the equipoise dependent upon stratifying the study population by the following risk factors: pre-hospital delay, location of infarct, and age. For example, the survival advantage associated with PPCI was lost after 71 minutes of PPCI-related time delay with people aged < 65 years compared with 155 minutes in people aged ≥ 65 years. The equipoise for people with anterior MI was 115 minutes compared with 112 minutes for non-anterior MI. The survival advantage associated with PPCI in people presenting ≤ 120 minutes after symptom onset was lost after 94 minutes compared with 190 minutes in people presenting > 120 minutes after symptom onset. These results are shown in Figure 4, with all 3 variables taken into account, as they can be co-linear and associated with one another.

Figure 4: Pinto 2006.[251] Adjusted analysis illustrating significant heterogeneity in the PPCI-related time delay (DB-DN time) for which the all-cause mortality rates with PPCI and fibrinolysis were comparable after the study population was stratified by pre-hospital delay, location of infarct, and age.



Source: Pinto D S et al. Circulation 2006;114:2019-25 Reproduced with permission of LIPPINCOTT WILLIAMS & WILKINS in the format reused in government report via Copyright Clearance Centre.

Ant = anterior, NonAnt = non-anterior. The DB-DN time at which the all-cause mortality benefit was lost was based on multivariate models. Variables included in the model were treatment type (PPCI or fibrinolysis), age, gender, race, diabetes mellitus, hypertension, angina, Killip class 2/3, Killip class 4, previous infarction, current smoking, stroke, pulse, systolic blood pressure, payer, symptom duration, infarct location, and discharge year. Hospital covariates included STEMI volume, PPCI volume, transfer-in rate, rural location and status as a teaching hospital.

5.3.1.4 Boersma 2006[33]

Methods

This meta-regression study analysed individual patient data from 22 RCTs (PPCI: n = 3380 versus fibrinolysis: n = 3383, search date 2002, outcome of all-cause mortality at 30 days) to examine the impact of both patient presentation delay and PPCI-related time delay on treatment effect. Patient presentation delay was defined as the time from symptom onset to randomisation and was evaluated at the individual patient level. People were categorised in advance into 5 subgroups with patient presentation delays of 0–1 hours, > 1–2 hours, > 2–3 hours, > 3–6 hours, and > 6 hours.

The authors stated that the time from randomisation to treatment is influenced by treatment allocation. Estimates of time to treatment based on observations after randomisation in individual participants can therefore be subject to bias, but observations at a hospital level may help to reduce this risk. Hence the authors obtained median times between randomisation and the start of PPCI or fibrinolysis from 153 hospitals, and the hospital-specific PPCI-related time delay was calculated. PPCI-related time delay was categorised into 5 groups: 0–35 minutes, > 35–50 minutes, > 50–62 minutes, > 62–79 minutes, and > 79 minutes.

All-cause mortality was analysed on an intention to treat basis and treatment differences were presented as adjusted OR (95% CI) for each presentation and PPCI-related time delay subgroup. Statistical evidence of heterogeneity was tested using the Breslow-Day test for RCT specific OR. The effect of presentation and PPCI-related time delay on the outcome was examined using multilevel logistic regression to address random and fixed effects at the patient and hospital levels of the study.

Patient presentation delay was assessed in the following subgroups selected in advance:

- age < 65 versus ≥ 65 years
- gender
- diabetes mellitus
- prior MI
- anterior versus non-anterior MI location
- systolic blood pressure (< 130 versus ≥ 130 mmHg)
- heart rate (< 70 versus ≥ 70 beats per minutes)
- hospital-level average annual PPCI volume
- study-level type of fibrinolytic agent used

A sensitivity analysis for the type of fibrinolytic agent used (streptokinase, t-PA, accelerated t-PA) was conducted.

Quality assessment

The meta-regression study used individual patient-level data (IPD), which is considered the 'gold standard' when analysing data in a systematic review.[287] In contrast to study-level analyses, IPD allows for time to event analysis. In addition, IPD permits the categorisation of individuals required for subgroup analyses.

The meta-regression analysis used the following covariates:

- Hospital level
  - PPCI-related time delay
  - average annual PPCI volume
- Study level
  - PPCI-related time delay
  - annual PCI volume
  - average number of participants randomised to PPCI per year
  - likelihood of PCI within 30 days after initial fibrinolysis
  - use of stents
  - use of GPIs
  - type of fibrinolytic agent used (streptokinase, t-PA, or accelerated t-PA)
  - single-centre versus multi-centre RCT
  - year of publication.

The meta-regression study defined its populations in advance for subgroup analysis of the effect of patient presentation delay. However, stratifying the patient population by patient presentation delays of < 2 hours versus ≥ 2 hours, and further splitting the populations by subgroups may result in greater uncertainty in the point estimate of effect for the outcome of all-cause mortality.

A summary of the quality assessment using an adapted GRADE system is presented in Table 15.

Table 15: Clinical evidence profile: Boersma 2006[33]

Quality assessment							Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Event rate : All-cause mortality		
Short-term all-cause mortality									
22	IPD of randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	PPCI-related time delay was at the hospital level(patient presentation delay at the patient level). Heterogeneity for PPCI superiority over fibrinolysis for PPCI-related time delay. Only considers PPCI-related time delays up to 2 hours, and presentation delays up to 12 hours.	According to patient presentation delay: Fibrinolysis Event (%) 0–1 hours: 6.0 > 1–2 hours: 6.2 > 2–3 hours: 7.3 > 3–6 hours: 9.5 > 6–12 hours: 12.7 PPCI Event (%) 0–1 hours: 4.7 > 1–2 hours: 4.2 > 2–3 hours: 5.1 > 3–6 hours: 5.6 > 6–12 hours: 8.5 According to PPCI-related time delay: Fibrinolysis Event (%) 0–35 minutes: 8.2 > 35–50 minutes: 6.8 > 50–62 minutes: 5.4 > 62–79 minutes: 9.5 > 79–120 minutes: 9.6 PPCI Event (%) 0–35 minutes: 2.8 > 35–50 minutes: 5.4 > 50–62 minutes: 4.8 > 62–79 minutes: 6.9 > 79–120 minutes: 6.6	MODERATE	CRITICAL

Results

The meta-regression study found that participants randomised to PPCI had 37% relative lower odds of 30-day all-cause mortality compared with those randomised to fibrinolysis after multi-level covariate adjustment (adjusted OR 0.63, 95% CI 0.42 to 0.84, p < 0.001).

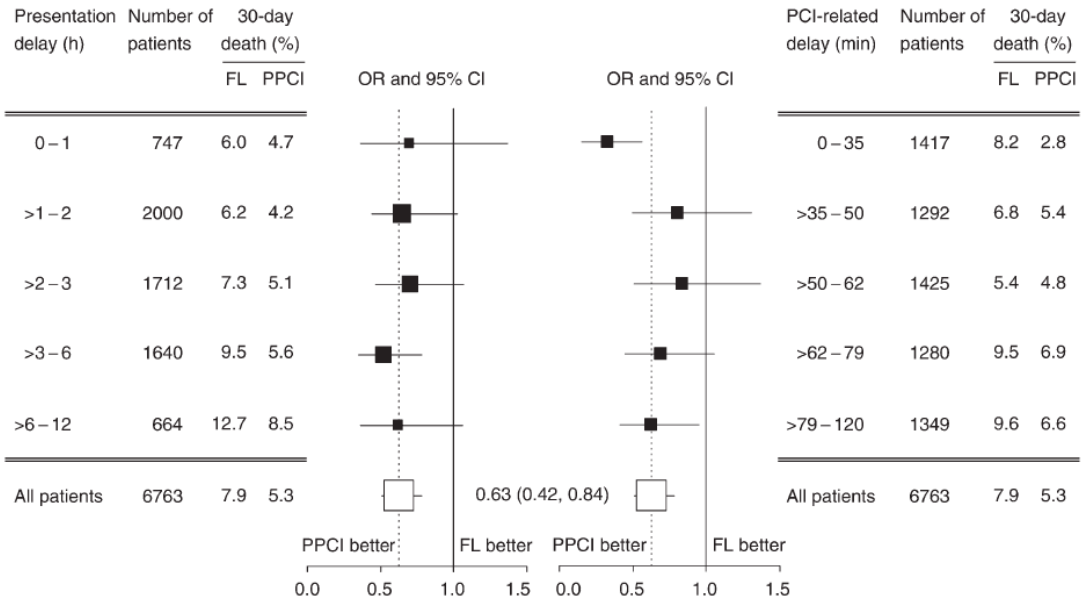
PPCI was consistently favoured over fibrinolysis for the outcome of 30-day all-cause mortality at all 5 patient presentation delays (0–1 hours, > 1–2 hours, > 2–3 hours, > 3–6, and > 6 hours), with no evidence of heterogeneity (pBreslow-Day = 0.9). All-cause mortality increased progressively with increasing patient presentation delay and the absolute benefit from PPCI increased from 1.3% in participants randomised in the first hour after symptom onset to 4.2% in those randomised after 6 hours.

For hospital-specific PPCI-related time delay, 30-day all-cause mortality was consistently lower in people who received PPCI versus fibrinolysis at all 5 time points (0–35 minutes, > 35–50 minutes, > 50–62 minutes, > 62–79 minutes, and > 79 minutes) (Figure 5). The study reported that there was evidence of heterogeneity across the 5 time points (pBreslow-Day = 0.05, and pBreslow-Day = 0.004 for the comparison of the first group versus groups 2 to 5). Our own sensitivity analysis found evidence of heterogeneity across all 5 groups (I^2 = 41%), while there was no evidence of heterogeneity in groups 2 to 5. This sensitivity analysis showed an adjusted odds ratio of 0.34 (95% CI 0.19 to 0.62) in group 1 (0–35 minute PPCI-related time delay) and 0.73 (95% CI 0.59 to 0.92) in groups 2 to 5 (> 35–120 minutes).

In the subgroup analyses that examined treatment effect and patient presentation delay (≤ 2 hours versus > 2 hours) PPCI was consistently favoured over fibrinolysis across all subgroups for 30-day all-cause mortality and there was no evidence of heterogeneity (pBreslow-Day = 0.9) (Figure 6).

In the 10 RCTs (n = 4172) that compared PPCI with fibrinolysis using accelerated t-PA, PPCI was associated with a 29% relative reduction in the odds of all-cause mortality; (7.4% fibrinolysis versus 5.6% PPCI; adjusted OR =0.71 (95% CI 0.46 to 0.98) with no evidence of heterogeneity in the treatment effect according to patient presentation delay (pBreslow-Day = 0.9). The results for PPCI-related time delay show that the treatment effect in favour of PPCI was highest in the first time point (0–35 minutes), as was found in the primary analysis (Figure 6). However the 95% CI in the sensitivity analyses were wide and mostly overlapping, and unlike the primary analysis there was no evidence of heterogeneity (pBreslow-Day = 0.3).

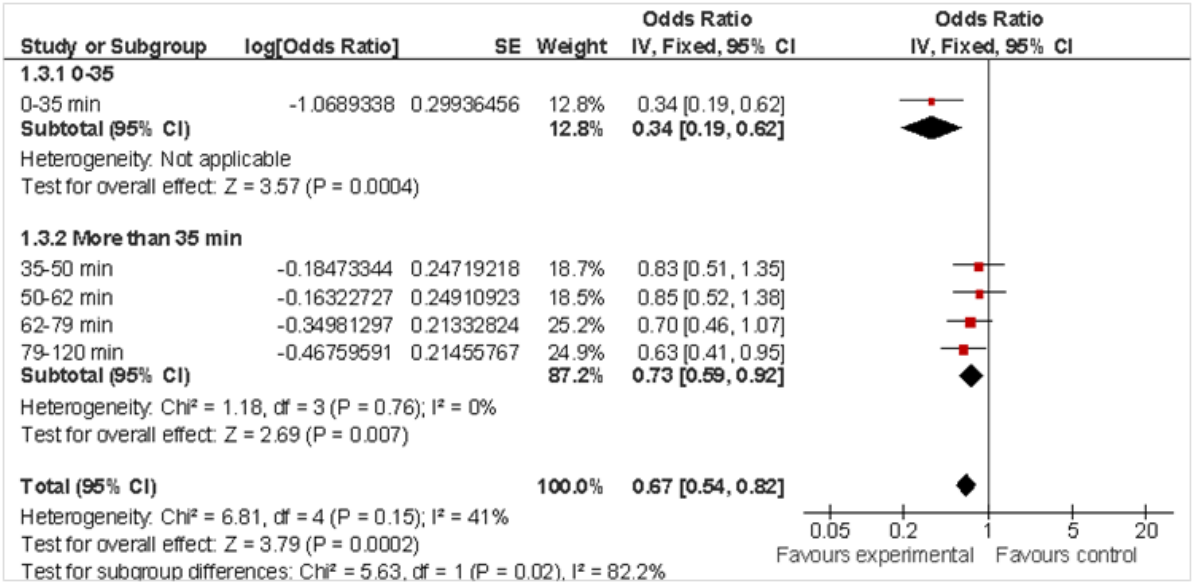
Figure 5: Boersma 2006[33], OR and 95% CI for 30-day death in patients randomised to PPCI versus fibrinolysis according to patient presentation delay and PPCI-related time delay.



Source: Boersma E, et al. Eur Heart J. 2006;27:779-88 Reproduced with permission of OXFORD UNIVERSITY PRESS in the format reuse in government report via Copyright Clearance Centre.

OR were adjusted for patient-, hospital-, and study-level covariates.

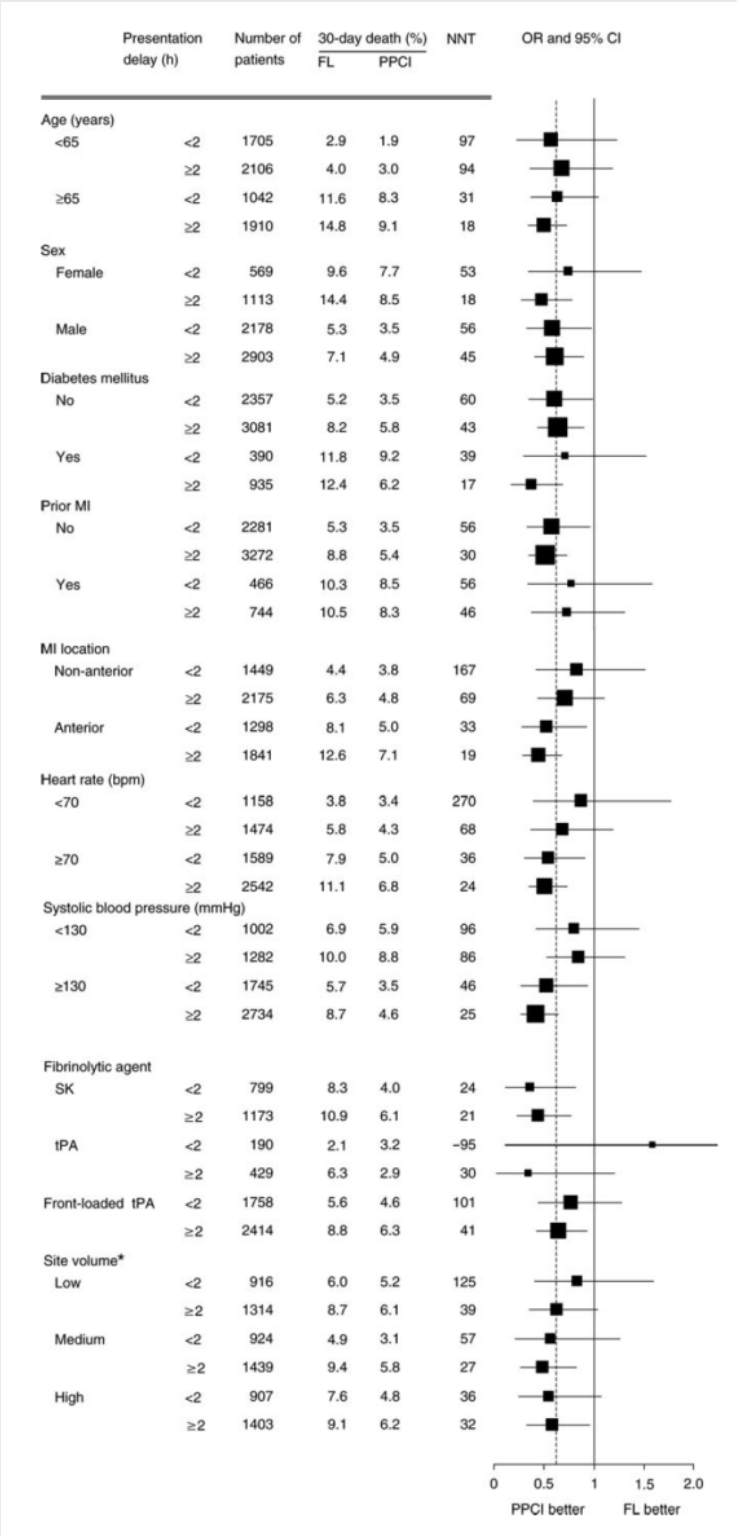
Figure 6: Boersma 2006[33] sensitivity analysis of PPCI related delay.



Source: Adapted from Boersma E, et al. Eur Heart J. 2006;27:779-88. Reproduced with permission of OXFORD UNIVERSITY PRESS in the format reuse in government report via Copyright Clearance Centre.

Sensitivity analysis demonstrating evidence of heterogeneity across all 5 groups (I^2 = 41%). There was no evidence of heterogeneity in groups 2 to 5. NNT (number needed to treat): the number of patients who need to be treated in order to prevent a death. OR were adjusted for patient-, hospital-, and study-level covariates.

Figure 7: Boersma 2006[33] subgroup analyses of presentation delay and selected patient-, study- and site-level characteristics.



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NNT (number needed to treat): the number of patients who need to be treated in order to prevent a death. OR were adjusted for patient-, hospital-, and study-level covariates.

**Site volume on-study only, classified by the number of patients randomised to percutaneous transluminal coronary angioplasty per site per year: low,<10 patients/site/year; medium,10–23 patients/site/year; high, ≥24 patients/site/year.*

5.3.1.5 Asseburg 2007[14]

Methods

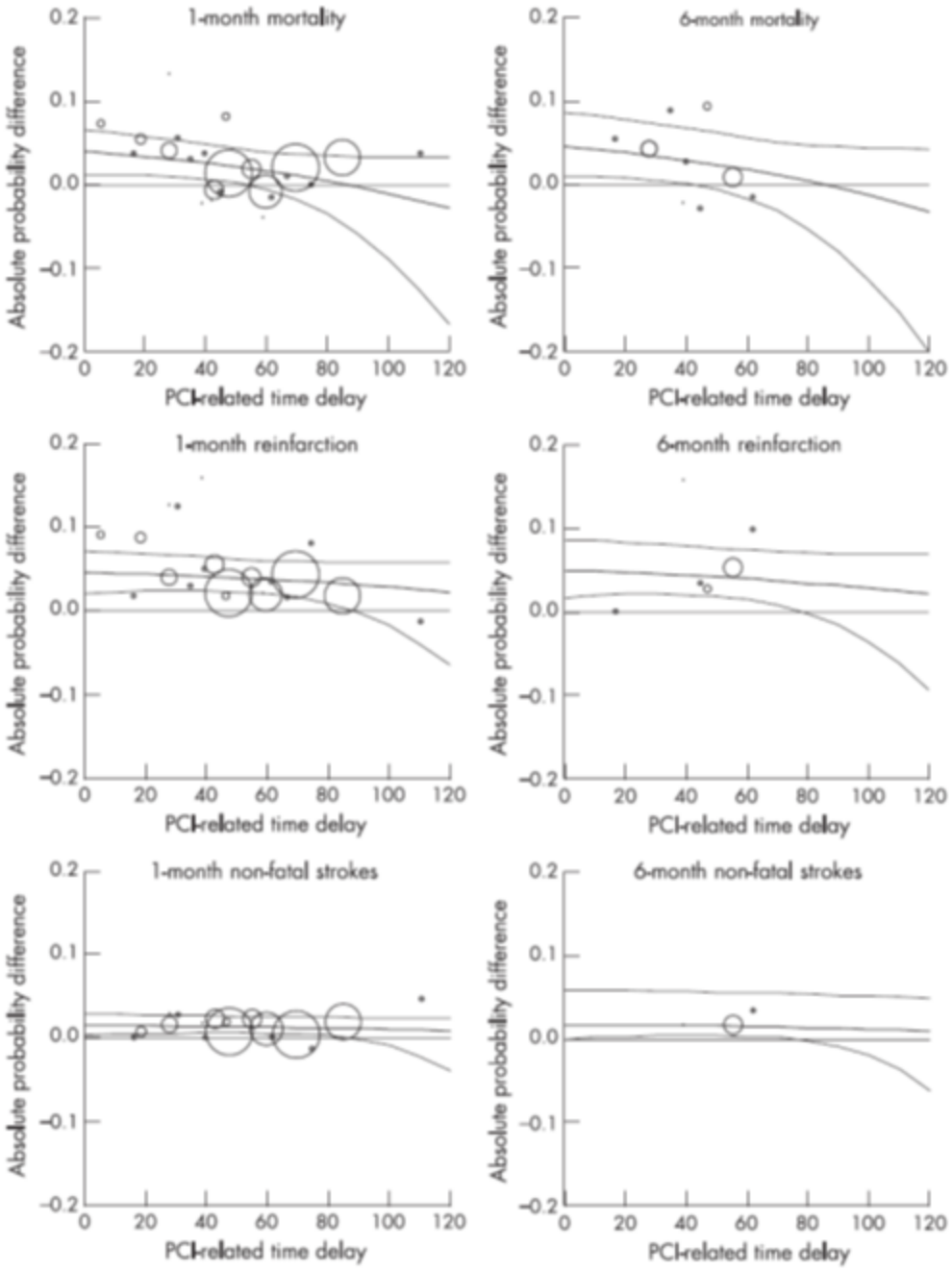
This meta-regression study pooled results from 22 RCTs and analysed the data at the study level (PPCI: n = 3760 versus fibrinolysis: n = 3758, search date 2004). The outcomes were 1-month all-cause mortality (22 RCTs), non-fatal reinfarction (20 RCTs) and non-fatal stroke (20 RCTs), and 6-month all-cause mortality (9 RCTs), non-fatal reinfarction (5 RCTs) and non-fatal stroke (2 RCTs).[14]

Quality assessment

The meta-regression study used RCT study-level data and as such the relationship described for PPCI-related time delay is an observational association across the RCTs. The results do not have the benefit of randomisation to underpin a causal association and may be biased by confounding. For example, PPCI-related time delay may be associated with other characteristics which may differ between the RCTs included in the meta-regression, but the meta-regression did not make any adjustment for, potential confounders. Furthermore, the meta-regression study may be subject to ecological fallacy (also known as aggregation bias), which is the mistaken assumption that a statistical association observed between 2 group-level variables is always equal to the association between the corresponding variables at the individual level. Thus, the average PPCI-related time delays obtained at the study level, and the relationship of PPCI-related time delays to the outcomes across RCTs may not be relevant to all of the individuals within the RCTs.

A summary of the quality assessment using an adapted GRADE system is presented in Table 16.

Figure 8: Asseburg 2007.[14] Treatment effect of PPCI relative to fibrinolysis, shown as the absolute probability differences for mortality, reinfarction and stroke.



Source: Reproduced from Heart, Asseburg et al. 97, 1244-1250, 2007 with permission from BMJ Publishing Group Ltd.

The graphs show means and 95% credible intervals plotted against PPCI-related time delay at 1-month (left) and 6-months follow-up (right). Positive values indicate that PPCI results in fewer clinical events. The circles represent individual clinical trials and their size is proportional to the trial sample size.

Table 16: Clinical evidence profile: Asseburg 2007[14]

Quality assessment							Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Equipoise OR (95%CI) comparing PPCI versus fibrinolysis	Quality	Importance
Short-term all-cause mortality									
22	Study level of randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision	No covariate adjustment	Equipoise: 90 minutes 0.68 (0.46–1.01)	LOW	CRITICAL
Longer-term all-cause mortality									
9	Study level of randomised trials	Serious (a)(b)	No serious inconsistency	No serious indirectness	Serious imprecision (e)	No covariate adjustment	Equipoise: 90 minutes 0.7 (0.42–1.18)	VERY LOW	IMPORTANT
Short-term non-fatal reinfarction									
20	Study level of randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision	No covariate adjustment	Equipoise: > 120 minutes 0.32 (0.20–0.51)	LOW	IMPORTANT
Longer-term non-fatal reinfarction									
5	Study level of randomised trials	Very serious (a) (c)	No serious inconsistency	No serious indirectness	Very serious imprecision (f)	No covariate adjustment	Equipoise: > 120 minutes 0.33 (0.2–0.67)	VERY LOW	IMPORTANT
Short-term non-fatal stroke									
17	Study level of randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision	No covariate adjustment	Equipoise: > 120 minutes 0.24 (0.11–0.50)	LOW	CRITICAL
Longer-term non-fatal stroke									
2	Study level of randomised trials	Very serious (a) (d)	No serious inconsistency	No serious indirectness	Very serious imprecision (f)	No covariate adjustment	Equipoise: > 120 min 0.26 (0.08–0.72)	VERY LOW	CRITICAL

(a) Study-level data that is subject to ecological fallacy. Ecological fallacy assumes that individual members of a group have the average characteristics of the group as a whole. Statistics that use group characteristics do not necessarily apply to individuals within the group, and do not account for the fact that individuals have a greater variability than the variability of their mean.
(b) < 10 RCTs (9).
(c) < 10 RCTs (5).
(d) < 10 RCTs (2).
(e) Wide confidence interval at equipoise.
(f) Equipoise not reached; confidence interval wide at longest time point examined of 120 minutes.

Results

The meta-regression analysis found that for 1-month all-cause mortality PPCI was favoured over fibrinolysis for a PPCI-related time delay of up to an 'equipoise' time of 90 minutes. At a PPCI-related time delay of 60 minutes there was a 97% probability that PPCI was superior over fibrinolysis. For the outcome of 6-month all-cause mortality, the 'equipoise' time was similar at 90 minutes, although the credible intervals were wider and for delays of up to 45 minutes there was more than a 95% probability that PPCI was superior to fibrinolysis. For delays up to around 60 minutes, the probability was 87%, while at 90 minutes the probability was below 50% (Figure 8).

For 6-month all-cause mortality the OR (95 Credible Interval (CrI)) of PPCI versus fibrinolysis was 0.54 (95% CrI 0.29 to 0.92) for a PPCI-related time delay of 30 minutes. A PPCI-related time delay of 60 minutes gave an OR of 0.77 (95% CrI 0.44 to 1.29), and at 90 minutes an OR of 1.15 (95% CrI 0.49 to 2.36). For non-fatal reinfarction the ORs at 30-, 60- and 90-minute PPCI-related time delays were 0.30 (95% CrI 0.14 to 0.59), 0.39 (95% CrI 0.21 to 0.72), 0.55 (95% CrI 0.29 to 1.27), respectively. For non-fatal stroke the ORs at 30-, 60- and 90-minute PPCI-related time delays were 0.47 (95% CrI 0.05 to 0.69), 0.56 (95% CrI 0.09 to 0.75) and 0.79 (95% CrI 0.08 to 1.43) respectively.

5.3.1.6 Tarantini 2010[296]

Methods

This meta-regression analysis pooled study-level data from 16 RCTs (search date 2008, outcome of 30-day all-cause mortality).[296] The study restricted its analysis to RCTs that used fibrin-specific agents. Fibrin-specific agents preferentially activate fibrin-bound plasminogen and have been associated with improved outcomes when compared with streptokinase. Unlike the other meta-regression studies identified in this review, Tarantini et al examined the relationship between the mortality risk of the person and the treatment benefit of PPCI relative to fibrinolysis. The study used all-cause mortality in the fibrinolytic arms of each of the trials as a surrogate for underlying mortality risk.

A fixed effect linear regression analysis modelled the log odds ratio for 30-day mortality (odds PPCI/odds fibrinolysis) as a linear function of the log odds of all-cause mortality in the fibrinolysis group. The analysis was used to explore the relationship between the benefit of PPCI over fibrinolysis and the all-cause 30-day mortality risk, and to determine the mortality risk at which the 30-day survival benefit of PPCI over fibrinolysis is nullified. Sensitivity analyses were performed by excluding the RCTs reporting the smallest and largest effect sizes.

Additional multiple linear regression analyses were performed to explore the relationship between absolute (and relative) reduction in risk of 30-day mortality, and mortality in the fibrinolysis group, time to treatment (patient presentation delay) and PPCI-related time delay. The results from each RCT were weighted by the inverse of the within-study variances.

Quality assessment

This exploratory meta-regression analysis used 30-day all-cause mortality in the fibrinolysis arms of the trials as a proxy for underlying patient baseline risk. However, this meta-regression is flawed as the measurement error in the covariate (fibrinolysis group risk) appears also in the dependent variable (treatment effect) causing an artefactual association. The meta-regression analysis used study-level data and might be subject to ecological bias. The study did not perform any covariate investigation or adjustment, and other variables that may impact mortality were not considered.

A summary of the quality assessment using an adapted GRADE system is presented in Table 17.

Table 17: Clinical evidence profile: Tarantini 2010[296]

Quality assessment							Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Equipoise	Quality	Importance
Short-term all-cause mortality									
16	Study level of randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision	No covariate adjustment	Equipoise between PPCI and fibrinolysis influenced by baseline all-cause mortality, regression analyses shows that an acceptable PPCI-related time delay has a wide range based mainly on different risk profiles.	LOW	CRITICAL

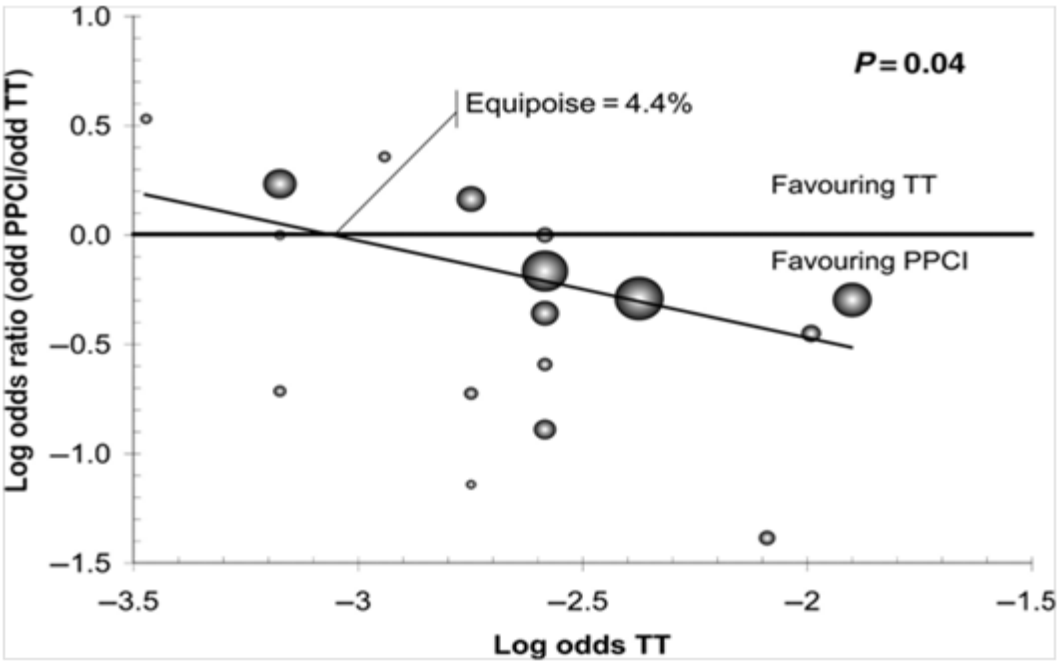
(a) Study-level data.

Results

The fixed-effect linear regression model found that at a baseline 30-day all-cause mortality risk of < 4.4%, it is unlikely that PPCI confers a survival benefit over fibrinolysis (Figure 9).Multiple regression analysis of study-level data showed that baseline mortality risk, PPCI-related time delay, and patient presentation delay were independently correlated with the 30-day absolute survival benefit of PPCI without any significant interactions between the variables.

The 'acceptable' PPCI-related time delay (the time that nullifies the advantage of PPCI over fibrinolysis) was influenced by the baseline mortality risk and by the patient presentation delay. Based on this this analysis, absolute 30-day mortality benefit of PPCI (versus fibrinolysis) can be calculated by the following equation: 0.59 (baseline mortality risk) − 0.033 (PPCI-related time delay) −0.0003 (patient presentation delay) −1.3. Although statistically significant, the weight of patient presentation delay is much lower than the weight of PPCI-related time delay, and both are lower than the weight of mortality risk as demonstrated by the coefficients: baseline all-cause mortality risk regression coefficient 0.51422 (95% CI 0.18 to 0.84, p = 0.004), PPCI-related time delay regression coefficient −0.003 (95% CI −0.05 to −0.006, p = 0.006) and patient presentation delay regression coefficient −0.0003 (95% CI −0.0005 to −0.00004, p = 0.03).

Figure 9: Tarantini 2010. Fixed-effect meta-regression analyses for the log-odds ratio (ln OR) of fibrinolysis versus PPCI on all-cause mortality (expressed as log-odds) of the control group at 30-day follow-up.



Source: Tarantini G, et al. Eur Heart J 2010;31:676-686. Reproduced with permission of OXFORD UNIVERSITY PRESS in the format reuse in a government report via Copyright Clearance Centre.

Higher (less negative) log odds TT indicates increasing baseline risk as assessed by fibrinolytic arm mortality. Negative values of the OR (y-axis) mean more benefits in all-cause mortality associated with PPCI, whereas the in all-cause mortality rate of the control group (x-axis) represents the risk profile of the patient population included in each trial. The size of the circle corresponds to the inverse variance of the log-odds ratio and thus is related to the statistical weight of the study.

5.3.2 Discussion of included meta-regression analyses

The results of the meta-regression studies are summarised in Table 18. The meta-regression studies that used RCT data identified very similar RCTs up to their respective search dates, and the RCTs included were relevant to our review.

Three meta-regression studies calculated the PPCI-related time delay associated with equipoise for the outcome of all-cause mortality, with values of 50.1 minutes [159], 90 minutes[14], and 114 minutes[251]. Pinto 2006 found that the equipoise time varied with the risk profile of the person in a 'real world' registry study, and this is supported by an exploratory study, which identified baseline all-cause mortality risk as a major determinant of acceptable PPCI-related time delay.[296] One meta-regression study found that PPCI was consistently favoured over fibrinolysis for PPCI-related time delays of up to 120 minutes for all-cause mortality.[33]

The 2 meta-regression studies that assessed patient presentation delay using individual patient data found that PPCI was consistently favoured over fibrinolysis for all-cause mortality.[33,339] One further meta-regression study found that increasing patient presentation delay was associated with increased all-cause mortality.[296]

The different equipoise values reported in our review may be explained by differences in the methodologies of the meta-regression studies. For example, Kent 2001 included only 10 RCTs which were also less recent than other studies, and used a simple linear regression model that is susceptible to extreme observations. Furthermore, their estimation of PPCI-related time delay was based on a combination of median and mean values of time-from-onset-to-treatment, time-from-randomisation-to-treatment, and time-from-hospitalisation-to-treatment, dependent on the available data in the separate RCTs. Asseburg 2007 included 22 RCTs, used Bayesian methods and their model incorporated measurement error in the PPCI-related time delay. The advantage of Bayesian methods compared with the approach used by Kent 2001 is that greater uncertainty in the data is automatically accounted for in the analysis.

The Boersma 2006 study has a methodological advantage compared with the other meta-regressions included in this review[14,159,296] because it analysed individual patient-level data as opposed to study-level data. Boersma 2006 adjusted for a number of patient-, hospital- and study-level covariates in its odds ratios, while Asseburg 2007 and other studies using RCT evidence did no such adjustment.[159,296] Adjustment for covariates reduces confounding that may have otherwise affected the relationship between the treatment benefit and the covariate under investigation. Asseburg 2007 also included the CAPTIM RCT[37] but Boersma 2006 excluded this RCT because over two-thirds of the people allocated to pre-hospital fibrinolysis underwent PCI within 30 days.

The Boersma 2006 finding that PPCI is favoured over fibrinolysis even at the longest PPCI-related time delay range of > 79 minutes to 120 minutes is consistent with the equipoise time found by Pinto 2006 of 114 minutes. Pinto 2006 used individual patient data from a 'real-world' registry, with multi-level adjustment for patient and hospital covariates. However, Pinto 2006 is based on observational non-randomised data and therefore it may be subject to greater bias compared with RCT evidence due to unknown confounders. Fibrin-specific fibrinolytic agents predominate in Pinto 2006, while streptokinase use was more frequent in the RCT pooled meta-regression studies with the exception of Tarantini 2010. Fibrin-specific agents have been demonstrated to be more clinically effective than streptokinase (GUSTO RCT).[300]

Pinto 2006 is derived from a large registry and hence the data allows for longer door-to-balloon and door-to-needle times. For example, in Pinto 2006 the average hospital-specific PPCI-related time delay is median (SD) = 77.8 (23.5) minutes, versus median (IQR) = 55 (37–74) minutes in Boersma 2006, and versus mean (SE) = 54.3 (2.2) minutes for Asseburg 2007. In particular, the results presented by Asseburg 2007 were extrapolated beyond the majority of the PPCI-related time delay data observed in the RCTs, particularly for the 6-month outcomes.

In summary, the meta-regression studies presented in this review indicate that PPCI is favoured over fibrinolysis for PPCI-related time delays of up to 2 hours. Boersma 2006 was identified as the meta-regression study that was of the highest quality, as it used individual patient-level data from the greatest number of appropriate RCTs, and it reported odds ratios that were adjusted for covariates. Boersma 2006 demonstrated that PPCI was superior to fibrinolysis for any patient presentation delay of 0–12 hours and also for any (hospital-specific) PPCI-related time delay of 0–2 hours. None of the meta-regression studies provide evidence regarding PPCI-related time delays beyond 2 hours.

Results from Pinto 2006 and Tarantini 2012 suggest that the time at which PPCI is equivalent to fibrinolysis is dependent upon the individual patient risk profile.

Table 18: Summary of results

Study	Assessed	Results
Kent 2001[159]	PPCI-related time delay	For PPCI-related time delay up to 50.1 minutes, PPCI favoured over fibrinolysis for 1-month all-cause mortality from RCT study-level data.
Zijlstra 2002[339]	Presentation-delay	PPCI favoured over fibrinolysis for 3 presentation time delays (< 2, 2–4, > 4 hours) from IPD for 1-month and 6-month all-cause mortality from IPD from RCTs.
Pinto 2006[251]	PPCI-related time delay	For PPCI-related time delay equipoise of 114 minutes (95% CI 96–132 minutes) from IPD from a large US registry in-hospital PPCI favoured over fibrinolysis for all-cause mortality; stratification by pre-hospital delay, location of MI, age gives heterogeneity in equipoise.
Boersma 2006[33]	Presentation delay	PPCI favoured over fibrinolysis from IPD from RCTs for 5 time groups: 0–1, > 1–2, > 2–3, > 3–6, > 6–12 hours for all-cause mortality and reinfarction; 0–1, > 1–2, > 2–3, > 3–6 hours for stroke, at 1 and 6 months.
	PPCI-related time delay	PPCI favoured over fibrinolysis from IPD from RCTs for all 5 time groups: 0–35, > 35–50, > 50–62, > 62–79, > 79–120 minutes for 30-day all-cause mortality. Greatest effect observed at 0–35 minutes.
	Subgroup analysis	PPCI favoured over fibrinolysis from IPD from RCTs for all subgroups regardless patient presentation delay (< 2 hours versus ≥ 2 hours).
Asseburg 2007[14]	PPCI-related time delay	For PPCI-related time delay equipoise of 90 minutes from RCT study-level data, PPCI favoured over fibrinolysis for all-cause mortality, reinfarction and stroke at 1 and 6 months.
Tarantini2010[296]	PPCI-related time delay	Equipoise between PPCI and fibrinolysis influenced by baseline all-cause mortality and varies according to patient risk profiles from RCT study-level data.

5.4 Economic evidence

Two analyses were included that compared PPCI and fibrinolysis and explored the impact of PPCI-related time delay (Bravo Vergel 2007[40], Wailoo 2010[119,322]). These are summarised in the economic evidence profile below (Table 19) and the economic evidence tables in Appendix H.

Both cost-effectiveness analyses use the RCT-based study-level meta-regression reported by Asseburg et al. in 2007 to inform the relative effectiveness of PPCI compared with fibrinolysis.[14] The analysis reported by Wailoo et al. in 2010[119,322] is an update of the modelling study reported by Bravo Vergel et al. in 2007[40] that incorporates an analysis of UK observational data from the National Infarct Angioplasty Project (NIAP) study for certain model inputs (see Table 19 for details). The NIAP study was set up by the Department of Health in collaboration with the British Cardiovascular Society and the British Cardiovascular Intervention Society and aimed to establish whether implementation of PPCI was feasible in the UK. It explored a number of areas including costs and time delays. The analysis reported in Wailoo 2010 along with the other results from the NIAP study informed the current Department of Health recommendations for PPCI. The analysis reported in Wailoo 2010 is judged to be more applicable to the guideline than that in Bravo Vergel 2007, as it has a more recent cost year and updated estimated model inputs with real-life data. Nevertheless, both analyses are presented here as the earlier Bravo Vergel 2007 analysis included relevant sensitivity analyses that were not reported in the Wailoo 2010 analysis and so it was considered helpful to inform decision-making.

One economic evaluation relating to this review question was selectively excluded due to the availability of more applicable evidence (Concannon 2010[61]). This is summarised in Appendix K, with reasons for exclusion given. See also the economic article selection flow diagram in Appendix E.

Table 19: Economic evidence profile: PPCI-related time delay (PPCI versus fibrinolysis)

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Bravo Vergel 2007[40] (UK)	Partially applicable (a)(b)	Potentially serious limitations (c)(d)(e)(f)	• Lifetime cost–utility analysis (QALYs) • Probabilistic model with 6-month comparative effectiveness data based on Asseburg meta-regression of RCTs[14] • Takes into account differences in further non-fatal MI and stroke, and mortality • Cost year: 2003/04	Average (delay 54 minutes): £2680 Time delay sensitivity analyses: • 30 minutes: £2740 • 60 minutes: £2670 • 90 minutes: £2590	Average (delay 54 minutes): 0.29 QALYs Time delay sensitivity analyses: • 30 minutes: 0.40 QALYs • 60 minutes: 0.26 QALYs • 90 minutes: 0.04 QALYs	Average (delay 54 minutes): £9241 per QALY gained Time delay sensitivity analyses: • 30 minutes: £6850 per QALY gained • 60 minutes: £10,269 per QALY gained • 90 minutes: £64,750 per QALY gained	<u>Probability cost effective (£20K/30K threshold)</u> • Average (delay 54 minutes): 90%/95% Time delay sensitivity analyses: • 30 minutes: 98%/99% • 60 minutes: 83%/91% • 90 minutes: 36%/45% <u>Other</u> • Time delay up to which PPCI cost effective (£20K/£30K threshold): 79/85 minutes • Incorporating reduced length of stay with PPCI improved cost effectiveness of PPCI; using effectiveness data only from fibrin-specific trials worsened it. Conclusions remained the same.
Wailoo 2010[119,322] (UK)	Directly applicable (b)	Potentially serious limitations (c)(e)(g)	• Update of Bravo-Vergel model[40] with: 1) 'real-world' cost data from NIAP 2) 'real-world' treatment delay estimates from NIAP 3) system level perspective where some people receive fibrinolysis in PPCI service, and vice versa	Average (delay 64 minutes): £829 Time delay sensitivity analyses: • Transferred (100 minutes): £664 • Not transferred (53 minutes):	Average (delay 64 minutes): 0.183 QALYs Time delay sensitivity analyses: • Transferred (100 minutes): −0.0848 QALYs • Not transferred (53 minutes): 0.24QALYs • Direct to	Average (delay 64 minutes): £4520 per QALY Time delay sensitivity analyses: • Transferred (delay 100 minutes): fibrinolysis dominates • Not transferred (delay 53	<u>Probability cost effective (£20K/30K threshold)</u> • Average (delay 64 minutes): 90%/95% Time delay sensitivity analyses: • Transferred (100 minutes): 38%/NR • Not transferred (53 minutes): 95%/NR • Direct to cardiac cath lab (56 minutes): 95%/NR • Not direct to cardiac cath lab (73 minutes): 75%/NR <u>Other</u> • Replacing post-acute revascularisation rates with those observed in NIAP

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
			4) Adjusted baseline mortality rates to reflect 'real-world' patient presentation delay. • Cost year: 2006/7	~£900 • Direct to cardiac cath lab (56 minutes): ~£900 • Not direct to cardiac cath lab (73 minutes): ~£800	cardiac cath lab (56 minutes): 0.23 QALYs • Not direct to cardiac cath lab (73 minutes): 0.13 QALYs	minutes) £3635 per QALY • Direct to cardiac cath lab (delay 56 minutes) £3817 per QALY gained • Not direct to cardiac cath lab (delay 73 minutes) £6112 per QALY gained	increased the ICER to £7070. Probability cost effective (£20K threshold) was ~90%.

(a) Current UK NHS context better reflected by Wailoo 2010 update.

(b) Some uncertainly about measurement and valuation methods of health-related quality of life due to unclear reporting but considered minor limitation (EQ-5D instrument used).

(c) Relative effectiveness of PPCI compared with fibrinolysis and the impact of PPCI-related time delay is from a study-level meta-regression based on a systematic review of literature (Asseburg 2007[14]). This found no mortality benefit from PPCI at a PPCI-related time delay of 90 minutes. However, an individual patient-level data analysis (Boersma 2006[33]), which was judged in the clinical review to be of higher methodological quality than that by Asseburg 2007, found a benefit in 1-month mortality for people with PPCI-related time delays of up to 120 minutes, and so there is uncertainty that the relative treatment effects in this economic evaluation are from the best available source. Three new RCTs that meet the inclusion criteria for clinical review have been published since Asseburg 2007 but are considered likely to have only a small impact on effect estimates as they contain low patient numbers relative to the total number of people included in the meta-analyses by Asseburg and Boersma. See the clinical review for more details.

(d) Ambulance costs not incorporated –these may be higher with PPCI due to more transfers or longer journeys; although other PPCI cost assumptions are generally conservative.

(e) All but 1 RCT included in the Asseburg meta-analysis used by both studies compared PPCI with in-hospital fibrinolysis, not pre-hospital fibrinolysis. See chapter 13 for further consideration of this distinction.

(f) Study funded by unrestricted educational grant to University of York from Cordis Ltd (manufacturer of medical devices used in PCI). Some authors also declared having received previous research funding or consultancy fees from various manufacturers of medical devices such as stents.

(g) Ambulance costs to first hospital not incorporated - may be higher with PPCI due to longer journeys.

The factor driving effectiveness in both the models is the PPCI-related time delay applied. In the analysis reported in Wailoo 2010,[322] which utilised observational data from the NIAP study, the delays were based on those observed on average for specific pathways of care. In interpreting the analysis the associated observed median call-to-balloon (CTB) times were also considered. These were:

- All people (PPCI-related time delay 64 minutes): CTB 131 minutes
- Transferred (PPCI-related time delay 100 minutes): CTB 167 minutes
- Not transferred (PPCI-related time delay 53 minutes): CTB 120 minutes
- Direct to cardiac catheter laboratory (PPCI-related time delay 56 minutes): CTB 123 minutes
- Not direct to cardiac catheter laboratory (PPCI-related time delay 73 minutes): CTB 140 minutes

5.5 Evidence statements

Clinical

None. All data summarised above.

Economic

- Two cost–utility analyses found that PPCI was cost effective compared to in-hospital fibrinolysis, except at long PPCI-related time delays. These analyses were assessed as directly or partially applicable with potentially serious limitations.
- The most applicable analysis,[119,322] based on the Asseburg 2007[14] study-level meta-regression, found that:
  - PPCI had a 90% probability of being cost effective at a threshold of £20,000 per QALY based on an average PPCI-related time delay of 64 minutes (relating to a median call-to-balloon time of 130 minutes).
  - PPCI was dominated (less effective and more costly) compared to fibrinolysis for people transferred from admitting hospitals to a separate PPCI centre with PPCI-related time delays of 100 minutes (relating to a median call-to-balloon time of 167 minutes).
  - PPCI had a higher probability of being cost effective (95% versus 75%) where access within the PPCI centre was by direct transfer to the cardiac catheter laboratory rather than via emergency departments or coronary care units within the same hospital, as PPCI-related time delay was shorter (56 versus 74 minutes; relating to median call-to-balloon times of 123 versus 140 minutes).

5.6 Recommendations and link to evidence

Recommendation	The current recommendations can be found at: www.nice.org.uk/guidance/ng185
Relative values of different outcomes	The GDG considered all-cause mortality and stroke (especially haemorrhagic stroke) as critical to decision-making. The GDG was specifically interested in the relationship between the PPCI-related time delay and the relative effects of PPCI and fibrinolysis on these outcomes. Some studies included in this review also reported the PPCI-related time delay at 'equipoise', defined as the PPCI-related time delay at which there is no difference in outcome between the 2 reperfusion strategies. Estimation of the PPCI-related time delay at equipoise relies on extrapolation of relatively limited data available for long PPCI-related time delays, and was therefore considered less important than the overall relationship between PPCI-related time delay and treatment effect. Myocardial reinfarction, major bleeding, heart failure, and unplanned revascularisation were considered important but information about these outcomes in this evidence review was limited. Minor bleeding, length of hospital stay and quality of life were considered less important to decision-making. No data were found for these outcomes.
Trade-off between clinical benefits and harms	The GDG were aware that PPCI and fibrinolysis are both accepted forms of reperfusion therapy for people who present within 12 hours of the onset of symptoms of acute STEMI.[285] Moreover, the benefits of reperfusion therapy in people with acute STEMI are critically dependent on the time from symptom onset to the initiation of treatment.[32,75] Reperfusion therapy must therefore be delivered as soon as possible after the onset of ischaemic symptoms to preserve myocardial function and improve longer-term survival ('time is muscle'). Meta-analyses of RCTs of PPCI versus fibrinolysis demonstrate that PPCI is associated with lower risk of death, reinfarction, stroke, recurrent ischaemia and bleeding.[14,32,157] The GDG accepted that this evidence confirms that PPCI is superior to fibrinolysis and reinforces current UK policy, which supports PPCI as the preferred reperfusion strategy if it can be delivered in a 'timely fashion'. The focus of this evidence review was the relationship between the therapeutic benefit of PPCI relative to fibrinolysis and the differential treatment delay between the 2 reperfusion strategies. The analyses of the RCTs in the review all refer to the same sources of evidence but employed different analytical methods. Two of the analyses in the review[159,339] only included a limited number of the available RCTs. Kent et al. carried out a simple linear regression analysis without any adjustment for potential confounding variables. Linear regression assumes that the relationship between PPCI-related time delay and the treatment difference between the 2 reperfusion methods is linear, and in the analysis the regression line was extrapolated beyond the limits of the data. Zijlstra et al used individual patient data and adjusted for potential confounders, but only assessed the impact of patient presentation delay on outcome. The GDG considered that the evidence in these 2 analyses has been superseded and is therefore only of limited relevance.

Pinto et al. reported an analysis of a large American registry of people with STEMI who were treated by PPCI or by fibrinolysis. The analysis adjusted for baseline imbalances in multiple covariates, but as this is a non-randomised study the GDG considered that residual confounding is likely. The analysis suggests that the benefit of PPCI relative to fibrinolysis is dependent on several baseline variables including PPCI-related time delay, presentation delay, location of infarct, and age. The GDG concluded that the Pinto analysis provides some evidence that the benefit of PPCI varies with patient risk, but the evidence is insufficient to inform guideline recommendations.

Asseburg et al. carried out an analysis of 22 trials using Bayesian methods and reported that PPCI was associated with lower rates of death, reinfarction, and stroke than fibrinolysis for up to 6 months after treatment. The mortality benefit of PPCI decreased with increasing PPCI-related time delay and at around 90 minutes delay there was 'equipoise' between PPCI and fibrinolysis. Data on mortality at trial-specific PPCI-related delays beyond 90 minutes were very limited and the credible intervals at long PPCI-related delays were very wide. The risks of stroke and reinfarction were consistently lower amongst participants assigned to PPCI but the credible intervals for these end points were also relatively wide at long PPCI-related time delays, indicating uncertainty about the effect of PPCI on these outcomes at longer treatment delays. The GDG were concerned that the Asseburg analysis was based on trial-level data, and information about the relative treatment effects at trial-specific PPCI-related time delays beyond 90 minutes is limited. Asseburg et al. did not analyse the impact of presentation delay on outcome. The Asseburg analysis was considered important because it was used for cost-effectiveness analyses included in the economic section of this review.

The Boersma analysis used individual patient-level data from 22 RCTs to assess the impact of presentation delay and hospital-specific PPCI-related time delay on the relative effects of PPCI and fibrinolysis on 30-day mortality. Multivariate modelling was used to adjust for potential confounders. The use of individual patient data in Boersma overcomes some of the limitations of the linear regression analyses. The use of hospital-specific (rather than trial-specific) PPCI-related time delays also allowed assessment of longer PPCI-related time delays than in the other analyses in this review. The GDG debated the value of adding data from RCTs[11,12,44] identified by this review and published since 2006 to the Boersma analysis, but concluded that this would be unlikely to have a significant impact on the overall results.

Boersma et al. reported that PPCI is associated with a consistent reduction in the odds of 30-day mortality relative to fibrinolysis across patient presentation delays ranging up to 12 hours. Absolute risk of 30-day mortality increased with increasing presentation delay and the absolute benefit of PPCI therefore also increased with presentation delay. Subgroup analyses suggested that the relationship between presentation delay and treatment effect was not influenced by multiple baseline variables including age and gender. In addition there was a 30-day survival advantage of PPCI for hospital-specific PPCI-related time delays of up to 120 minutes. There was evidence of heterogeneity such that PPCI was associated with a 67% reduction in the odds of 30-day mortality for PPCI-related time delays of up to 35 minutes but a 28% reduction in people with longer PPCI-related time delays. This might be due to the play of chance but the GDG noted that in people treated by fibrinolysis at hospitals with PPCI-related time delays of 0–35 minutes the 30-day mortality was 8.2%. Hospitals with short PPCI-related time delays may have preferentially enrolled high risk people into the randomised trials and these people may have gained greater

absolute benefit from PPCI. Data from RCTs of PPCI versus fibrinolysis do not extend beyond these time periods and the relative effects of the 2 reperfusion strategies at presentation delays beyond 12 hours and PPCI-related time delays beyond 120 minutes are uncertain. Nevertheless, the GDG considered that the Boersma analysis provides the most reliable information about the impact of treatment delays on the relative effects of PPCI and fibrinolysis on 30-day mortality.

When the scope of this guideline was written, age ethnicity and sex were identified as equalities groups that should be specifically considered due to concern that were being used in clinical practice as reasons to deterring offering coronary reperfusion therapy. Highlighting these characteristics was felt to be proportionate from an equalities perspective based on an assessment of evidence and risk. The Boersma subgroup analysis did not demonstrate any difference in relation to age or sex, and no evidence was identified to suggest that eligibility should be decided on these factors or ethnicity. The GDG agreed it was important to state in the recommendation that eligibility should therefore not be determined by these factors.

Tarantini et al. analysed trial-specific data from 16 RCTs that compared PPCI with fibrinolysis using fibrin-specific agents. This analysis suggests that the benefit of PPCI is confined to people at higher baseline risk (using 30-day mortality in the fibrinolysis group as a surrogate for baseline risk). The analysis assumes a linear relationship between 30-day mortality and estimated baseline risk, and suggests that fibrinolysis might be associated with a mortality benefit in people at very low baseline mortality risk. A model incorporating presentation delay, PPCI-related time delay, and baseline patient risk was developed. The statistical association between these variables and 30-day mortality was strongest for baseline risk, and stronger for PPCI-related time delay than for presentation delay. The analysis did not consider other outcomes (for example stroke, myocardial reinfarction and bleeding). The GDG considered that the Tarantini analysis is exploratory and cannot inform treatment recommendations.

The GDG debated some differences between the 2 reperfusion strategies. Fibrinolysis can be administered early in the treatment pathway by intravenous injection (either in the pre-hospital setting or in the emergency department of a hospital). In these circumstances fibrinolysis is given on the basis of a clinical assessment and the presence of ST-segment elevation on a 12-lead electrocardiogram, but without angiographic confirmation of thrombotic coronary artery occlusion. Hence there is a risk that fibrinolysis may be administered inappropriately to people who have other causes of chest pain or ST-segment elevation (for example aortic dissection, apical ballooning syndrome, pericarditis, oesophagitis).[160] Fibrinolysis may also be contraindicated in around 25% of people with evolving STEMI because of bleeding risk or comorbidity.[150,285]

In people with thrombotic coronary artery occlusion fibrinolytic treatment restores coronary artery patency within 90 minutes in around 75% of cases, but complete reperfusion with normal (TIMI 3) coronary flow in the infarct-related artery is observed in around 50% of people.[300] Call-to-needle times therefore provide information about the time to treatment but not about the time to reperfusion. In this respect a call-to-needle or door-to-needle time interval represents a time to the initiation of a treatment (which may or may not be effective at restoring coronary blood flow) whereas a time to balloon inflation represents a time to proven restoration of blood flow. Call-to-needle and call-to-balloon times are therefore physiologically different measures. In

clinical practice people who fail to reperfuse after fibrinolysis can be identified by persistent ST-segment elevation on an electrocardiogram recorded 60–90 minutes after the start of treatment. These people may be offered coronary arteriography and 'rescue' PCI, which requires emergency transfer of the person to an interventional cardiac catheter laboratory (see chapter 15 – Rescue PCI).

Following successful fibrinolysis, the infarct-related artery is likely to contain a residual stenosis, the severity of which influences the risk of reocclusion.[328] With pharmacological intervention reocclusion after angiographically successful fibrinolysis occurs in around 18% to 32% of people within 3 months.[316] People with STEMI who are treated by fibrinolysis may therefore be considered for early (< 24 hours) coronary angiography and revascularisation and this also requires early transfer to an interventional cardiology service. A strategy of routine early coronary angiography after fibrinolysis is discussed elsewhere in this guideline.

Fibrinolysis is associated with a risk of bleeding and up to 13% of people require blood transfusion.[10,26,300] In addition intracranial bleeding occurs in around 1% of people within 24 hours of treatment and most of these people will die or be left with major disability.[157,299,313] Although the benefit of fibrinolysis is critically dependent on the delay to treatment,[32] the risk of haemorrhagic stroke is not influenced by treatment delay, but is increased by female gender, advanced age, low body weight, blood pressure and previous cerebrovascular disease.[120]

PPCI requires transfer of a person with evolving STEMI to an interventional cardiac catheter laboratory, and this delays the delivery of reperfusion treatment relative to fibrinolysis. Some people may be ineligible for PPCI because of comorbidity or bleeding risk but people transferred to a PPCI service will generally be assessed by an experienced clinical team and when appropriate undergo coronary arteriography. This allows assessment of the extent of coronary artery disease and angiographic confirmation of thrombotic coronary artery occlusion before any intervention is carried out. Treatment by PPCI typically restores normal (TIMI 3) flow in over 90% of cases[300], although tissue level perfusion may be restored in a smaller proportion of people.[130] Hence, for people treated by PPCI the call-to-balloon time is likely to be the same as the call-to-reperfusion time, but for people treated by fibrinolysis the call-to-needle time is likely to be substantially shorter than the call-to-reperfusion time. In contemporary practice, which involves the widespread use of coronary artery stents, the reocclusion rate after successful PPCI is low.

The GDG considered that fibrinolysis is most likely to be superior to PPCI if it is administered very soon after the onset of symptoms (so that the person falls within the 'golden hour',[32] and when the PPCI-related time delay is likely to be relatively long (for instance because of a very long travel time). The number of people in the Boersma analysis with both short presentation delays and long PPCI-related time delays, and the relative benefits of the 2 reperfusion strategies for these people are unknown. The STREAM (Strategic Reperfusion Early After Myocardial Infarction) trial randomised 1892 people within 3 hours of the onset of symptoms of STEMI to a pharmaco-invasive strategy (pre-hospital fibrinolysis, followed by rescue PCI if appropriate, and routine angiography within 24–48 hours) or to PPCI, provided that the anticipated PPCI-related delay was longer than 1 hour at the time of enrolment.[11] The primary end-point (a composite of death, shock, congestive heart failure, or reinfarction up to 30 days after enrolment) occurred in 12.4% of the fibrinolysis group and 14.3% of the PPCI group, but this difference was not

	statistically significant. Moreover, fibrinolysis was associated with a significant excess risk of haemorrhagic stroke that required a protocol amendment (reduction in the dose of fibrinolytic in people 75 years of age or older) during the trial. The impact of the protocol amendment on efficacy of the pharmacoinvasive strategy was not reported.[11] The GDG considered that it is necessary to set a single reperfusion strategy for all people within a locality to ensure that the potential benefits of reperfusion therapy are delivered efficiently and effectively to all eligible people with acute STEMI. Allocation of people to bespoke reperfusion strategies on the basis of different baseline risk profiles is not practicable and unlikely to be cost effective. The GDG agreed that there are very few areas in England and Wales where people could not be transferred to a PPCI service within 90–105 minutes of the first medical contact. A relatively short door-to-balloon time of 30 minutes is realistic if the travel time is long, as the PPCI centre will be pre-warned, the operating team will be activated, and on arrival the patient can be taken immediately to the cardiac catheter laboratory. Hence it should be possible to deliver PPCI to most of the population of England and Wales with a PPCI-related delay of less than 120 minutes. On the other hand, the benefits of PPCI will only be fully realised if emergency services and PPCI centres can consistently deliver the shortest possible call-to-balloon and door-to-balloon times. This requires that reperfusion eligible people with acute STEMI are transported directly to a fully operational PPCI centre regardless of the time of presentation. The GDG noted that such a uniform policy of PPCI has the potential disadvantage that ambulance crews and emergency departments will become de-skilled in the administration of fibrinolysis. The most recent report from MINAP shows that the number of people treated by fibrinolysis continues to decline, and the proportions that are treated within call-to-needle and door-to-needle time targets is also decreasing.[204] The GDG concluded that it is not possible to define precise estimates of the time limits at which PPCI is more clinically and cost effective than fibrinolysis. Nevertheless the available evidence suggests that PPCI is superior to fibrinolysis in terms of 30-day mortality for presentation delays of up to 12 hours and PPCI-related time delays of up to 120 minutes. None of the analyses in this review provided evidence that fibrinolysis is superior to PPCI at any time delay or in any specific subgroup. Moreover there is convincing evidence that fibrinolysis is associated with a higher risk of haemorrhagic stroke, reinfarction and bleeding. The GDG therefore recommended that PPCI should be the preferred reperfusion strategy, and that people with acute STEMI who are eligible for reperfusion therapy should be offered coronary angiography (with follow-on PPCI if indicated) if: • presentation is within 12 hours of onset of STEMI, and • PPCI can be delivered within 120 minutes of the time when fibrinolysis could have been given. Evidence for reperfusion therapy in people who present more than 12 hours after the onset of symptoms of acute STEMI is very limited.[271] The GDG made a consensus recommendation that a PPCI strategy should be considered if the person has evidence of continuing myocardial ischaemia.
Economic considerations	**PPCI-related time delay:** The cost effectiveness of PPCI relative to fibrinolysis in the 2 cost-effectiveness analyses considered is based on the study-level meta-regression reported by Asseburg et al.[14] In that analysis the benefit of PPCI over fibrinolysis decreased

	with increasing PPCI-related time delay. Consequently the cost-effectiveness analyses found that the cost effectiveness of PPCI relative to fibrinolysis also decreased with increasing PPCI-related time delay. The clinical review for this guideline also identified other evidence syntheses addressing this issue, of which a patient-level meta-analysis reported by Boersma et al. was judged to be of the highest methodological quality.[33] This analysis found that PPCI was favoured in terms of 30-day mortality up to a PPCI-related time delay of 120 minutes (no data was available beyond this time). The Boersma analysis therefore suggests that the benefits of PPCI over fibrinolysis may extend over longer PPCI-related time delays than was suggested by the Asseburg meta-regression and this may alter the conclusions about cost effectiveness in relation to PPCI-related time delay. As reported in the clinical review, the odds ratio for 30-day mortality for PPCI compared to fibrinolysis based on the analysis reported by Boersma was 0.63 overall. In a sensitivity analysis undertaken to explore heterogeneity, the odds ratio was 0.34 in group 1 (PPCI-related time delay of 0–35 minutes) and 0.73 in groups 2 to 5 (35–120 minutes). The more conservative odds ratio of 0.73 for a delay of 35–120 minutes is similar to the odds ratio of 0.77 given in the Asseburg analysis for a 60-minute PPCI-related time delay. In the cost-effectiveness analyses[40,119,322] PPCI was cost effective compared to fibrinolysis for these odd ratios. It is therefore considered likely that if the effectiveness estimates from the patient-level meta-analysis reported by Boersma were used to update the cost-effectiveness analyses, PPCI would be cost effective for PPCI-related time delays of up to 120 minutes. **Patient presentation delay:** The clinical review also looked for evidence about the effect of patient presentation delay on outcomes. The analysis reported by Boersma found that relative effects were constant but that absolute benefits increased with increasing patient presentation delay. The published cost-effectiveness analyses did not explore the effect of patient presentation delay on cost effectiveness. However, cost effectiveness will increase as absolute benefits increase, since more QALYs will be gained. **Patient risk profile:** The clinical review also looked for evidence about the effect of patient risk profile on outcomes. The GDG concluded that the Pinto and Tarantini analyses provide some evidence that the benefit of PPCI varies with patient risk; the cost effectiveness of different strategies is likely to vary between high- and low-risk groups, but the available evidence is insufficient to make recommendations based on risk-stratification.
Quality of evidence	The studies included in this evidence review have several important limitations that reduce their relevance to contemporary practice. The meta-regression studies included in this review report retrospective analyses of pooled data from relatively old and small RCTs. Since these RCTs were published there have been significant changes in clinical practice that might affect estimates of clinical and cost effectiveness of both reperfusion strategies. Several of the trials used streptokinase, but fibrin-specific fibrinolytic agents have fewer side effects and improve outcomes.[299,300,313] In most of the trials fibrinolysis was administered in-hospital but pre-hospital treatment may also offer advantages, which are discussed elsewhere in this guideline.(See pre-hospital lysis, chapter 13) [31,38,63,202] Several of the trials enrolled people before the availability of bare metal and drug-eluting stents[72], and pharmacological agents that are known to improve the outcome of PPCI, including antithrombins (bivalirudin),

	antiplatelet agents (prasugrel, ticagrelor) and GPIs.[209,211,223,226,234,275,323,333] The analyses generally only analysed the impact of treatment time delays on short-term outcomes, which may more readily be attributable to differences in interventions. Information about the comparative longer-term results of PPCI and fibrinolysis in contemporary practice is relatively limited and confined to large registry studies.[17,106,286] Nevertheless, the benefits of fibrinolysis persist over 10 years and the GDG considered the mortality benefit of PPCI over fibrinolysis is also likely to persist over the longer term.[17] Our searches identified additional RCTs that have reported results since the Asseberg and Boersma analyses were published.[11,13,44] These trials showed effects that were consistent with the previous data and the GDG considered that they would be unlikely to influence the overall results of the meta-regression analyses. The GDG agreed the amount of work required to update the published meta-regression analyses with these recent RCTs outweighed the impact the updated results would have on decision-making.
Other considerations	No specifically designed RCT addresses the issue of the extent to which PPCI-related time delay (or presentation delay or risk profile) influences the relative benefits of PPCI and fibrinolysis. The GDG debated the implications of the roll out of PPCI services for the effective delivery of fibrinolysis to a small and diminishing number of people with acute STEMI in England. Pre-hospital fibrinolysis requires that ambulance services are appropriately trained in the diagnosis and pre-hospital management of people with STEMI. Maintenance of these skills across an ambulance workforce covering a remote geographical area is likely to be challenging and incur substantial cost. Transmission of ECGs to hospitals for diagnosis could reduce the number of incorrect diagnoses and the training needs of ambulance staff, but the set-up costs might be large. In areas where the roll-out of PPCI has been completed, ambulance services no longer carry fibrinolytic therapy. Ambulances still carry fibrinolytics in areas where a significant number of people are still treated by fibrinolysis (Dorset, Hereford and Worcester, Cumbria, Isle of Wight and Wales)[242] (Prof Quinn, NHS evidence: personal communication 2012). PPCI audit data have shown that if 75% of people were to achieve call-to-balloon times of < 150 minutes, this equates to a median call-to-balloon time of < 120 minutes, which was the cost effective time interval reported by NIAP.[80] The Care Quality Commission therefore introduced a performance standard that required PPCI services to achieve call-to-balloon times of < 150 minutes in > 75% of people. This target assesses the whole patient pathway, including performance of both the emergency (ambulance) and hospital (PPCI centre) components of the pathway. The British Cardiovascular Intervention Society (BCIS) also audits the performance of PPCI centres by reporting their performance against a 'door-to-balloon' time target of < 90 minutes.[183] Current UK Department of Health guidance recommends that in the absence of a medical contraindication or justifiable delay, reperfusion by PPCI should be achieved within 90 minutes of arrival at the angioplasty hospital (that is a 90 minute door-to-balloon time), and within 150 minutes of a person's call for help (that is a 150 minute call-to-balloon time). If a PPCI service cannot be reached because journey times are too long, pre-hospital fibrinolysis is considered preferable to in-hospital fibrinolysis. For people who receive fibrinolytic therapy this should be administered within 30 minutes of arrival of the ambulance (if fibrinolytic therapy is to be administered in a pre-hospital

	setting) or within 30 minutes of arrival at hospital (30 minutes door-to-needle time). These existing standards for reperfusion services are likely to be updated when the recommendations in this guideline are incorporated into the forthcoming Quality Standards for 'Acute coronary syndromes including myocardial infarction'.

6 Facilitated primary percutaneous coronary intervention (fPPCI)

6.1 Introduction

Acute STEMI is usually caused by thrombotic occlusion of a major coronary artery. As discussed elsewhere in this guideline, the mainstay of treatment is restoration of coronary artery flow by either mechanical (PPCI) or pharmacological (fibrinolysis) intervention.

PPCI is carried out without prior administration of fibrinolysis, but some drugs are usually given in advance of the procedure. These drugs may include opiate analgesia, anti-emetic, aspirin, an ADP receptor antagonist, and an anticoagulant. Unlike fibrinolytics and GPIs, these drugs are not given with the expectation that they will re-open the occluded coronary artery.

Facilitated PPCI describes a strategy in which 1 or more drugs are given before an individual with STEMI arrives in the cardiac catheter laboratory for PPCI. The intention of this 'upstream' pharmacological intervention is to re-open the occluded coronary artery or to inhibit propagation of the coronary artery thrombus while the person is en route to the cardiac catheter laboratory, thereby 'facilitating' the PPCI procedure. The drugs that have been used for facilitated PPCI include fibrinolytics, GPIs, or a combination of these agents. In a facilitated PPCI strategy, all people still undergo early angiography and PPCI if indicated. This differentiates facilitated PPCI from rescue PCI, in which people treated by fibrinolysis undergo early angiography and PCI only if they have electrocardiographic evidence of failed reperfusion.

This question will address the issue of whether fibrinolytic agents, GPIs or both agents should be administered before arrival in the cardiac catheter laboratory in people undergoing PPCI – that is, facilitated PPCI (fPPCI). The GDG were also interested to know whether 'upstream' administration of heparin confers advantages in people with STEMI undergoing coronary angiography, with follow-on PPCI if indicated.

6.2 Review question: What is the clinical and cost effectiveness of facilitated primary PCI (fPPCI) compared to primary PCI (PPCI) in people with STEMI?

For full details see review protocol in Appendix C.

6.3 Clinical evidence

We searched for RCTs comparing the effectiveness of facilitated primary percutaneous coronary intervention (fPPCI) versus PPCI.

Twenty-one studies (23 papers) were included in the review (2 of the studies were each reported in 2 different papers).[21,89,94,97-99,107,153,169,171,179,187,192,247,272,276,298,302,312,314,315,340] Study characteristics, including details of background therapy, are summarised in Table 20.

Evidence from these studies are summarised in the clinical GRADE evidence profiles. See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

Some studies[97,98,170,171,276,276,302,303] reported data that were unsuitable for meta-analysis or GRADE (data were presented as percentages or only p values were given). These data have been summarised in a separate table (Table 26), and have not been included in the evidence statements.

No studies were found that looked at upstream administration of heparin as the main facilitating agent for fPPCI.

Two meta-analyses (Keeley 2006 and DeLuca 2009)[73,157] were found and their reference lists searched for relevant studies. These meta-analyses included some additional studies that we did not include in our review because they were either abstracts or did not meet our inclusion criteria due to the following reasons: different drugs were used for the pre-catheter laboratory versus in-catheter laboratory treatment; the timing of outcome measures was pre-PCI; sample size was less than 50 for drugs for which we already had sufficient data; stents were used in less than 50% of people; timing of administration of the drug was not pre-catheter laboratory and so not consistent with our definition of fPPCI; the intervention arm was fibrinolysis not fPPCI; streptokinase was used as the main drug.

Study data were divided into the following categories:

- GPIs: fPPCI versus PPCI (with or without GPI)
- GPIs: fPPCI (pre-catheter laboratory) versus routine catheter laboratory administration of GPI
- Fibrinolytics (tenecteplase): fPPCI versus PPCI
- Combination: GPI + fibrinolytic – fPPCI versus PPCI

Due to the large number of different comparisons used, further post-hoc sensitivity analyses were carried out, on type of GPI and type of background treatment, reported in appendix N.

6.3.1 Operational definition: facilitated PPCI (fPPCI)

In people with acute STEMI, facilitated PPCI is the use of pharmacological agents (GPIs, fibrinolytics or heparin OR a combination of any of these classes of drug) before an anticipated PPCI:

- with the intention of improving coronary patency
- given any time before arrival in the catheter laboratory (for example, administered in the ambulance or hospital emergency room)
- people must also be on a background of at least 1 oral antiplatelet agent, and may have been given an antithrombin:
  - older studies: aspirin with/without heparin
  - recent studies: aspirin and clopidogrel (or other ADP antagonist) with/without heparin.

6.3.2 Operational definition: control group (PPCI)

In people with acute STEMI the intended reperfusion strategy is PPCI, with or without placebo or adjunctive therapy and the:

- Adjunctive therapy:
  - must be given in the catheter laboratory or at time of PPCI
  - should ideally be the same drug as given in the fPPCI group.
- People must also be on a background of at least 1 antiplatelet agent:
  - older studies: aspirin with/without heparin
  - recent studies: aspirin and clopidogrel (or other ADP antagonists) with/without heparin
  - should ideally be the same as in the fPPCI group.

Table 20: Summary of studies included in the review

Study	n	Randomised groups: drugs used and treatment			Where / when study drugs administered	Time of drug administration	% people who had PCI and stents
		fPPCI	PPCI	Other arm			
Combination therapy (GPI + fibrinolytic)							
ELLIS 2008 (FINESSE trial)[98] and ELLIS 2009 (1 year results)[97]	2452	Combination fPPCI: abciximab (GPI) + ½ dose reteplase	PPCI: abciximab (immediately before PCI) + placebo	Mono fPPCI: abciximab (GPI)	Before catheterisation / angiography	Door to balloon (median): 2.2 hours (132 minutes) in all groups. Drug to balloon: 90 minutes overall.	PCI: 92% overall Stents: unclear/ 87% stated in another publication
Fibrinolytics							
ASSENT 2006 / VANDEWERF 2006[312] (ASSENT-4 study)	1667	Tenecteplase (No GPI allowed)	PPCI alone (GPI at discretion)	-	Pre-catheterisation	Symptom onset to drug (median): 153 minutes fPPCI, n/a PPCI Drug to balloon (median): 104 minutes fPPCI, n/a PPCI	PCI: 89% overall Stents: 83% overall
THIELE 2011 (LIPSIA-STEMI trial)[302]	162	Tenecteplase (+ clopdogrel background)	PPCI alone (+ clopdogrel background)	-	Pre-hospital	Drug to balloon (median): 91 minutes fPPCI, n/a PPCI	PCI: 93% fPPCI and 98% PPCI Stents: 100%
KANAKAKIS 2009 (ATHENS-PCI trial)[153]	284	Tenecteplase	PPCI alone	-	Pre-catheterisation	Drug to balloon (median): 121 minutes fPPCI, n/a PPCI	PCI: 94% fPPCI and 88% PPCI Stents: 71% fPPCI and 77% PPCI
LIU 2012 [179]	152	Reteplase	PPCI alone	-	Pre-treated before angiography	Symptom onset to drug (mean): 3.2 hours fPPCI, n/a PPCI Symptom onset to first dilation: 5.1 hours fPPCI and 4.1 hours PPCI	PCI: 97% fPPCI and 96% PPCI Stents: 96% fPPCI and 94% PPCI
GPIs (fPPCI versus PPCI trials)							
MEHILLI 2009 (BRAVE-3 trial)[192] and SCHULTZ 2010B[272] (1	800	Abciximab	Placebo	-	ICU	Symptom onset to drug* (median): 255 minutes fPPCI and 260 minutes PPCI	PCI: 96% (fPPCI) and 97% (PPCI) Stents: 92% (fPPCI)

Study	n	Randomised groups: drugs used and treatment			Where / when study		Time of drug administration	% people who had
year results)							Drug* to -PCI (mean): 47 minutes in both groups	and 93% (PPCI)
VANTHOF 2008 (ON-TIME 2 trial)[315] and TENBERG 2010[298] (3 year results)	984	Tirofiban	Placebo	-	Early (pre-hospital)	-	PCI immediately after angio: 99% in both groups. Drug*to angiography (median): 55 minutes in both groups.	PCI: 99% overall Stents: 90% overall
LEMAY 2009 (ASSIST trial)[167]	400	Eptifibatide (GPI) (+ heparin)	PPCI (heparin)	-	Before catheterisation / angiography		Drug to balloon: 43 minutes fPPCI, n/a PPCI. Symptom onset to drug (mean): 196 minutes fPPCI and 194 minutes PPCI.	PCI: 92% overall Stents: 93% overall
ZORMAN 2002[340]	163	Abciximab	PPCI (no abciximab)	Abciximab just before PCI**	Given immediately after initial heparin and aspirin, in the emergency department.		Symptom onset to PCI: 297 minutes versus 346 minutes Drug pre-treatment time (range): 10–105 minutes fPPCI and n/a PPCI.	PCI: 93% (fPPCI) and 100% (PPCI) Stents: 59% (fPPCI) and 69% (PPCI)
fPPCI: pre-catheter laboratory administration (upstream) versus catheter laboratory administration (downstream) trials								
ZEYMER 2005 (INTAMI pilot trial)[336]	102	Eptifibatide	Selective use of Eptifibatide 86% given eptifibatide immediately before PCI or during PCI	-	ER	Later/none (optional at time of PCI)	Timings for each of the groups were not reported.	PCI: 87% and 94% in each arm Stents: 73% (early group), 74% (later group)
OHLMANN 2012 (MISTRAL study)[247,248]	256	Abciximab	Abciximab	-	Ambulance	Cath lab, just before PCI	'Upstream' group received drug 65 minutes before 'downstream' group	PCI: 91% and 88% in each arm Stents: 100%
BELLANDI 2006[21]	55	Abciximab	Abciximab	-	ER	Cath lab, just before	Drug to balloon (mean): 49 minutes 'upstream' and 18 minutes 'downstream'	PCI: 100% overall Stents: 100%

Study	n	Randomised groups: drugs used and treatment			Where / when study		Time of drug administration	% people who had
						PCI		
GABRIEL 2006 (ERAMI trial)[107]	80	Abciximab(in ER) + placebo (in cath lab)	Placebo (in ER) + Abciximab (in cath lab)	-	ER	Cath lab, just before PCI	Drug to balloon (mean): 'upstream' group received drug 42 minutes before 'downstream' group	PCI: 93% overall Stents: most patients
MAIOLI 2007 (RELAX-AMI trial)[187]	210	Abciximab	Abciximab	-	ER	Cath lab, just before PCI	Drug to balloon (median): 55 minutes 'upstream' and 14 minutes 'downstream'	PCI: 100% overall Stents: 100%
DUDEK 2010[89]	73	Abciximab	Abciximab	Selective use (22%) abciximab during PCI	ER	Cath lab, just before PCI	Drug to balloon (mean): 87 minutes 'upstream' and 21 minutes 'downstream'	PCI: 100% overall Stents: 84% ('upstream' group) and 96% ('downstream' group)
ZORMAN 2002[340]	163	Abciximab	Abciximab	PPCI (no abciximab)**	emergency department	After angiography, before PCI	Symptom onset to PCI: 297 minutes 'upstream' versus 374 minutes 'downstream' Drug pre-treatment time (range): 10–105 minutes in 'upstream' group.	PCI: 93% ('upstream' group) and 100% ('downstream' group) Stents: 59% ('upstream' group) and 69% ('downstream' group)
LEE 2003 (TIGER-PA pilot trial)[171]	100	Tirofiban	Tirofiban	-	ER	Cath lab, just before PCI	Time from door to drug (mean): 56 minutes 'upstream' and 82 minutes 'downstream' groups. Drug to -PCI (mean): 33 minutes in 'upstream', n/a 'downstream'	PCI: 100% overall Stents: 94%
EL-KHOURY 2010	320	Tirofiban	Tirofiban	-	Pre-	Cath lab,	Drug given 48 minutes earlier in	PCI: 84% overall

Study	n	Randomised groups: drugs used and treatment			Where / when study		Time of drug administration	% people who had
(AGIR-2 trial)[94]					hospital	just before PCI	the 'upstream' group.	Stents: 70%
SHEN 2008[276]	172	Tirofiban	Tirofiban	-	ER	Cath lab, just before PCI	Time of drug administration was not reported.	PCI: 100% overall Stents: 99%
EMRE 2006[99]	66	Tirofiban	Tirofiban	-	ER	Cath lab, just before PCI	Door to drug (mean): 18 minutes 'upstream' and 52 minutes 'downstream'	PCI: 100% overall Stents: 100%
VANTHOF 2004 (ON-TIME trial)[314]	507	Tirofiban	Tirofiban	-	Pre-hospital	Cath lab, just before PCI	Pre-treatment time was median 59 minutes longer in 'upstream' versus 'downstream' group.	PCI: 89% overall Stents: 73%

**The term 'drug' in the PPCI arm represents placebo, as no antithrombotic drug was given in this arm.*
*** Data for this arm have not been included in the review, because it was not relevant to the review question.*

Table 21: Summary of background therapies used in the studies included in the review

Study	Background drugs in fPPCI arm (pre-or during PCI)				Background drugs same in PPCI arm?
	Aspirin	Other oral antiplatelets (loading dose)	Heparin	GPIs	
Combination therapy (GPI + fibrinolytic)					
ELLIS 2008 (FINESSE trial) and ELLIS 2009 (1 year results)	✓ pre-catheterisation	X	✓ LMWH or UFH pre-catheterisation	X	✓
Fibrinolytics					
ASSENT 2006 / VANDEWERF 2006 (ASSENT-4 study)	✓ pre-catheterisation	Clopidogrel (post-PCI if stent deployed)	✓ UFH pre-catheterisation	X	✓

Study	Background drugs in fPPCI arm (pre-or during PCI)				Background
THIELE 2011 (LIPSIA-STEMI trial)	✓	✓ Clopidogrel (600 mg)	✓	X	✓
KANAKAKIS 2009 (ATHENS-PCI trial)	✓ pre-catheterisation	✓ Clopidogrel (300 mg in patients with stents / 75 mg in patients without stents): given immediately before PCI	✓ UFH pre-catheterisation	✓ Eptifibatide (GPI) given immediately before PCI	✓
LIU 2012	✓	✓ Clopidogrel (pre-PCI and post-PCI)	X	At physician discretion	✓
GPIs (fPPCI versus PPCI trials)					
MEHILLI 2009 (BRAVE-3 trial) and SCHULTZ 2010B (1 year results)	✓	✓ Clopidogrel (pre-PCI and post-PCI)	✓	X	✓
VANTHOF 2008 (ON-TIME 2 trial) and TENBERG 2010 (3 year results)	✓	✓ Clopidogrel (600 mg)	✓	X	✓
LEMAY 2009 (ASSIST trial)	✓ pre-catheterisation	X	✓ randomised	✓ pre-catheterisation, if required for 'bail out'	✓
ZORMAN 2002	✓	X No mention of clopidogrel	✓	X	✓
fPPCI: pre-catheter laboratory administration (upstream) versus in-catheter laboratory administration (downstream) trials					
ZEYMER 2005	✓	Clopidogrel (post-PCI if	✓	X	✓

Study	Background drugs in fPPCI arm (pre-or during PCI)				Background
(INTAMI pilot trial)		stent deployed)			
OHLMANN 2012 (MISTRAL study)	✓	Clopidogrel (post-PCI at physician's discretion)	✓	x	x
BELLANDI 2006	✓	Clopidogrel (post-PCI)	✓	X	✓
GABRIEL 2006 (ERAMI trial)	✓	Optional clopidogrel or ticlopidine (post-PCI)	✓	X	✓
MAIOLI 2007 (RELAX-AMI trial)	✓	Clopidogrel (post-PCI)	✓	X	✓
DUDEK 2010	✓	✓ Clopidogrel (600 mg)	✓	X	✓
ZORMAN 2002	✓	X No mention of clopidogrel	✓	X	✓
LEE 2003 (TIGER-PA pilot trial)	✓	Optional clopidogrel or ticlopidine (post-PCI if stent deployed)	X	X	✓
EL-KHOURY 2010 (AGIR-2 trial)	✓	✓ Clopidogrel (600 mg)	✓	X	✓
SHEN 2008	✓	✓ Clopidogrel (450 mg)	✓	X	✓
EMRE 2006	✓	✓ Clopidogrel (300 mg)	✓	X	✓
VANTHOF 2004 (ON-TIME trial)	✓	Clopidogrel (post-PCI)	✓	X	✓

LMWH = low molecular weight heparin, UFH = unfractionated heparin.

6.4 Clinical evidence: evidence profiles

6.4.1 GPIs: fPPCI versus PPCI – all GPIs

Table 22: Clinical evidence profile: fPPCI with GPIs – fPPCI versus PPCI – all GPIs

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	GPIs (all): fPPCI	PPCI (placebo/no drug)	Relative (95% CI)	Absolute	Quality	Importance
Mortality - all-cause (in-hospital) (assessed with: Zorman)												
1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	Very serious (b)	None	0/56 (0%)	5/51 (9.8%)	RR 0.08 (0 to 1.46)	90 fewer per 1000 (from 98 fewer to 45 more)	VERY LOW	CRITICAL
Mortality - all-cause (short-term) (assessed with: ASSIST; BRAVE-3; ON-TIME2)												
3	Randomised trials	Very serious (c)	No serious inconsistency	No serious indirectness	Very serious (b)	None	31/1075 (2.9%)	33/1075 (3.1%)	RR 0.94 (0.58 to 1.52)	2 fewer per 1000 (from 13 fewer to 16 more)	VERY LOW	CRITICAL
Mortality - all-cause (longer-term) (assessed with: ASSIST; BRAVE-3; ON-TIME2; Zorman)												
4	Randomised trials	Very serious (d)	Serious (e)	No serious indirectness	Very serious (b)	None	52/1125 (4.6%)	54/1119 (4.8%)	RR 0.96 (0.66 to 1.38)	2 fewer per 1000 (from 16 fewer to 18 more)	VERY LOW	CRITICAL
Stroke - all-cause (short-term) (assessed with: ASSIST; BRAVE-3; FINESSE; ON-TIME2)												
4	Randomised trials	Very serious (f)	No serious inconsistency	No serious indirectness	Very serious (b)	None	11/1889 (0.58%)	17/1870 (0.91%)	RR 0.65 (0.31 to 1.36)	3 fewer per 1000 (from 6 fewer to 3 more)	VERY LOW	CRITICAL
Stroke - all-cause (longer-term) (assessed with: ASSIST; BRAVE-3)												
2	Randomised	Very serious	Serious (e)	No serious	Very serious	None	3/602	5/598	RR 0.63	3 fewer per 1000 (from 7	VERY	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	GPIs (all): fPPCI	PPCI (placebo/no drug)	Relative (95% CI)	Absolute	Quality	Importance
	trials	(g)		indirectness	(b)		(0.5%)	(0.84%)	(0.17 to 2.4)	fewer to 12 more)	LOW	
Stroke - fatal (short-term) (assessed with: FINESSE)												
1	Randomised trials	Serious (h)	No serious inconsistency	No serious indirectness	Very serious (b)	None	3/814 (0.37%)	0/795 (0%)	RR 6.84 (0.35 to 132.14)	Not estimable as zero events in 1 arm	VERY LOW	CRITICAL
Reinfarction or non-fatal reinfarction or recurrent myocardial infarction (short-term) (assessed with: ASSIST; BRAVE-3; FINESSE; ON-TIME2)												
4	Randomised trials	Very serious (f)	No serious inconsistency	No serious indirectness	Very serious (b)	None	13/1893 (0.69%)	34/1881 (1.8%)	RR 1.02 (0.64 to 1.64)	0 more per 1000 (from 7 fewer to 12 more)	VERY LOW	IMPORTANT
Reinfarction or non-fatal reinfarction or recurrent myocardial infarction (longer-term) (assessed with: ASSIST; BRAVE-3)												
2	Randomised trials	Very serious (g)	No serious inconsistency	No serious indirectness	Very serious (b)	None	16/602 (2.7%)	13/598 (2.2%)	RR 1.22 (0.59 to 2.52)	5 more per 1000 (from 9 fewer to 33 more)	VERY LOW	IMPORTANT
Major bleeding (in-hospital) (assessed with: Zorman)												
1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Serious (i)	None	16/56 (28.6%)	6/51 (11.8%)	RR 2.43 (1.03 to 5.73)	168 more per 1000 (from 4 more to 556 more)	LOW	IMPORTANT
Major bleeding (short-term) (assessed with: BRAVE-3; FINESSE; ON-TIME2)												
3	Randomised trials	Serious (j)	No serious inconsistency	No serious indirectness	Serious (i)	None	65/1688 (3.9%)	42/1671 (2.5%)	RR 1.53 (1.04 to 2.24)	13 more per 1000 (from 1 more to 31 more)	LOW	IMPORTANT
Heart failure (in-hospital) (assessed with: Zorman)												
1	Randomised trials	Very serious	No serious inconsistency	No serious indirectness	No serious imprecision	None	4/56 (7.1%)	15/51 (29.4%)	RR 0.24 (0.09 to	224 fewer per 1000 (from 94	LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	GPIs (all): fPPCI	PPCI (placebo/no drug)	Relative (95% CI)	Absolute	Quality	Importance
		(a)							0.68)	fewer to 268 fewer)		
Heart failure (short-term) (assessed with: ASSENT)												
1	Randomised trials	Serious (k)	No serious inconsistency	No serious indirectness	Very serious (b)	None	15/201 (7.5%)	22/199 (11.1%)	RR 0.68 (0.36 to 1.26)	35 fewer per 1000 (from 71 fewer to 29 more)	VERY LOW	IMPORTANT
Heart failure (longer-term) (assessed with: ASSENT)												
1	Randomised trials	Serious (k)	No serious inconsistency	No serious indirectness	Serious (i)	None	15/201 (7.5%)	24/199 (12.1%)	RR 0.62 (0.33 to 1.14)	224 fewer per 1000 (from 94 fewer to 268 fewer)	LOW	IMPORTANT
Repeat revascularisation (repeat or urgent revascularisation) (short-term)												
1	Randomised trials	Serious (k)	No serious inconsistency	No serious indirectness	Very serious (b)	None	8/201 (4%)	4/199 (2%)	RR 1.98 (0.61 to 6.47)	20 more per 1000 (from 8 few to 110 more)	VERY LOW	IMPORTANT
Repeat revascularisation (repeat or urgent revascularisation) (longer-term)												
1	Randomised trials	Serious (k)	No serious inconsistency	No serious indirectness	Very serious (b)	None	8/201 (4%)	6/199 (3%)	RR 1.32 (0.47 to 3.74)	10 more per 1000 (from 16 fewer to 83 more)	VERY LOW	IMPORTANT

(a) 1/1 study poor/unclear randomisation, allocation concealment and blinding.
(b) Confidence interval crosses both default MIDs (0.75 and 1.25) and line of no effect.
(c) 1/3 studies poor/unclear randomisation;3/3 studies poor/unclear allocation concealment; 1/3 studies poor/open blinded.
(d) 1/4 studies poor/unclear randomisation; 4/4 studies poor/unclear allocation concealment; 2/4 studies single or unblinded.
(e) Heterogeneity: I^2 >50% and <75%.
(f) 4/4 studies poor/unclear allocation concealment; 2/4 studies poor/open blinded.
(g) 2/2 studies poor/unclear allocation concealment; 1/2 studies poor/open blinded.
(h) 1/1 study poor/unclear allocation concealment.

(i) Confidence interval crosses1 MID (1.25).
(j) 3/3 studies poor/unclear allocation concealment.
(k) 1/1 study unclear allocation concealment and poor blinding.
(l) Confidence interval crosses 1 default MID (0.75) and line of no effect.

6.4.2 GPIs: pre-catheter laboratory versus in-catheter laboratory administration – all GPIs

Table 23: Clinical evidence profile: fPPCI with GPIs – pre-catheter laboratory versus in-catheter laboratory administration – all GPIs

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	FPPCI (Early)	Later - all GPIs	Relative (95% CI)	Absolute	Quality	Importance
Mortality - all-cause (in-hospital) (assessed with: AGIR-2; MISTRAL; Zorman)												
3	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Very serious (b)	None	7/339 (2.1%)	14/349 (4%)	RR 0.54 (0.23 to 1.27)	18 fewer per 1000 (from 31 fewer to 11 more)	VERY LOW	CRITICAL
Mortality - all-cause (short-term) (assessed with: Bellandi; Dudek; Emre; ERAMI; INTAMI-pilot; MISTRAL; ON-TIME)												
7	Randomised trials	Very serious (c)	No serious inconsistency	No serious indirectness	Serious (d)	None	19/544 (3.5%)	11/552 (2%)	RR 1.73 (0.85 to 3.52)	15 more per 1000 (from 3 fewer to 50 more)	VERY LOW	CRITICAL
Mortality - all-cause (longer-term) (assessed with: MISTRAL; ON-TIME; Zorman)												
3	Randomised trials	Very serious (e)	No serious inconsistency	No serious indirectness	Very serious (b)	None	13/428 (3%)	15/429 (3.5%)	RR 0.87 (0.42 to 1.78)	5 fewer per 1000 (from 20 fewer to 27 more)	VERY LOW	CRITICAL
Stroke - all-cause (In-hospital) (assessed with: AGIR-2)												
1	Randomised trials	Serious (f)	No serious inconsistency	No serious indirectness	Very serious (b)	None	1/156 (0.64%)	2/164 (1.2%)	RR 0.53 (0.05 to 5.74)	6 fewer per 1000 (from 12 fewer to 58 more)	VERY LOW	CRITICAL
Stroke - all-cause (short-term) (assessed with: INTAMI-pilot; ON-TIME)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	FPPCI (Early)	Later - all GPIs	Relative (95% CI)	Absolute		
2	Randomised trials	Very serious (g)	No serious inconsistency	No serious indirectness	Very serious (b)	None	0/298 (0%)	1/305 (0.33%)	RR 0.35 (0.01 to 8.51)	2 fewer per 1000 (from 3 fewer to 25 more)	VERY LOW	CRITICAL
Reinfarction or non-fatal reinfarction or recurrent myocardial infarction (in-hospital) (assessed with: MISTRAL)												
1	Randomised trials	Very serious (h)	No serious inconsistency	No serious indirectness	Very serious (b)	None	2/127 (1.6%)	2/129 (1.6%)	RR 1.02 (0.15 to 7.1)	0 more per 1000 (from 13 fewer to 95 more)	VERY LOW	IMPORTANT
Reinfarction or non-fatal reinfarction or recurrent myocardial infarction (short-term) (assessed with: Bellandi; Dudek; Emre; ERAMI; INTAMI-pilot; MISTRAL; ON-TIME; RELAX-AMI)												
8	Randomised trials	Very serious (i)	No serious inconsistency	No serious indirectness	Very serious (b)	None	11/649 (1.7%)	10/657 (1.5%)	RR 1.09 (0.49 to 2.42)	1 more per 1000 (from 8 fewer to 22 more)	VERY LOW	IMPORTANT
Reinfarction or non-fatal reinfarction or recurrent myocardial infarction (longer-term) (assessed with: MISTRAL; ON-TIME)												
2	Randomised trials	Very serious (j)	No serious inconsistency	No serious indirectness	Very serious (b)	None	9/372 (2.4%)	11/373 (2.9%)	RR 0.82 (0.34 to 1.95)	5 fewer per 1000 (from 19 fewer to 28 more)	VERY LOW	IMPORTANT
Bleeding (in-hospital) (assessed with: Zorman)												
1	Randomised trials	Very serious (k)	No serious inconsistency	No serious indirectness	Serious (d)	None	16/56 (28.6%)	11/56 (19.6%)	RR 1.45 (0.74 to 2.85)	88 more per 1000 (from 51 fewer to 363 more)	VERY LOW	IMPORTANT
Major bleeding (in-hospital) (assessed with: AGIR-2)												
1	Randomised trials	Serious (f)	No serious inconsistency	No serious indirectness	Very serious (b)	None	2/156 (1.3%)	6/164 (3.7%)	RR 0.35 (0.07 to 1.71)	24 fewer per 1000 (from 34 fewer to 26 more)	VERY LOW	IMPORTANT
Major bleeding (short-term) (assessed with: Bellandi; Dudek; Emre; ERAMI; INTAMI-pilot; ON-TIME; RELAX-AMI)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**FPPCI (Early)**	**Later - all GPIs**	**Relative (95% CI)**	**Absolute**		
7	Randomised trials	Very serious (l)	No serious inconsistency	No serious indirectness	Very serious (b)	None	17/522 (3.3%)	14/537 (2.6%)	RR 1.24 (0.63 to 2.46)	6 more per 1000 (from 10 fewer to 38 more)	VERY LOW	IMPORTANT
Heart failure (in-hospital) (assessed with: Zorman)												
1	Randomised trials	Very serious (k)	No serious inconsistency	No serious indirectness	Serious (m)	None	4/56 (7.1%)	10/56 (17.9%)	RR 0.40 (0.13 to 1.20)	107 fewer per 1000 (from 155 fewer to 36 more)	VERY LOW	IMPORTANT

(a) 2/3 studies poor/unclear randomisation; 2/3 studies poor/unclear allocation concealment; 2/3 studies poor/open blinded.
(b) Confidence interval crosses both default MIDs (0.75 and 1.25) and line of no effect.
(c) 7/7 studies poor/unclear randomisation; 5/7 studies poor/unclear allocation concealment; 4/7 studies poor/open blinded; 3/7 studies no/unclear ITT analysis.
(d) Confidence interval crosses 1 default MID (1.25) and line of no effect.
(e) 3/3 studies poor/unclear randomisation; 3/3 studies poor/unclear allocation concealment; 1/3 studies poor/open blinded.
(f) 1/1 study poor/open blinded; 1/1 study no/unclear ITT analysis.
(g) 2/2 studies poor/unclear randomisation; 1/2 studies poor/unclear allocation concealment; 1/2 studies poor/open blinded; 1/2 studies no/unclear ITT analysis.
(h) 1/1 study poor/unclear randomisation; 1/1 study poor/unclear allocation concealment.
(i) 8/8 studies poor/unclear randomisation; 6/8 studies poor/unclear allocation concealment; 5/8 studies poor/open blinded; 4/8 studies no/unclear ITT analysis.
(j) 2/2 studies poor/unclear randomisation; 2/2 studies poor/unclear allocation concealment.
(k) 1/1 study poor/unclear randomisation, allocation concealment and blinding.
(l) 7/7 studies poor/unclear randomisation; 5/7 studies poor/unclear allocation concealment; 5/7 studies poor/open blinded; 4/7 studies no/unclear ITT analysis.
(m) Confidence interval crosses 1 default MID (0.75) and line of no effect.

6.4.3 Fibrinolytics: fPPCI versus PPCI – all fibrinolytics

Table 24: Clinical evidence profile: fPPCI with fibrinolytics – fPPCI versus PPCI: all fibrinolytics

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Fibrinolytics (all) fPPCI	PPCI	Relative (95% CI)	Absolute	Quality	Importance
Mortality- all-cause (in-hospital) (assessed with: ASSENT; ATHENS)												
2	Randomised trials	Very serious (a)	Very serious (b)	No serious indirectness	No serious imprecision	None	23/862 (2.7%)	5/904 (0.55%)	RR 4.33 (1.74 to 10.75)	18 more per 1000 (from 4 more to 54 more)	VERY LOW	CRITICAL
Mortality - all-cause (short-term) (assessed with: ASSENT; LIPSIA-STEMI)												
2	Randomised trials	Very serious (c)	No serious inconsistency	No serious indirectness	Serious (d)	None	60/903 (6.6%)	45/909 (5%)	RR 1.34 (0.92 to 1.95)	17 more per 1000 (from 4 fewer to 47 more)	VERY LOW	CRITICAL
Mortality - all-cause (longer-term) (assessed with: Liu)												
1	Randomised trials	Very serious (e)	No serious inconsistency	No serious indirectness	Very serious (f)	None	1/72 (1.4%)	6/71 (8.5%)	RR 0.16 (0.02 to 1.33)	71 fewer per 1000 (from 83 fewer to 28 more)	VERY LOW	CRITICAL
Stroke - all-cause (in-hospital) (assessed with: ATHENS; ASSENT-4)												
2	Randomised trials	Very serious (g)	No serious inconsistency	No serious indirectness	No serious imprecision	None	16/972 (1.6%)	0/979 (0%)	RR 17.06 (2.29 to 127.32)	-	LOW	CRITICAL
Stroke - all-cause (short-term) (assessed with: LIPSIA-STEMI; ASSENT-4)												
2	Randomised trials	Very serious (h)	No serious inconsistency	No serious indirectness	Serious (d)	None	8/909 (0.88%)	2/916 (0.22%)	RR 4.00 (0.86 to 18.67)	7 more per 1000 (from 0 fewer to 39 more)	VERY LOW	CRITICAL
Stroke - non-fatal (in-hospital) (assessed with: ATHENS)												

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Fibrinolytics (all) fPPCI**	**PPCI**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
1	Randomised trials	Very serious (g)	No serious inconsistency	No serious indirectness	Very serious (f)	None	1/143 (0.7%)	0/141 (0%)	RR 2.96 (0.12 to 72.01)	-	VERY LOW	CRITICAL
Reinfarction or non-fatal reinfarction or recurrent MI (short-term) (assessed with: ASSENT; LIPSIA-STEMI; LIU 2012)												
3	Randomised trials	Very serious (i)	No serious inconsistency	No serious indirectness	Serious (d)	None	55/957 (5.7%)	37/969 (3.8%)	RR 1.51 (1.00 to 2.26)	19 more per 1000 (from 0 more to 48 more)	VERY LOW	IMPORTANT
Intracranial bleeding or intracranial haemorrhage (in-hospital) (assessed with: ASSENT; ATHENS)												
2	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision	None	8/862 (0.93%)	0/904 (0%)	RR 18.04 (1.04 to 311.96)	-	LOW	CRITICAL
Intracranial bleeding or intracranial haemorrhage (short-term) (assessed with: ASSENT)												
1	Randomised trials	Very serious (j)	No serious inconsistency	No serious indirectness	Very serious (f)	None	1/829 (0.12%)	1/838 (0.12%)	RR 1.01 (0.06 to 16.13)	0 more per 1000 (from 1 fewer to 18 more)	VERY LOW	CRITICAL
Intracranial bleeding or intracranial haemorrhage (longer-term) (assessed with: Liu)												
1	Randomised trials	Very serious (e)	No serious inconsistency	No serious indirectness	No serious imprecision (k)	None	0/72 (0%)	0/71 (0%)	not pooled	not pooled	LOW	CRITICAL
Major bleeding (in-hospital) (assessed with: ASSENT; ATHENS)												
2	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	Serious (d)	None	54/862 (6.3%)	42/904 (4.6%)	RR 1.35 (0.91 to 2)	16 more per 1000 (from 4 fewer to 46 more)	VERY LOW	IMPORTANT
Major bleeding (longer-term) (assessed with: Liu)												
1	Randomised trials	Very serious	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/72 (0%)	0/71 (0%)	not pooled	not pooled	LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Fibrinolytics (all) fPPCI	PPCI	Relative (95% CI)	Absolute	Quality	Importance
		(e)			(k)							
Minor bleeding (in-hospital) (assessed with: ASSENT)												
1	Randomised trials	Very serious (j)	No serious inconsistency	No serious indirectness	Serious imprecision (m)	None	210/719 (29.2%)	159/763 (20.8%)	RR 1.4 (1.17 to 1.68)	83 more per 1000 (from 35 more to 142 more)	VERY LOW	IMPORTANT
Minor bleeding (longer-term) (assessed with: Liu)												
1	Randomised trials	Very serious (e)	No serious inconsistency	No serious indirectness	Very serious (f)	None	8/72 (11.1%)	7/71 (9.9%)	RR 1.13 (0.43 to 2.94)	13 more per 1000 (from 56 fewer to 191 more)	VERY LOW	IMPORTANT
Heart failure (in-hospital) (assessed with: ATHENS)												
1	Randomised trials	Very serious (g)	No serious inconsistency	No serious indirectness	No serious imprecision	None	24/143 (16.8%)	5/141 (3.5%)	RR 4.73 (1.86 to 12.06)	132 more per 1000 (from 30 more to 392 more)	LOW	IMPORTANT
Heart failure (short-term) (assessed with: ASSENT; LIPSIA-STEMI)												
2	Randomised trials	Very serious (c)	No serious inconsistency	No serious indirectness	No serious imprecision	None	103/887 (11.6%)	78/896 (8.7%)	RR 1.34 (1.01 to 1.77)	30 more per 1000 (from 1 more to 67 more)	LOW	IMPORTANT
Heart failure (longer-term) (assessed with: Liu)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious (l)	None	2/72 (2.8%)	9/71 (12.7%)	RR 0.22 (0.05 to 0.98)	99 fewer per 1000 (from 3 fewer to 120 fewer)	MODERATE	IMPORTANT
Repeat revascularisation (repeat or urgent revascularisation) (short-term) (assessed with: ASSENT)												
1	Randomised	Very	No serious	No serious	No serious	None	53/805	28/818	RR 1.92	31 more per	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Fibrinolytics (all) fPPCI	PPCI	Relative (95% CI)	Absolute		
	trials	serious (j)	inconsistency	indirectness	imprecision		(6.6%)	(3.4%)	(1.23 to 3.01)	1000 (from 8 more to 69 more)		

(a) 1/2 studies poor/unclear randomisation; 1/2 studies poor/unclear allocation concealment; 2/2 studies poor/open blinded; 2/2 studies no/unclear ITT analysis.
(b) Unexplained heterogeneity I2 >75%.
(c) 1/2 studies poor/unclear randomisation; 1/2 studies poor/unclear allocation concealment; 2/2 studies poor/open blinded; 1/2 studies no/unclear ITT analysis.
(d) Confidence interval crosses 1 default MID (1.25) and line of no effect.
(e) Randomisation and allocation concealment not reported. Unblinded.
(f) Confidence interval crosses both default MIDs (0.75 and 1.25) and line of no effect.
(g) 1/1 studies poor/unclear randomisation; 1/1 studies poor/unclear allocation concealment; 1/1 studies poor/open blinded;1/1 studies no/unclear ITT analysis.
(h) 1/2 studies poor/unclear randomisation; 1/2 studies poor/unclear allocation concealment; 2/2 studies poor/open blinded; 1/2 studies no / unclear ITT analysis.
(i) 2/3 studies poor/unclear randomisation; 2/3 studies poor/unclear allocation concealment; 3/3 studies poor/open blinded; 1/3 studies no/unclear ITT analysis.
(j) 1/1 study poor/unclear allocation concealment; 1/1 study poor/open blinded; 1/1 study no/unclear ITT analysis.
(k) Zero events in both arms.
(l) Confidence interval crosses 1 default MID (0.75)(m) Confidence interval crosses 1 default MID (1.25).

6.4.4 Combination: GPI plus fibrinolytic

Table 25: Clinical evidence profile: fPPCI with combination of GPI plus fibrinolytic – fPPCI versus PPCI: abciximab + reteplase

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	GPIs: Abciximab + retepalse fPPCI	PPCI	Relative (95% CI)	Absolute		
Stroke - all-cause (short-term) (assessed with: FINESSE)												
1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Very serious (b)	None	4/805 (0.5%)	8/795 (1%)	RR 0.49 (0.15 to 1.63)	5 fewer per 1000 (from 9 fewer to 6 more)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	GPIs: Abciximab + retepalse fPPCI	PPCI	Relative (95% CI)	Absolute	Quality	Importance
Stroke - fatal (short-term) (assessed with: FINESSE)												
1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision.	None	0/805 (0%)	0/795 (0%)	Inestimable as zero events in each arm		MODERATE	CRITICAL
Intracranial bleeding or intracranial haemorrhage (short-term) (assessed with: FINESSE)												
1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Very serious (b)	None	0/805 (0%)	1/795 (0.1%)	RR 0.33 (0.01 to 8.07)	1 fewer per 1000 (from 1 fewer to 9 more)	VERY LOW	CRITICAL
Major bleeding (short-term) (assessed with: FINESSE)												
1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Serious (c)	None	33/805 (4.1%)	21/795 (2.6%)	RR 1.55 (0.91 to 2.66)	15 more per 1000 (from 2 fewer to 44 more)	LOW	IMPORTANT
Minor bleeding (short-term) (assessed with: FINESSE)												
1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Serious (c)	None	48/805 (6%)	34/795 (4.3%)	RR 1.39 (0.91 to 2.14)	17 more per 1000 (from 4 fewer to 49 more)	LOW	IMPORTANT
Heart failure (short-term) (assessed with: FINESSE)												
1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Very serious (b)	None	54/828 (6.5%)	52/806 (6.5%)	RR 1.01 (0.7 to 1.46)	1 more per 1000 (from 19 fewer to 30 more)	VERY LOW	IMPORTANT
Repeat revascularisation; (short-term) (assessed with: FINESSE)												
1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision	None	111/828 (13.4%)	111/806 (13.8%)	RR 0.97 (0.76 to 1.24)	4 fewer per 1000 (from 33 fewer to 33 more)	MODERATE	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	GPIs: Abciximab + retepalse fPPCI	PPCI	Relative (95% CI)	Absolute	Quality	Importance
Recurrent MI (short-term) (assessed with: FINESSE)												
1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Very serious (b)	None	17/828 (2.1%)	15/806 (1.9%)	RR 1.10 (0.55 to 2.19)	2 more per 1000 (from 8 fewer to 22 more)	VERY LOW	IMPORTANT

(a) 1/1 study unclear allocation concealment.
(b) Confidence interval crosses both default MIDs (0.75 and 1.25) and line of no effect.
(c) Confidence interval crosses 1 default MID (1.25) and line of no effect.

Table 26: Results of studies with data unsuitable for meta-analysis or GRADE: data written as reported in studies

Reference	Treatment groups	Outcomes and time points, % people (best treatment)										
		In-hospital		Short-term					Longer-term			
		Major bleed	Minor bleed	Mortality (all-cause)	Major bleed	Minor bleed	Re-MI / non-fatal MI	TVR	Mortality (all-cause)	Re-MI / nonfatal MI	TVR	Stroke
FINESSE	1. Combination fPPCI Abciximab + reteplase	-	-	5.5%	-	-	-	-	6.3%	-	-	-
	2. fPPCI Abciximab			5.2%					7.4%			
	3. PPCI			4.5%					7.0%			
LIPSIA-STEMI	1. fPPCI Tenecteplase	-	-	-	5%	4.9%	-	-	-	-	-	-
	2. PPCI				6.2%	7.4%						

Reference	Treatment groups	Outcomes and time points, % people (best treatment)										
TIGER-PA	1. fPPCI Early tirofiban	-	-	2%	2%	10%	0%	0%	-	-	-	-
	2 fPPCI Later tirofiban			2%	2%	6%	2%	2%				
Shen 2008	1. fPPCI Early tirofiban	5.3%*	3.5%*	3.5%*	-	-	0%	0%	3.5%*	1.8%*	1.8%*	-
	1. fPPCI Later tirofiban	8.8%*	1.8%*	5.3%*			0%	0%	5.3%*	1.8%*	1.8%*	

*For all studies there was no significant difference between any of the comparison groups (except for those with an * where significance was not specified)*

6.5 Economic evidence

No relevant economic evaluations were identified that compared facilitated PPCI with PPCI in people with STEMI.

One economic evaluation relating to this review question was selectively excluded due to a combination of limited applicability and methodological limitations.[59] This is summarised in Appendix K, with reasons for exclusion given. See also the economic article selection flow diagram in Appendix E.

6.6 Evidence statements

Clinical

GPIs: fPPCI versus PPCI (no drug or placebo)

Very low quality evidence suggested that there was too much uncertainty to determine whether fPPCI or PPCI differed in their association with occurrence of:

- all-cause mortality in hospital (1 study, 163 participants), in the short term [3 trials, 2150 participants] or in the longer term [4 trials, 2244 participants],
- non-fatal stroke in the short term (4 trials, 3759 participants) or longer term [2 trials, 1200 participants],
- fatal stroke [1 study, 1609 participants], or
- reinfarction (non-fatal or recurrent myocardial infarction in the short term [4 studies, 3774] or longer term [2 studies, 1200 participants].

Low quality evidence suggested that PPCI may have a greater association than fPPCI in reduced incidence of major bleeding:

- in-hospital [1 study, 107 participants]
- in the short term [3 studies, 3359 participants], but there was some uncertainty.

Low quality evidence showed that PPCI was associated with a clinically effective reduction in heart failure in-hospital when compared to fPPCI [1 study, 107 participants].

Very low quality evidence suggested that there was too much uncertainty to determine whether fPPCI or PPCI differed in their association with occurrence of heart failure in the short term [1 study, 400 participants].

Low quality evidence suggested that fPPCI may have a greater association than PPCI in reduced incidence of heart failure in the longer term, but there was some uncertainty [1 study, 400 participants].

Very low quality evidence suggested that there was too much uncertainty to determine whether fPPCI or PPCI differed in their association with occurrence of repeat revascularisation (or urgent revascularisation) in the short or longer term [1 study, 400 participants].

GPIs: pre-catheter laboratory versus in-catheter laboratory administration – all GPIs

Very low quality evidence suggested that there was too much uncertainty to determine whether fPPCI or PPCI differed in their association with occurrence of:

- all-cause mortality in-hospital [3 studies, 688 participants],

- all-cause mortality in the longer term [3 studies, 857 participants],
- stroke in-hospital [1 study, 320 participants] or in the short term [2 studies, 603 participants],
- reinfarction (non-fatal or recurrent myocardial infarction) in-hospital [1 study, 256 participants], in the short term [8 studies, 1306] or in the longer term [2 studies, 745 participants], or
- major bleeding in-hospital [1 study, 320 participants], or in the short term [7 studies, 1059].

Very low quality evidence suggested that PPCI may have a greater association with reduced occurrence of all-cause mortality in the short term [7 studies, 1096 participants], and in-hospital bleeding [1 study, 112 participants] but there was some uncertainty.

Very low quality evidence suggested that PPCI may have a greater association with reduced occurrence of heart failure in-hospital [7 studies, 112 participants], but there was some uncertainty.

Fibrinolytics: fPPCI versus PPCI – all fibrinolytics

Very low quality evidence showed that PPCI has a greater association when compared with fPPCI with reduced occurrence of:

- all-cause mortality in hospital [2 studies, 1766 participants], or
- minor bleeding in-hospital [1 study, 1482 participants].

Low quality evidence showed that PPCI has a greater association when compared with fPPCI with reduced occurrence of:

- intracranial bleeding or haemorrhage in-hospital [2 studies, 1766 participants],
- stroke in-hospital [2 studies, 1951 participants],
- heart failure in-hospital [1 study, 184 participants] or in the short term [2 studies, 1783 participants], or
- repeat or urgent revascularisation in the short term [1 study, 1623 participants].

Very low quality evidence suggested that PPCI may have a greater association when compared with fPPCI with reduced occurrence of:

- all-cause mortality in the short term [2 studies, 1812 participants],
- stroke in the short term [2 studies, 1825 participants],
- reinfarction (non-fatal or recurrent myocardial infarction) in the short term [3 studies, 1926 participants], or
- major bleeding in-hospital [2 studies, 1766 participants], but there was some uncertainty.

Moderate quality evidence suggested that fPPCI may have a greater association when compared with PPCI with reduced occurrence of heart failure in the longer term [1 study, 143 participants].

Very low quality evidence suggested that there was too much uncertainty to determine whether fPPCI and PPCI differed in their association with occurrence of:

- all-cause mortality in the longer term [1 study, 143 participants],
- stroke in-hospital [1 study, 184 participants],
- intracranial bleeding or haemorrhage in the short term [1 study, 1667 participants], or
- minor bleeding in the longer term [1 study, 143 participants].

Effect sizes could not be determined for intracranial bleeding or haemorrhage or major bleeding in the longer term.

Combination: GPI + fibrinolytic – fPPCI versus PPCI – abciximab plus reteplase

Very low quality evidence suggested that there was too much uncertainty to determine whether a combination of GPI and fibrinolytic in fPPCI or PPCI differed in their association with reduced occurrence of:

- stroke in the short-term [1 study, 1600 participants],
- recurrent myocardial infarction in the short term [1 study, 1634 participants],
- intracranial bleeding haemorrhage in the short term [1 study, 1600 participants], or
- heart failure in the short-term [1 study, 1634 participants].

Low quality evidence suggested that PPCI had a greater association when compared to a combination of GPI and fibrinolytic in fPPCI with reduced occurrence of major or minor bleeding in the short term [1 study, 400 participants].

Moderate quality evidence showed that there was no clinically important difference between a combination of GPI and fibrinolytic in fPPCI compare to PPCI in their association with reduced occurrence of repeat revascularisation in the short term [1 study, 1634 participants].

Effect sizes could not be determined for occurrence of stroke in the short-term.

Economic

- No relevant economic evaluations were identified that compared facilitated PPCI with PPCI in people with STEMI.

6.7 Recommendations and link to evidence

Recommendations	**The current recommendations can be found at: www.nice.org.uk/guidance/ng185**
Relative values of different outcomes	For this review question the GDG considered the outcomes of all-cause mortality, stroke, intracranial bleeding and quality of life as critical to decision-making. Myocardial reinfarction, heart failure, major bleeding and subsequent revascularisation were considered important, and minor bleeding and length of hospital stay as less important to decision-making. No data were found for cardiovascular mortality, quality of life or length of hospital stay.
Trade-off between clinical benefits and harms	Facilitation of PPCI using pharmacological agents appears to increase the patency of the infarct-related coronary artery at the time of PPCI. In a meta-analysis of trials of facilitated PPCI versus standard PPCI the rate of TIMI-3 (normal) flow at the initial coronary angiogram was approximately doubled in people pre-treated with GPI, fibrinolytic, or combination therapy.[157,158] The evidence review in this chapter suggests that this angiographic advantage does not translate into a beneficial effect on clinical outcomes, regardless of whether people were pre-treated with GPI, fibrinolytic, or a combination of both agents. Subgroup analyses examining the impact of facilitation with specific drugs also showed no evidence of benefit. The results were consistent regardless of whether people were pre-treated with conjunctive aspirin and clopidogrel, or with aspirin alone. Moreover pre-treatment with GPI or fibrinolytic was associated with an increased risk of bleeding complications. The GDG debated whether administration of intravenous GPI or fibrinolytic therapy to people with acute STEMI before arrival in the catheter laboratory for PPCI might

	increase the call-to-balloon time, thereby adversely affect clinical outcomes. The data in this review do not provide consistent evidence of an increase in time to PPCI in the facilitated group, but the GGD agreed that this is a plausible explanation for the failure of facilitation to result in better clinical outcomes. The GDG also noted that a proportion of the people in the standard PPCI arms of these trials would have been treated with GPI, either because of suspected intracoronary thrombus with ischaemic complications, or as part of routine use of GPI in people with acute STEMI undergoing PPCI.[273,274] This may have diluted the potential benefit of the facilitation strategy. In addition, although facilitation may double the proportion of people with patent infarct-related arteries at the time of the initial coronary angiogram, this advantage is only likely to impact a relatively small number of people over a short time period and may be insufficient to translate into significant clinical benefit. The GDG concluded that facilitation with GPI, fibrinolytic therapy, or a combination of both agents does not improve clinical outcomes, but there is some evidence that facilitation is associated with harm with increased bleeding, particularly with a fibrinolytic agent. The GDG therefore recommended that a strategy of facilitation using GPI or fibrinolytic therapy should not be used routinely in people with acute STEMI who are eligible for PPCI.
Economic considerations	No health economic evidence was found for this question. Use of intravenous GPIs or fibrinolytic agents before arrival in the catheter laboratory would be associated with additional cost. Since the GDG interpretation of the clinical evidence was that facilitation with intravenous GPIs or fibrinolytic agents did not improve clinical outcomes, it was concluded that fPPCI would incur additional costs for no clinical benefit and therefore could not be a cost effective treatment strategy.
Quality of evidence	The GDG noted that of the 21 studies found (23 publications), evidence for none of the outcomes of interest was judged to be of high quality; predominately the evidence was of low to very low quality. Some of the studies were over 10 years old, with publication dates ranging from 2001 to 2010. Methodological limitations included lack of detail or clarity in randomisation and concealment processes and lack of clarity about intention to treat analysis. The ADMIRAL trial was not included in this evidence review because it was not possible to extract separate data for people treated before arrival in the catheter laboratory versus those treated in the catheter laboratory.[198] The GDG noted that the ASSENT trial (using fibrinolysis) was terminated early due to significantly more strokes in the fPPCI arm. The primary end point of this trial was mortality.[312]
Other considerations	The GDG noted various definitions of facilitated PPCI. The term was considered to be potentially confusing as all people receive some antithrombotic treatment in advance of a PPCI procedure (for example, aspirin and ADP receptor antagonist). However, this review specifically refers to upstream treatment with intravenous GPI and fibrinolytic agents, followed by transfer to a catheter laboratory as soon as possible with the intention of proceeding to PPCI. Facilitated PPCI is not current practice in the NHS (GDG expert opinion). The GDG debated the evidence and discussed the potential place of fPPCI in UK practice. The GDG considered the possible role of fPPCI in people with longer transfer times but concluded that there was no evidence to support this approach. Moreover, it was noted that the data all pre-date the introduction of the new more potent oral antiplatelet agents that have a faster onset of action than clopidogrel, have been the subject of NICE Technology Appraisal (see chapter 17),[223,226] and are becoming

	increasingly used in the treatment of people with STEMI.

7 Radial versus femoral arterial access for primary percutaneous coronary intervention

7.1 Introduction

Percutaneous coronary intervention is carried out via a catheter inserted into the arterial system from a femoral, brachial or radial artery. The transfemoral approach has dominated the growth of percutaneous coronary intervention over the past 3 decades, but more recently radial access has gained increasing popularity, mainly because of perceived advantages for patient safety. The British Cardiovascular Intervention Society (BCIS) 2011 audit returns show that use of radial arterial access for PPCI has steadily increased over time from 32.7% in 2008[182] to 57.6% of PPCI procedures in 2011 (Ludman PF: unpublished evidence 2012).

It has also been recognised that bleeding complications in people with acute coronary syndromes (ACS) are associated with morbidity and mortality.[93,188,256] People with STEMI constitute a high risk subset of ACS patients who require emergency reperfusion therapy and aggressive pharmacological treatment with antiplatelet and anticoagulant drugs, and are therefore at increased risk of bleeding.

There has been debate about the relative risks and benefits of femoral and radial arterial access routes for PCI, particularly with regard to potential differences in rates of procedural success and access site bleeding.[29,51,55,147,321] The radial artery lies close to the skin surface, making externally applied compression more likely to control bleeding than is the case for the larger and more deeply positioned femoral artery. On the other hand, the radial artery is a small calibre artery prone to spasm, which may only accept smaller French gauge catheters. Use of radial arterial access for PPCI procedures may prevent future use of the radial artery as a coronary artery bypass conduit or for an arteriovenous fistula for renal dialysis. Other factors that influence the choice of arterial access include the need for concomitant right ventricular pacing or intra-aortic balloon counterpulsation, which lead some operators to favour a femoral approach. Given these factors there has been increasing debate as to the preferred route of arterial access for PPCI in people with STEMI.

The GDG therefore considered the clinical and cost effectiveness of radial access compared to femoral access for coronary angiography with a view to follow-on PPCI in people with STEMI.

7.2 Review question: What is the clinical and cost effectiveness of radial access compared to femoral access for coronary angiography and, if appropriate, follow-on PPCI in people with STEMI managed by PPCI?

For full details see review protocol in Appendix C.

7.3 Clinical evidence

Nine studies were included in the review reported in 11 papers.[39,57,58,108,139,148,149,175,194,262,264] Evidence from these studies are summarised in the clinical GRADE evidence profiles. See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

A summary of the studies included in the review is given in Table 27. Definitions of outcomes of interest that varied between studies are given in Table 28. Use of adjunctive drug therapy is given in

Table 30. Individual study results for vascular access complications and haematomas are given in Table 31. Angiographic procedural times for individual studies are given in Table 32.

7.3.1 Summary of included studies

Table 27: Summary of studies included in the review for radial access versus femoral access PPCI

Study	Definition of population	Number of patients	Outcomes	Percentage of people undergoing PPCI, facilitated PPCI or rescue PCI
Brasselet 2007[39]	ACS with ST-elevation and sustained chest pain	n = 114	In-hospital all-cause mortality, major bleeding, minor bleeding, angiographic procedural success, hospital stay, fluoroscopy time, access site crossover	PPCI Radial: 26/57 (46%) Femoral: 32/57 (56%) Rescue PCI Radial: 28/57 (49%) Femoral: 20/57 (35%) Facilitated PPCI Radial: 3/57 (3%) Femoral: 5/57 (9%)
Gan 2009[108]	STEMI recruited within 12 hours of symptom onset Typical chest pain lasting > 30 minutes and < 12 hours, nitrate losing efficacy, ST-segment elevation > 0.1 mV in limb leads or > 0.2 mV in 2 or adjacent chest leads	n = 195	In-hospital all-cause mortality, reinfarction, minor bleeding, hospital stay, angiographic procedural success, fluoroscopy time, access site crossover, vascular access site complications; 9-month all-cause mortality, reinfarction, repeat revascularisation, CABG	PPCI for radial and femoral access
Hou 2010[139]	Acute MI (no further details given)	n = 200	30-day all-cause mortality, reinfarction, major bleeding, minor bleeding, repeat revascularisation, angiographic procedural success, hospital stay, fluoroscopy time, access site crossover, vascular access site complications	Unclear
Li 2007[175]	People with acute MI within 12 hours onset of chest pain (no further details given)	n = 370	Minor bleeding, angiographic procedural success, access site crossover	Unclear
RADIAMI 2009[57]	Presence of MI defined as retrosternal pain lasting > 20 minutes, but < 12 hours, resistant to	n = 100	In-hospital all-cause mortality, reinfarction, major bleeding, minor bleeding, repeat revascularisation,	PPCI 100%

Study	Definition of population	Number of patients	Outcomes	Percentage of people undergoing PPCI, facilitated PPCI or rescue PCI
	nitroglycerin, and ECG changes; ST-segment elevation of at least 1 mV in 2 neighbouring leads or new left bundle branch block, found in the qualifying ECG		stroke, CABG, angiographic procedural success, fluoroscopy time, total radiographic contrast media used in procedure, access site crossover	
RADIAMI II 2011[58]	Presence of MI defined as retrosternal pain lasting > 20 minutes, but < 12 hours, resistant to nitroglycerin, and ECG changes; ST-segment elevation of at least 1 mV in 2 neighbouring leads or new left bundle branch block, found in the qualifying ECG	n = 108	In-hospital all-cause mortality, reinfarction, major bleeding, minor bleeding, repeat revascularisation, CABG, fluoroscopy time, total radiographic contrast media used in procedure, access site crossover	PPCI 100%
RIFLE-STEACS 2012[262]	Presenting within 24 hours of symptom onset, people with acute ST-segment-elevation acute coronary syndrome	n = 1001	30-day all-cause mortality (reported as cardiac death and defined as any death due to cardiac cause, procedure-related death, and death of unknown cause), reinfarction, stroke, target vessel revascularisation, major bleeding, minor bleeding, procedural success, access site crossover	PPCI Radial: 459/501 (92%) Femoral: 466/500 (93%) Rescue PCI Radial: 41/500 (8.2%) Femoral: 35/501 (7.0%)
RIVAL 2011[148,149,194]	(1) presenting with signs or symptoms of acute MI lasting ≥ 20 minutes and (2) definite ECG changes compatible with STEMI persistent ST-segment elevation (of ≥ 2 mm in 2 contiguous precordial leads or > 1 mm in ≥ 2 limb leads) or new left bundle branch block or Q wave in 2 contiguous leads	n = 1958	In-hospital all-cause mortality, major bleeding, access site crossover, vascular access site complications	RCT; data extracted for the STEMI population (RCT recruited people with STEMI, NSTEMI and unstable angina). In the STEMI subgroup the initial reperfusion strategy was PPCI in 74.1%, fibrinolysis in 11.9%, and facilitated PPCI in 4.3%. No reperfusion therapy was given to 10.8%. PPCI Radial: 702/955 (73.5%) Femoral: 749/1003 (74.7%) Secondary PCI Radial: 253/955 (26.5%) Femoral: 254/1003 (25.3%)

Study	Definition of population	Number of patients	Outcomes	Percentage of people undergoing PPCI, facilitated PPCI or rescue PCI
TEMPURA 2003[264]	Acute MI within 12 hours from onset into study, presence of both prolonged chest pain lasting ≥ 30 minutes unresponsiveness to nitroglycerin and ECG changes (ST-segment elevation of ≥ 1 mm in ≥ 2 contiguous ECG leads)	n = 149	In-hospital all-cause mortality, reinfarction, major bleeding, repeat revascularisation, angiographic procedural success hospital stay, fluoroscopy time, total radiographic contrast media used in procedure, access site crossover; 9-month all-cause mortality, reinfarction, repeat revascularisation	PPCI Radial: 100% Femoral: 100%

Table 28: Individual study definitions of the outcomes: repeat revascularisation, major bleeding, minor bleeding and vascular access site complications

Study	Repeat revascularisation	Major bleeding	Minor bleeding	Vascular access site complications
Brasselet 2007[39]	Not reported	TIMI major bleeding: intracranial haemorrhage or ≥ 5g/dl decrease in the haemoglobin concentration or ≥ 15% absolute decrease in the haematocrit	TIMI minor bleeding: observed blood loss and ≥ 3 to < 5 g/dl decrease in the haemoglobin concentration or ≥ 10% decrease in the haematocrit; or no observed blood loss and ≥ 4 g/dl decrease in the haemoglobin concentration or ≥ 12% decrease in the haematocrit	Pseudoaneursym [haematoma > 4 cm, ecchymosis < 4 cm]
TEMPURA 2003[264]	Target lesion revascularisation	Bleeding requiring blood transfusion or surgical repair, or cerebral bleeding	Not reported	Not reported
Li 2007[175]	Not reported	Not reported	Local haematoma	Not reported
Gan 2009[108]	Target lesion revascularisation	Reported but not defined	Forearm haematoma	Pseudoaneurysm, arteriovenous fistula
RADIAMI 2009[57]	Target lesion revascularisation	Fatal bleeding, bleeding requiring blood transfusion, operation or resulting in a drop of haemoglobin count of > 3 g/dl or any intracranial haemorrhage	Bleeding complications that did not meet the criterion for major bleeding complications; reported in the study table as haematoma > 5 cm	Not reported
Hou 2010[139]	Target lesion revascularisation	Haemoglobin loss of ≥ 2 mmol/litre and administration of blood transfusions and needing vascular repair	Haematoma < 5 cm not requiring specific treatment	Pseudoaneurysm
RADIAMI II 2011[58]	Target lesion revascularisation	Fatal bleeding, bleeding requiring blood transfusion, operation or resulting in a drop of haemoglobin count of > 3 g/dl or any intracranial haemorrhage	Bleeding complications that did not meet the criterion for major bleeding complications; reported in the study table as haematoma > 5 cm	Not reported
RIVAL 2011[148,149,194]	Not reported	TIMI major bleeding: intracranial haemorrhage or ≥ 5 g/dl decrease in the haemoglobin concentration or ≥ 15% absolute decrease in the haematocrit	Bleeding events that did not meet the criteria for major bleeding and required the transfusion of 1 unit of blood or modification of the drug regimen (cessation of antiplatelet or antithrombotic therapy)	Pseudoaneurysm needing closure, large haematoma (as judged by investigator), arteriovenous fistula, or

Study	Repeat revascularisation	Major bleeding	Minor bleeding	Vascular access site complications
				an ischaemic limb needing surgery
RIFLE-STEACS 2012[262]	Target lesion revascularisation	TIMI major bleeding: intracranial haemorrhage or ≥ 5g/dl decrease in the haemoglobin concentration or ≥ 15% absolute decrease in the haematocrit	TIMI minor bleeding: observed blood loss and ≥ 3 to < 5 g/dl decrease in the haemoglobin concentration or ≥ 10% decrease in the haematocrit; or no observed blood loss and ≥ 4 g/dl decrease in the haemoglobin concentration or ≥ 12% decrease in the haematocrit	Not reported

Table 29: Angiographic procedure characteristics and GPI usage

Study	Stents (%) or number per person if percentage not reported		GPIs (%)		Femoral artery closure device
	Radial access	Femoral access	Radial access	Femoral access	
Brasselet 2007[39]	Stents (n), mean (SD) per person = 1.15 (0.36)	Stents (n), mean (SD) per person = 1.28 (0.61)	0	0	In the femoral artery, the arterial sheath was withdrawn without vascular closure devices and closure achieved by manual compression, people allowed to ambulate after 12 hours.
TEMPURA 2003[264]	100 (drug-eluting stent use not reported)	100 (drug-eluting stent use not reported)	0	0	Arterial sheath removed 3–4 hours later outside the laboratory.
Li 2007[175]	Not reported	Not reported	Not reported	Not reported	The sheath was removed when activated clotting time was > 150 seconds to 1180 seconds; haemostasis was completed using manual compression for 10–15 minutes followed by a pressure bandage for 8–12 hours.
Gan 2009[108]	100 (all drug-eluting)	100 (all drug-eluting)	31.1	35.4	Arterial sheath removed approximately 4 hours after completion of the PPCI, when activated clotting time was > 150 seconds. Thereafter puncture point was bandaged for at least 12 hours, and affected leg immobilised for at least 12 hours.
RADIAMI 2009[57]	99 (drug-eluting stent use not reported)	100 (drug-eluting stent use not reported)	95 (all GPIs) Abciximab: 44	92 (all GPIs) Abciximab: 42	Not reported
Hou 2010[139]	97 (Use of drug-eluting stents not reported)	95 (drug-eluting stent use not reported)	Not reported	Not reported	Sheath was removed 6 hours after PPCI and homeostasis was achieved by manual compression of at least 15 minutes and a

Study	Stents (%) or number per person if percentage not reported		GPIs (%)		Femoral artery closure device
					pressure bandage was applied and left on for 24 hours.
RADIAMI II 2011[58]	98 (drug-eluting stent use not reported)	100 (drug-eluting stent use not reported)	Abciximab: 43 (other GPIs not reported)	Abciximab: 44 (other GPIs not reported)	Vascular closure device used routinely
RIVAL 2011[148,149,194]	94	96	34.5	31.1	Use of vascular closure device was at the discretion of treating physician
	≥ 1 drug-eluting 24	≥ 1 drug-eluting 22			
RIFLE-STEACS 2012[262]	Stents (n), mean (SD) per person = 1.43 (1.0)	Stents (n), mean (SD) per person = 1.41 (0.9)	67.4	69.9	Not reported

Table 30: Adjunctive drug therapy

Study	Adjunctive drug therapy
Brasselet 2007[39]	Participants were pre-treated with an intravenous bolus of heparin as follows: unfractionated heparin 50 IU/kg with an upper limit of 4000 IU in people > 75 years, or low molecular weight heparin (30 mg) intravenously and 1 mg/kg subcutaneously in people < 75 years, and a bolus of aspirin (250 mg) intravenously. When complimentary PCI was required, abciximab was conventionally given. After completion of PPCI, subcutaneous low molecular heparin was injected twice/day at most during first 72 hours if necessary. All people received clopidogrel (300 mg), followed by 75 mg daily for 1 year, plus oral aspirin 75–300 mg/day.
TEMPURA 2003[264]	Heparin given after arterial puncture (men: 6000 units, women: 5000 units). Any fibrinolytic agents were not given before or after PPCI. GP IIb/IIIa inhibitors were not given as not licensed in Japan. Once daily aspirin (162 mg or more) and ticlopidine (200 mg) were started as soon as possible after stent implantation and continued.
Li 2007[175]	All participants received aspirin and clopidogrel before PPCI, adjunctive bolus heparin was determined by body weight (70–100 IU/Kg).
Gan 2009[108]	All participants received 300 mg aspirin, 300 mg clopidogrel on diagnosis. 30000 IU heparin administered after sheath insertion. Additional heparin during procedure dependent upon person's body mass (100 IU/kg). GP IIb/IIIa inhibitors were given dependent based on clinical need. After implantation of drug eluting stents, participants were treated with 1000 IU/kg low molecular heparin twice a day for 5–7 days and 150 mg aspirin plus 75 mg aspirin plus 75 mg clopidogrel daily for 12 months.
RADIAMI	Verapamil (5mg) after puncture of radial artery; dose was repeated in the case of a spasm, until reaching a total dose of 15 mg. Dependent on

Study	Adjunctive drug therapy
2009[57]	activated clotting time result heparin (70 U/kg) was administered. Fibrinolytic drugs and platelet GPIs were administered during the intervention based on clinical need. Heparin administration was continued after the intervention only in the presence of clinical indications. Abciximab was administered to a similar percentage of people in both groups (44% versus 42%, radial and femoral respectively).
Hou 2010[139]	Participants received 300 mg aspirin, 300 mg clopidogrel on diagnosis, and subcutaneous Fragmin (5000U) or FraxiParin (4100U) for all participants. Further 5000IU heparin given during procedure. GP IIb/IIIa inhibitors and stents were given during procedure dependent based on clinical need.
RADIAMI II 2011[58]	After placing the sheath, activated clotting time was determined and heparin was administered in doses that permitted the obtaining of activated clotting time of 350–450 seconds during procedures performed without the use of abciximab, and 250–350 seconds when abciximab was used. Whether to use abciximab was a decision left to the operator.
RIVAL 2011[148,149,194]	Antithrombotic regimen (including GPIs) used for PPCI was at the discretion of treating physician.
RIFLE-STEACS 2012[262]	Procedural anticoagulation was achieved with preliminary administration of bolus 70 UI/kg heparin, supplemented during procedure to maintain activated clotting time of > 250 seconds. The choice of additional antithrombotic agents (such as GPIs or bivalirudin) or different revascularisation strategies (for example thrombectomy or direct stenting) was at the discretion of treating physician and institutions standard procedure. All anticoagulants were discontinued at the end of the procedure unless clinically warranted. GPI bolus were followed by a ≥ 12 hour infusion. All participants were pre-treated with aspirin and a loading dose of clopidogrel (300–600 mg), and were discharged on dual antiplatelet therapy for ≥ 12 months at the discretion of the treating physician.

Table 31: Individual study results for vascular access site complications and haematoma formation

	Vascular access site complications (n/total group population)		Haematoma (n/total group population)	
Study	Radial access	Femoral access	Radial access	Femoral access
TEMPURA 2003[264]	Not reported		Not reported	
Brasselet 2007[39]	0/57 (0%)	0/57 (0%)	2/57 (3.5%)	11/57 (19.3%)
Li 2007[175]	Not reported		2/184 (1.1%)*	7/186 (3.8%)
Gan 2009[108]	2/90 (2.2%)	10/105 (9.3%)	Not reported	
RADIAMI 2009[57]	Not reported		5/50 (10%)‡	8/50 (16%)
Hou 2010[139]	0/100 (0%)	2/100 (2%)*	2/100 (2%)¥	6/100 (6%)
RADIAMI II 2011[58]	Not reported		8/49 (16.3%) NS	12/59 (20.3%)
RIVAL 2011[148,149,194]	12/955 (1.3%)	35/1003 (3.5%)	Not reported	
RIFLE-STEACS 2012[262]	Not reported		Not reported	

*Compared with femoral access group, *: p = 0.16; ¥: p = 0.28; ‡: p = 0.37; NS: Not significant.*

Table 32: Individual study angiographic procedure times

Study	Angiographic procedure time (minutes), mean (SD)		p value compared
	Radial access	Femoral access	
Brasselet 2007[39]	28 (14)	26 (18)	p = 0.72
TEMPURA 2003[264]	44 (18)	51 (21)	p = 0.033
Li 2007[175]	56.2 (12.1)	58.4 (15.1)	Not significant
Gan 2009[108]	29.8 (4.4)	27.9 (4.0)	p < 0.05
RADIAMI 2009[57]	58.3 (17.8)	55.1 (18.4)	p = 0.38
Hou 2010[139]	37.2 (7.1)	35.7 (8.1)	p = 0.17
RADIAMI II 2011[58]	53.7 (20.6)	47.5 (19.6)	Not significant
RIVAL 2011[148,149,194]	128 (89 to 221)*	120 (80 to 100)*	p = 0.0968
RIFLE-STEACS 2012[262]	214 (1435 to 375)¥	198 (135 to 393)	p = 0.290

** = door to PCI end (minutes), median (IQR), ¥ = door-to-balloon time (minutes) median (IQR).*

Table 33: Clinical evidence profile: radial access PPCI versus femoral access PPCI

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Radial	Femoral	Relative (95% CI)	Absolute	Quality	Importance
All-cause mortality ≤ 30 days [39,57,58,108,139,148,149,194,262,264]												
8	Randomised trials	Very serious (a)	No serious inconsistency	Very serious (b)	No serious imprecision	None	51/1878 (2.7%)	96/1947 (4.9%)	RR 0.54 (0.39 to 0.75)	23 fewer per 1000 (from 12 fewer to 30 fewer)	VERY LOW	CRITICAL
All-cause mortality longer-term [108,264]												
2	Randomised trials	Very serious (c)	No serious inconsistency	No serious indirectness	Very serious (d)	None	2/152 (1.3%)	4/154 (2.6%)	RR 0.59 (0.13 to 2.66)	11 fewer per 1000 (from 23 fewer to 43 more)	VERY LOW	CRITICAL
Reinfarction ≤ 30 days [57,58,108,139,148,149,194,262,264]												
7	Randomised trials	Very serious (e)	No serious inconsistency	Very serious (f)	Very serious (d)	None	18/1796 (1%)	27/1865 (1.4%)	RR 0.71 (0.4 to 1.26)	4 fewer per 1000 (from 9 fewer to 4 more)	VERY LOW	IMPORTANT
Reinfarction longer-term [108,264]												
2	Randomised trials	Very serious (c)	No serious inconsistency	No serious indirectness	Very serious (d)	None	3/152 (2%)	1/154 (0.65%)	RR 2.28 (0.35 to 15.06)	8 more per 1000 (from 4 fewer to 91 more)	VERY LOW	IMPORTANT
Major bleeding ≤ 30 days [39,57,58,108,139,148,149,194,262,264]												
8	Randomised trials	Very serious (a)	No serious inconsistency	Very serious (b)	Serious (g)	None	27/1878 (1.4%)	43/1947 (2.2%)	RR 0.67 (0.42 to 1.06)	7 fewer per 1000 (from 13 fewer to 1 more)	VERY LOW	IMPORTANT
Minor bleeding ≤ 30 days [39,57,58,108,139,148,149,175,194,262]												
8	Randomised	Very	No serious	Very serious	Serious (g)	None	71/1985	92/2061	RR 0.81	8 fewer per	VERY	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Radial	Femoral	Relative (95% CI)	Absolute	Quality	Importance
	trials	serious (a)	inconsistency	(b)			(3.6%)	(4.5%)	(0.6 to 1.09)	1000 (from 18 fewer to 4 more)	LOW	
Repeat revascularisation ≤ 30 days [57,58,139,262,264]												
5	Randomised trials	Very serious (h)	No serious inconsistency	Very serious (i)	Very serious (d)	None	8/776 (1%)	9/782 (1.2%)	RR 0.91 (0.37 to 2.28)	1 fewer per 1000 (from 7 fewer to 15 more)	VERY LOW	IMPORTANT
Repeat revascularisation longer-term [108,264]												
2	Randomised trials	Very serious (c)	No serious inconsistency	No serious indirectness	Very serious (d)	None	15/152 (9.9%)	17/154 (11%)	RR 0.82 (0.44 to 1.54)	20 fewer per 1000 (from 62 fewer to 60 more)	VERY LOW	IMPORTANT
CABG ≤ 30 days [57,58,108]												
3	Randomised trials	Very serious (j)	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/189 (0%)	0/214 (0%)	Not pooled	Not pooled	LOW	IMPORTANT
CABG longer-term [108]												
1	Randomised trials	Very serious (k)	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/79 (0%)	0/88 (0%)	Not pooled	Not pooled	LOW	IMPORTANT
Stroke ≤ 30 days [57,148,149,194,262]												
3	Randomised trials	Very serious (l)	No serious inconsistency	Serious (m)	Very serious (d)	None	9/1505 (0.6%)	8/1554 (0.51%)	RR 1.15 (0.46 to 2.88)	1 more per 1000 (from 3 fewer to 10 more)	VERY LOW	CRITICAL
Access site crossover [39,57,58,108,139,148,149,175,194,262,264]												
9	Randomised trials	Very serious	No serious inconsistency	No serious indirectness	No serious imprecision	None	120/2062 (5.8%)	35/2133 (1.6%)	RR 3.42 (2.38 to	40 more per 1000 (from 23	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Radial	Femoral	Relative (95% CI)	Absolute	Quality	Importance
		(n)							4.93)	more to 64 more)		
Procedural success [39,57,58,108,139,148,149,175,194,262,264]												
9	Randomised trials	Very serious (n)	No serious inconsistency	Very serious (o)	No serious imprecision	None	1800/1932 (93.2%)	1842/1971 (93.5%)	RR 1 (0.98 to 1.01)	0 fewer per 1000 (from 19 fewer to 9 more)	VERY LOW	IMPORTANT
Fluoroscopy time (better indicated by lower values) [39,57,58,139,264]												
5	Randomised trials	Very serious (y)	No serious inconsistency	No serious indirectness	No serious imprecision	None	333	338	-	MD 0.27 lower (0.73 lower to 0.19 higher)	VERY LOW	IMPORTANT
Total radiographic contrast media used in procedure (better indicated by lower values) [39,57,58,264]												
4	Randomised trials	Very serious (p)	No serious inconsistency	Very serious (q)	Very serious (r)	None	233	238	-	MD 1.17 higher (8.5 lower to 10.84 higher)	VERY LOW	IMPORTANT
Vascular access site complications [108,139,148,149,194]												
3	Randomised trials	Very serious (s)	No serious inconsistency	Very serious (t)	No serious imprecision	None	13/1155 (1.1%)	46/1203 (3.8%)	RR 0.3 (0.17 to 0.55)	27 fewer per 1000 (from 17 fewer to 32 fewer)	VERY LOW	IMPORTANT
Hospital stay (better indicated by lower values) [39,57,139,264]												
5	Randomised trials	Very serious (u)	No serious inconsistency	Very serious (v)	No serious imprecision	None	374	384	-	MD 0.63 lower (0.78 to 0.47 lower)	VERY LOW	IMPORTANT
Procedure length (better indicated by lower values) [39,57,58,108,139,175,264]												
7	Randomised trials	Very serious (w)	No serious inconsistency	Very serious (x)	No serious imprecision	None	607	628	-	MD 1.66 higher (0.73 to 2.59 higher)	VERY LOW	IMPORTANT

(a) 4 out of 8 studies unclear randomisation, 7 out of 8 studies unclear allocation concealment.

(b) 2 out of 8 studies unclear population, 3 out of 8 studies not or unclear if all PPCI.
(c) 2 out of 2 studies unclear randomisation, 2 out of 2 studies unclear allocation concealment.
(d) Confidence interval of effect size crosses 2 default MIDs (0.75, 1.25) and line of no effect.
(e) 3 out of 7 studies unclear randomisation, 6 out of 7 studies unclear allocation concealment.
(f) 1 out of 7 studies unclear if STEMI population, 3 out of 7 studies not or unclear if PPCI.
(g) Confidence interval of effect size crosses 1 default MID (0.75) and line of no effect.
(h) 2 out of 5 studies unclear randomisation, 5 out of 5 studies unclear allocation concealment.
(i) 1 out of 5 studies unclear if STEMI population, 4 out of 5 studies not or unclear PPCI.
(j) 1 out of 3 studies unclear randomisation, 3 out of 3 studies unclear allocation concealment.
(k) Unclear randomisation, unclear allocation concealment.
(l) 1 out of 3 studies unclear randomisation, 2 out of 3 studies unclear allocation concealment.
(m) 1 out of 3 studies not all PPCI.
(n) 5 out of 9 studies unclear randomisation, 8 out of 9 studies unclear allocation concealment.
(o) 3 out of 9 studies unclear if STEMI population, 3 out of 9 studies unclear or not PPCI.
(p) 2 out of 4 studies unclear randomisation, 4 out of 4 studies unclear allocation concealment.
(q) 2 out of 4 unclear if STEMI population, 1 out of 4 studies unclear if all PPCI.
(r) Confidence interval of effect size crosses 2 default MIDs for continuous outcome.
(s) 2 out of 3 studies unclear randomisation, 3 out of 3 studies unclear allocation concealment.
(t) 1 out of 3 unclear if STEMI population, 2 out of 3 studies not or unclear PPCI.
(u) 4 out of 5 studies unclear randomisation, 4 out of 5 studies unclear allocation concealment.
(v) 1 out of 5 unclear if STEMI population, 1 out of 5 studies unclear if PPCI.
(w) 5 out of 7 studies unclear randomisation, 7 out of 7 studies unclear allocation concealment.
(x) 2 out of 7 studies unclear if STEMI population, 1 out of 7 studies unclear if PPCI.
(y) 3 out of 5 studies unclear randomisation, 5 out of 5 studies unclear allocation concealment.

7.4 Economic evidence

No relevant economic evaluations were identified that compared radial access with femoral access for coronary angiography and PPCI in people with STEMI.

One economic evaluation relating to this review question was excluded due to a combination of limited applicability and methodological limitations.[264] This is summarised in Appendix K, with reasons for exclusion given. See also the economic article selection flow diagram in Appendix E.

A comparative cost analysis was undertaken for this question, which can be found in Appendix L.

7.5 Evidence statements

Clinical

All-cause mortality

- Very low quality evidence showed that radial access PPCI has a clinically effective association when compared to femoral access PPCI with reduced all-cause mortality rates at ≤ 30 days [8 studies, n = 3825].
- Very low quality evidence suggested that radial access PPCI potentially has a clinically effective association when compared to femoral access PPCI with reduced all-cause mortality in the longer term, but the direction of the estimate of effect could favour either intervention [2 studies, n = 306].

Reinfarction

- Very low quality evidence suggested that radial access PPCI potentially has a clinically effective association when compared to femoral access PPCI at reducing reinfarction rates at ≤ 30 days, but the direction of the estimate of the effect could favour either intervention [7 studies, n = 3661].
- Very low quality evidence suggested that femoral access PPCI potentially has a clinically effective association when compared to radial access PPCI with reduced reinfarction rates in the longer term, but the direction of the estimate of effect could favour either intervention [2 studies, n = 306].

Major bleeding

- Very low quality evidence suggested that radial access PPCI potentially has a clinically effective association when compared to femoral access PPCI with reduced major bleeding incidence at ≤ 30 days [8 studies, n = 3825].

Minor bleeding

- Very low quality evidence suggested that there may be no clinical difference between radial access PPCI and femoral access PPCI with the association with minor bleeding incidence at ≤ 30 days [8 studies, n = 4046].

Repeat revascularisation

- Very low quality evidence suggested that there may be no clinical difference between radial access PPCI and femoral access PPCI with an association with repeat revascularisation rates at ≤ 30 days, but the direction of the estimate of effect could favour either intervention [5 studies, n = 1558].
- Very low quality evidence suggested that there may be no clinical difference between radial access PPCI and femoral access PPCI with repeat revascularisation rates in the longer term, but the direction of the estimate of effect could favour either intervention [2 studies, n = 308].

CABG

- The difference is uncertain between radial access PPCI and femoral access PPCI at reducing CABG at ≤ 30 days as no comparative analysis could be carried out [3 studies, n = 403].
- The difference is uncertain between radial access PPCI and femoral access PPCI at reducing CABG in the longer term as no comparative analysis could be carried out [1 study, n = 168].

Stroke

- Very low quality evidence suggested that there may be no clinical difference between the association of radial access PPCI and femoral access PPCI with reduced stroke incidence at ≤ 30 days, but the direction of the estimate of effect could favour either intervention [3 studies, n = 3059].

Access site crossover

- Low quality evidence showed that femoral access PPCI is more clinically effective when compared radial access PPCI at reducing rate of access site crossover during PPCI [9 studies, n = 4195].

PPCI procedural success

- Very low quality evidence showed that there is no clinical difference between radial access PPCI and femoral access PPCI and PPCI procedural success [9 studies, n = 3903].

Fluoroscopy time of PPCI

- Low quality evidence showed that there is no clinical difference between radial access PPCI and femoral access PPCI at and PPCI fluoroscopy time [5 studies, n = 671].

Total radiographic contrast media used during PPCI procedure

- Very low quality suggested that there may be no clinical difference between radial access PPCI and femoral access PPCI at reducing total radiographic contrast media used, but the direction of the estimate of effect could favour either intervention [4 studies, n = 471].

Vascular access site complications

- Very low quality evidence showed that radial access PPCI is more clinically effective when compared to femoral access PPCI at reducing vascular access site complications at ≤ 30 days [4 studies, n = 2416].

Hospital stay

- Very low quality evidence showed that radial access PPCI is more clinically effective when compared femoral access PPCI at reducing hospital stay [4 studies, n = 644].

Procedure length

- Very low quality evidence showed that femoral access PPCI is more clinically effective when compared with radial access at reducing procedure length [7 studies, n = 1235].

Economic

- One original comparative cost analysis found that PPCI carried out by femoral access was more costly than PPCI carried out by radial access. There was insufficient evidence to reliably predict the size of the cost difference. This analysis was assessed as directly applicable with minor limitations.

7.6 Recommendations and link to evidence

Recommendations	The current recommendations can be found at: www.nice.org.uk/guidance/ng185
Relative values of different outcomes	For this review question the GDG considered the outcomes of all-cause mortality, stroke and intracranial bleeding as critical to decision-making. Myocardial reinfarction, unplanned revascularisation, major bleeding, procedural success and access site crossover were considered important, and minor bleeding, vascular access site complication and length of hospital stay as less important to decision-making. No data were found for intracranial bleeding, heart failure, renal failure, quality of life, inability to cross the lesion, radiation exposure or patient experience.
Trade-off between clinical benefits and harms	The randomised trials included in this review provide evidence that radial arterial access for PPCI is associated with lower short-term all-cause mortality and reduced bleeding when compared with femoral arterial access. In addition, radial arterial access is associated with fewer vascular access site complications and shorter hospital stay, but more access site crossover. There was no evidence of benefit of radial arterial access PPCI versus femoral arterial access for the outcome of stroke. The association between access and non-access site bleeding and mortality in people with acute coronary syndrome has been the subject of intense research over the last decade. Hypothetical mechanisms linking bleeding and mortality in acute coronary syndrome include the haemodynamic consequences of blood loss, complications related to blood transfusion, and the need to modify antithrombotic medication.[283] Nevertheless, a clear causal relationship between bleeding and mortality has not been confirmed and it is possible that major bleeding simply identifies people with an underlying mortality risk.[180,283,317] The RIVAL trial enrolled 7021 people with acute coronary syndrome and reported that radial and femoral arterial access routes were associated with similar rates of the primary outcome (a composite of death, myocardial infarction, stroke, or non-CABG-related major bleeding within 30 days). Major non-CABG-related bleeding rates were also similar between the 2 arterial access groups, but radial access was associated with a lower risk of vascular complications. The GDG noted that the definition of major non-CABG-related bleeding used in RIVAL was conservative (a large access site haematoma requiring transfusion of 1 unit of blood was classified as minor bleeding). In a post-hoc analysis, using a definition of non-CABG-related major bleeding from the ACUITY trial (that included large haematomas and pseudoaneurysms requiring intervention)[289] the bleeding rate was significantly lower with radial than with femoral arterial access.[149] In a pre-specified subgroup analysis of RIVAL involving 1958 people with STEMI, radial arterial access was associated with a 61% reduction in the hazard of 30 day all-cause mortality but no significant difference in major bleeding. Similar results were reported in 1451 people who were treated by PPCI (74% of people with STEMI) but the rate of major non-CABG related bleeding using the ACUITY definition was lower with radial access (1.86% versus 4.68%).[194] The absolute number of deaths and major bleeds were similar, both in the trial overall and in the STEMI subgroup, but the relationship between bleeding and mortality was not explored. Moreover, 70% of non-CABG-related major bleeds occurred at non-access sites and the GDG agreed that the reduction in mortality associated with radial arterial access in the STEMI subgroup in RIVAL could not easily be explained by a reduction in bleeding.[149] The mortality advantage associated with radial arterial access in the STEMI subgroup remained highly significant after adjustment for baseline variables, centre radial volume, and operator radial experience (interaction p = 0.0001).[194]

	The RIFLE-STEACS trial randomised 1001 people with STEMI (92% PPCI) to radial versus femoral arterial access at 4 high volume radial centres. Radial arterial access was associated with a 4% absolute reduction in 30 day mortality and a 4.2% absolute reduction in access site bleeding, but no difference in non-access site bleeding (which accounted for 53% of all bleeding events). In RIFLE-STEACS most cardiac deaths occurred within 48 hours of STEMI, and it was difficult to ascertain the role of bleeding in these deaths.[262] In the RIVAL trial 25.6% of people assigned to femoral access received a femoral vascular closure device (VCD) but information about use of these devices in the STEMI subgroup is not available. The use of VCDs for femoral artery access was not reported in RIFLE-STEACS, and some members of the GDG were concerned that the high rate of femoral access site bleeding reported in this trial (6.8%) is inconsistent with current UK experience. The use of VCDs was also not reported in several of the other trials in this review. Evidence confirming that VCDs are beneficial is inconsistent and most studies of these devices excluded people at high risk of access site complications, including people undergoing PPCI. To date no appropriately sized randomised trial has been undertaken, but 5 large (> 10,000 patient) registries suggest that VCDs lower rates of vascular complications relative to manual compression.[64] Hence, the GDG considered that greater use of VCDs in the trials in this review might have resulted in lower rates of femoral arterial access site bleeding. The GDG concluded that evidence in favour of radial arterial access for PPCI is insufficient to recommend radial access for all PPCI procedures. The GDG agreed that operators should consider the potential advantages of radial access when selecting the arterial access route for PPCI, taking account of individual patient characteristics and preferences, as well as operator and institutional experience.
Economic considerations	No health economic evidence was found for this question. A comparative costing analysis was therefore undertaken. This identified that although radial access led on average to fewer complications, more crossovers and slightly shorter procedures, all these effects were too small to make an appreciable difference to the cost of the 2 procedures. The analysis showed that the equipment costs for a standard femoral procedure are slightly higher than those for radial procedures, due to the use of a femoral vascular closure device or an external compression device in a proportion of femoral patients (£50–£130), which are both somewhat more expensive than a radial artery compression device used in radial patients (£10–£14). The final potential difference in costs was due to a reduction in length of stay for radial patients. It was impossible to identify comparable current data on lengths of hospital stay for the UK. While the evidence all indicates that radial procedures are associated with shorter lengths of stay, the absolute reduction was uncertain and may be small. The GDG agreed that the difference of 1.3 days seen in the BCIS 2011 audit of interventional procedures[183] was likely to be the maximum possible reduction in length of stay for radial patients, which would correspond to a saving of £425. Hence, the costing analysis suggested that it was very likely that radial access PPCI procedures are cheaper than femoral procedures, but this difference could range from £50 to £450. In cost-effectiveness analysis, radial access would dominate (be less costly and more effective than) femoral access with regard to short-term all-cause mortality, major bleeding and minor bleeding because the evidence of the clinical review indicates

	that radial access is of superior efficacy. This finding however depends on the generalisability of the clinical results, as discussed below.
Quality of evidence	The GDG noted that the trials in this review only recruited people in whom both radial and femoral arterial access were considered feasible. The trials generally excluded people at high risk of bleeding (for example, bleeding diathesis), where difficulty with radial access was anticipated (for example, height less than 150 cm, vascular tortuosity, age > 75 years), or if femoral access was preferred (for example, haemodynamic instability, previous CABG, or requirement for IABP or temporary pacing). There was also variation between studies in terms of definitions of the intervention, the adjunctive treatment, and the outcome measurement. In the large RIVAL trial the effect of arterial access route on the primary outcome was neutral and results in the subgroup of people with STEMI (28%) may be less reliable than in the whole trial. The smaller studies in the review lack statistical power for clinically important outcomes and information about quality in these trials is limited. Notably, definitions of major and minor bleeding varied across trials. The open designs and lack of blinded adjudication of end points also increase the likelihood of inadvertent bias. Moreover, the trials were generally initiated by proponents of the radial technique and the PPCI procedures were carried out by experienced radial operators. The GDG concluded that the results of the trials are not transferable to all PPCI services, and cannot be generalised to all people with STEMI who are candidates for PPCI.
Other considerations	The recently reported STEMI-RADIAL trial randomised 707 PPCI patients to radial versus femoral arterial access at 4 high volume radial centres (> 80% PPCI done radially) in the Czech Republic. The trial reported that radial access was associated with an 80% relative reduction in the risk of arterial access and bleeding complications, but no significant difference in the rates of death, MI or stroke at 30 days.[27] The GDG were concerned that a recommendation favouring unrestricted use of radial arterial access for people with STEMI might increase the time taken to gain arterial access in some cases. This could delay the time to reperfusion and limit the overall benefit of PPCI.

8 Thrombus extraction during primary percutaneous coronary intervention

8.1 Introduction

Acute STEMI is usually caused by complete thrombotic occlusion of a major coronary artery. The mechanism of the occlusion is rupture or erosion of a pre-existing atheromatous plaque, which exposes the plaque contents to the circulating blood and activates platelets and the coagulation cascade, and leads to formation of the occlusive thrombus. The newly-formed thrombus is soft, friable and only loosely adherent to the vessel wall. In attempting to re-open the occluded artery during PPCI, guidewires, balloon catheters and stents may all be passed down the artery. These devices may dislodge the thrombus, which can travel along the artery and cause a new obstruction downstream. If this distal obstruction remains, it may negate much of the benefit of re-opening the vessel more proximally.[129]

Because of the damage done by distal embolisation of a pre-formed thrombus, there has been interest in trying to remove the thrombus mechanically. The simplest devices used to remove a thrombus are hollow aspiration catheters; the end of the catheter is positioned close to the thrombus and suction is then applied at the other end of the catheter using a syringe. Aspiration catheters of this type are now used in a high proportion of PPCI procedures in the UK. In addition to these simple aspiration catheters, there are several powered mechanical devices which can be used to fragment and aspirate the thrombus if the thrombus burden appears large.

This chapter reviews the clinical and cost effectiveness of thrombus aspiration and mechanical thrombus extraction in people with acute STEMI who are treated by PPCI.

8.2 Review question: What is the clinical and cost effectiveness of using thrombus extraction devices (catheter aspiration devices, mechanical thrombectomy devices) during PPCI compared with PPCI alone for the treatment of STEMI in adults?

For full details see review protocol in Appendix C.

8.3 Clinical evidence

Nineteen studies reported in 21 papers were included in the review.[3,6,23,45,47,56,76,87,88,141,152,173,176,177,197,207,265,278,288,294,319] Evidence from these studies are summarised in the clinical GRADE evidence profiles. See also the study selection flow chart in Appendix E, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J. Six studies compared mechanical thrombus extraction PPCI versus standard PPCI.[3,6,23,173,197,207] Thirteen studies compared thrombus aspiration PPCI versus standard PPCI.[45,47,56,76,87,141,152,176,178,265,278,288,294,319] Evidence from these are summarised in Table 34.

Table 34: Summary of included studies

Study	Intervention / comparison	Device	Population	Outcomes
AIMI 2006[3]	Mechanical thrombus extraction vs no extraction	AngioJet rheolytic; 5F LF140 RT catheter	n = 480	30 day all-cause mortality, stroke
Antoniucci 2004[6]	Mechanical thrombus extraction vs no extraction	AngioJet rheolytic; 4F catheter	n = 100	1-month all-cause mortality, reinfarction, stroke, target vessel revascularisation, minor and major bleeding
Beran 2002[23]	Mechanical thrombus extraction vs no extraction	X-sizer catheter system; 7F catheter	n = 61	30-day all-cause mortality, target vessel revascularisation
Bulum 2012[45]	Thrombus aspiration vs no extraction	Export aspiration catheter; 6F catheter	n = 60	6-month all-cause mortality, reinfarction, stroke, target lesion revascularisation
DEAR-MI 2006[278]	Thrombus aspiration vs no extraction	Pronto extraction catheter; 6F catheter	n = 148	30-day all-cause mortality, target vessel revascularisation
De Luca 2006[76]	Thrombus aspiration vs no extraction	Diver CE aspiration; 7F catheter	n = 76	6-month all-cause mortality, reinfarction, heart failure
EXPIRA 2010[265]	Thrombus aspiration vs no extraction	Export aspiration catheter	n = 175	2-year all-cause mortality, reinfarction, target vessel revascularisation
EXPORT 2008[56]	Thrombus aspiration vs no extraction	Export aspiration catheter; 6F thrombus aspiration	n = 249	30-day reinfarction
INFUSE-AMI 2012[288]	Thrombus aspiration vs no extraction	Export aspiration catheter; 4F catheter	n = 452	30-day all-cause mortality, reinfarction, stroke, heart failure
ITTI 2012[177]	Thrombus aspiration vs no extraction	7F Thrombuster II aspiration catheter	n = 47	6-month all-cause mortality, reinfarction, stroke
JETSTENT 2010[197]	Mechanical thrombus extraction vs no extraction	AngioJet rheolytic thrombectomy system; 4F catheter	n = 501	1- and 6-month all-cause mortality, major bleeding, reinfarction, target vessel revascularisation
Kaltoft 2006[152]	Thrombus aspiration vs no extraction	Rescue catheter; 7F catheter	n = 215	30-day all-cause mortality, reinfarction
Liistro 2009[176]	Thrombus aspiration vs no extraction	Export aspiration catheter; 6F catheter	n = 111	6-month reinfarction, target vessel revascularisation, heart failure
Napodano 2003[207]	Mechanical thrombus extraction vs	X-Sizer catheter system	n = 92	30-day all-cause mortality, reinfarction, stroke, heart failure, minor and major

Study	Intervention / comparison	Device	Population	Outcomes
	no extraction			bleeding
PIHRATE 2010[87,88]	Thrombus aspiration vs no extraction	Diver CE aspiration; 6F catheter	n = 196	In-hospital all-cause mortality, reinfarction, target vessel revascularisation 6-month all-cause mortality, reinfarction
REMEDIA 2005[47]	Thrombus aspiration vs no extraction	Diver CE aspiration; 6F catheter	n = 99	30-day all-cause mortality, reinfarction, stroke, target vessel revascularisation
TAPAS 2008[294,319]	Thrombus aspiration vs no extraction	Export aspiration catheter; 4F catheter	n = 1071	30-day all-cause mortality, reinfarction, major bleeding, target vessel revascularisation and 1-year all-cause mortality, reinfarction, target vessel revascularisation
VAMPIRE 2008[141]	Thrombus aspiration vs no extraction	TransVascular aspiration catheter (TVAC); 7F catheter	n = 355	In-hospital and 8-month all-cause mortality, reinfarction, target vessel revascularisation
X AMINE ST 2005[173]	Mechanical thrombus extraction vs no extraction	X-Sizer catheter system	n = 201	1- and 6-month all-cause mortality, reinfarction, stroke, target vessel revascularisation

Table 35: Clinical evidence profile: thrombus aspiration PPCI versus standard PPCI and mechanical thrombus extraction PPCI versus standard PPCI

Quality assessment							Summary of findings					
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	PPCI with thrombus extraction	PPCI alone	Relative (95% CI)	Absolute	Quality	Importance
Mortality ≤ 30 days[3,6,23,47,87,88,141,152,173,197,207,278,288,294]												
13	Randomised trial	Very serious (a)	No serious inconsistency	No serious indirectness	Very serious (d)	None	49/1991 (2.5%)	52/1964 (2.2%)	RR 0.93 (0.64 to 1.37)	2 more per 1000 (from 10 fewer to 10 more)	VERY LOW	CRITICAL
Mortality ≤ 30 days – Thrombus aspiration[47,87,88,152,278,288 141,294]												
7	Randomised trial	Very serious (c)	No serious inconsistency	No serious indirectness	Serious (s)	None	25/1266 (2%)	35/1250 (2.7 %)	RR 071 (0.43 to 1.17)	8 fewer per 1000 (from 10 fewer to 11 more)	VERY LOW	CRITICAL
Mortality ≤ 30 days – Mechanical thrombus extraction[3,6,23,173,197,207]												
6	Randomised trial	Very serious (e)	No serious inconsistency	No serious indirectness	Serious (b)	None	24/725 (3.3%)	17/714 (2.4%)	RR 1.39 (0.76 to 2.57)	9 more per 1000 (from 6 fewer to 37 more)	VERY LOW	CRITICAL
Mortality longer-term[45,76,87,88,141,173,177,197,265,319]												
9	Randomised trial	Very serious (f)	No serious inconsistency	No serious indirectness	No serious imprecision	None	45/1338 (3.4%)	68/1313 (5.2%)	RR 0.66 (0.46 to 0.95)	18 fewer per 1000 (from 3 fewer to 28 fewer)	LOW	CRITICAL
Mortality longer-term – Thrombus aspiration[45,76,87,88,141,177,265,319]												
7	Randomised trial	Very serious (g)	No serious inconsistency	No serious indirectness	No serious imprecision	None	32/982 (3.3%)	53/968 (5.5%)	RR 0.61 (0.4 to 0.93)	21 fewer per 1000 (from 4 fewer to 33 fewer)	LOW	CRITICAL
Mortality longer-term – Mechanical thrombus extraction[173,197]												
2	Randomised	Very serious	No serious	No serious	Serious	None	13/356 (3.7%)	15/345	RR 0.84	7 fewer per	VERY	CRITICAL

Quality assessment							Summary of findings					
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	PPCI with thrombus extraction	PPCI alone	Relative (95% CI)	Absolute	Quality	Importance
	trial	(h)	inconsistency	indirectness	(s)			(4.3%)	(0.41 to 1.74)	1000 (from 26 fewer to 32 more)	LOW	
Reinfarction ≤ 30 days[6 47,56,87,88,141,152,173,197,207,288,294]												
11	Randomised trial	Very serious (i)	No serious inconsistency	No serious indirectness	Serious (s)	None	14/1764 (0.8%)	26/1746 (1%)	RR 0.56(0.3 to 1.04)	7 fewer per 1000 (from 10 fewer to 1 more)	VERY LOW	IMPORTANT
Reinfarction ≤ 30 days – Thrombus aspiration[47,56,87,88,152,288 141,294],												
7	Randomised trial	Very serious (j)	No serious inconsistency	No serious indirectness	Very serious (d))	None	9/1321 (0.7%)	18/1305 (0.9%)	RR 0.54 (0.26 to 1.31)	6 fewer per 1000 (from 10 fewer to 2 more)	VERY LOW	IMPORTANT
Reinfarction ≤ 30 days – Mechanical thrombus extraction[6,173,197,207]												
4	Randomised trial	Very serious (k)	No serious inconsistency	No serious indirectness	Very serious (d)	None	5/452 (1.1%)	8/441 (1.8%)	RR 0.61 (0.2 to 1.86)	7 fewer per 1000 (from 15 fewer to 16 more)	VERY LOW	IMPORTANT
Reinfarction longer-term[45,76,87,88,141,173,176,177,197,265,319]												
10	Randomised trial	Very serious (l)	No serious inconsistency	No serious indirectness	No serious imprecision	None	22/1401 (1.6%)	41/1362 (3%)	RR 0.55 (0.34 to 0.9)	13 fewer per 1000 (from 3 fewer to 20 fewer)	LOW	IMPORTANT
Reinfarction longer-term – Thrombus aspiration[45,76,87,88,141,176,177,265,319]												
8	Randomised trial	Very serious (m)	No serious inconsistency	No serious indirectness	No serious imprecision	None	18/1015 (1.7%)	34/1037 (3.4%)	RR 0.55 (0.32 to 0.94)	15 fewer per 1000 (from 2 fewer to 22 fewer)	LOW	IMPORTANT
Reinfarction longer-term – Mechanical thrombus extraction[173,197]												
2	Randomised	Very serious	No serious	No serious	Very serious	None	4/356 (1.1%)	7/345	RR 0.56	9 fewer per	VERY	IMPORTANT

Quality assessment							Summary of findings					
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	PPCI with thrombus extraction	PPCI alone	Relative (95% CI)	Absolute	Quality	Importance
	trial	(h)	inconsistency	indirectness	(d)			(2%)	(0.17 to 1.89)	1000 (from 18 fewer to 18 more)	LOW	
Stroke ≤ 30 days[3,6,47,173,197,207,288]												
7	Randomised trial	Very serious (n)	No serious inconsistency	No serious indirectness	Very serious (d)	None	8/969 (0.83%)	5/952 (0.53%)	RR 1.42 (0.54 to 3.69)	2 more per 1000 (from 2 fewer to 14 more)	VERY LOW	IMPORTANT
Stroke ≤ 30 days – Thrombus aspiration[47,288]												
2	Randomised trial	No serious limitation	No serious inconsistency	No serious indirectness	Very serious (d)	None	1/277 (0.36%)	2/271 (0.74%)	RR 0.59 (0.08 to 4.42)	3 fewer per 1000 (from 7 fewer to 25 more)	LOW	IMPORTANT
Stroke ≤ 30 days – Mechanical thrombus extraction[3,6,173,197,207]												
5	Randomised trial	Very serious (o)	No serious inconsistency	No serious indirectness	Very serious (d)	None	7/692 (1%)	3/681 (0.44%)	RR 1.87 (0.6 to 5.82)	4 more per 1000 (from 2 fewer to 21 more)	VERY LOW	IMPORTANT
Stroke longer-term[45,173,177,197]												
4	Randomised trial	Very serious (p)	No serious inconsistency	No serious indirectness	Very serious (d)	None	4/410 (0.98%)	1/398 (0.25%)	RR 2.43 (0.48 to 12.35)	4 more per 1000 (from 1 fewer to 29 more)	VERY LOW	IMPORTANT
Stroke longer-term – Thrombus aspiration[45,177]												
2	Randomised trial	Very serious (q)	No serious inconsistency	No serious indirectness	Very serious (d)	None	1/54 (1.9%)	0/53 (0%)	RR 2.88 (0.12 to 67.29)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW	IMPORTANT
Stroke longer-term – Mechanical thrombus extraction[173,197]												
2	Randomised trial	Very serious (h)	No serious inconsistency	No serious indirectness	Very serious (d)	None	3/356 (0.84%)	1/345 (0.29%)	RR 2.29 (0.34 to 15.26)	4 more per 1000 (from 2 fewer to	VERY LOW	IMPORTANT

Quality assessment							Summary of findings					
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	PPCI with thrombus extraction	PPCI alone	Relative (95% CI)	Absolute	Quality	Importance
										41 more)		
Heart failure ≤ 30 days[87,88,207,288]												
3	Randomised trial	Very serious (r)	No serious inconsistency	No serious indirectness	Serious (s)	None	19/375 (5.1%)	31/365 (8.5%)	RR 0.6 (0.35 to 1.03)	34 fewer per 1000 (from 55 fewer to 3 more)	VERY LOW	IMPORTANT
Heart failure ≤ 30 days – Thrombus aspiration[87,88,288]												
2	Randomised trial	Very serious (t)	No serious inconsistency	No serious indirectness	Serious (s)	None	14/329 (4.3%)	21/319 (6.6%)	RR 0.65 (0.33 to 1.24)	23 fewer per 1000 (from 44 fewer to 16 more)	VERY LOW	IMPORTANT
Heart failure ≤ 30 days – Mechanical thrombus extraction[207]												
1	Randomised trial	Very serious (u)	No serious inconsistency	No serious indirectness	Very serious (d)	None	5/46 (10.9%)	10/46 (21.7%)	RR 0.5 (0.19 to 1.35)	109 fewer per 1000 (from 176 fewer to 76 more)	VERY LOW	IMPORTANT
Heart failure longer-term[76,176]												
2	Randomised trial	Very serious (t)	No serious inconsistency	No serious indirectness	Very serious (d)	None	2/90 (2.2%)	6/94 (6.4%)	RR 0.41 (0.1 to 1.68)	38 fewer per 1000 (from 57 fewer to 43 more)	VERY LOW	IMPORTANT
Heart failure longer-term – Thrombus aspiration[76,176]												
2	Randomised trial	Very serious (t)	No serious inconsistency	No serious indirectness	Very serious (d)	None	2/90 (2.2%)	6/94 (6.4%)	RR 0.41 (0.1 to 1.68)	38 fewer per 1000 (from 57 fewer to 43 more)	VERY LOW	IMPORTANT
Heart failure longer-term – Mechanical thrombus extraction												

Quality assessment							Summary of findings					
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	PPCI with thrombus extraction	PPCI alone	Relative (95% CI)	Absolute	Quality	Importance
0	No evidence available					None	0/0 (0%)	0/0 (0%)	Not pooled	Not pooled		IMPORTANT
Unplanned target vessel revascularisation ≤ 30 days[6,23,47,87,88,197,207,278 141,173,294]												
10	Randomised trial	Very serious (v)	No serious inconsistency	No serious indirectness	Serious (s)	None	8/885 (0.9%)	32/1414 (2.3%)	RR 0.79 (0.51 to 1.22)	6 fewer per 1000 (from 14 fewer to 6 more)	VERY LOW	IMPORTANT
Unplanned target vessel revascularisation ≤ 30 days – Thrombus aspiration[47,87,88,278 141,294]												
5	Randomised trial	Very serious (w)	No serious inconsistency	No serious indirectness	Very serious (d)	None	28/929 (3%)	34/920 (3.77%)	RR 0.83 (0.51 to 1.34)	6 more per 1000 (from 12 fewer to 12 more)	VERY LOW	IMPORTANT
Unplanned target vessel revascularisation ≤ 30 days – Mechanical thrombus extraction[6,23,173,197,207]												
5	Randomised trial	Very serious (x)	No serious inconsistency	No serious indirectness	Very serious (d)	None	4/485 (0.82%)	7/474 (1.5%)	RR 0.61 (0.2 to 1.84)	6 fewer per 1000 (from 12 fewer to 12 more)	VERY LOW	IMPORTANT
Unplanned target vessel revascularisation longer-term[45,141,173,176,197,265,319]												
7	Randomised trial	Very serious (y)	No serious inconsistency	No serious indirectness	No serious imprecision	None	114/1242 (9.2%)	154/1226 (12.6%)	RR 0.73 (0.58 to 0.92)	34 fewer per 1000 (from 10 fewer to 53 fewer)	LOW	IMPORTANT
Unplanned target vessel revascularisation longer-term – Thrombus aspiration[45,141,176,265,319]												
5	Randomised trial	Very serious (o)	No serious inconsistency	No serious indirectness	Serious (s)	None	93/886 (10.5%)	117/881 (13.3%)	RR 0.79 (0.61 to 1.02)	28 fewer per 1000 (from 52 fewer to 3 more)	VERY LOW	IMPORTANT
Unplanned target vessel revascularisation longer-term – Mechanical thrombus extraction[173,197]												
2	Randomised trial	Very serious (p)	No serious inconsistency	No serious indirectness	No serious imprecision	None	21/356 (5.9%)	37/345 (10.7%)	RR 0.55 (0.33 to	48 fewer per 1000	LOW	IMPORTANT

Quality assessment							Summary of findings					
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	PPCI with thrombus extraction	PPCI alone	Relative (95% CI)	Absolute	Quality	Importance
									0.91)	(from 10 fewer to 72 fewer)		
Major bleeding[6,197 173,294]												
4	Randomised trial	Very serious (z)	No serious inconsistency	No serious indirectness	Serious (b)	None	31/881 (3.5%)	24/872 (2.8%)	RR 1.28 (0.76 to 2.15)	8 more per 1000 (from7 fewer to 32 more)	VERY LOW	IMPORTANT
Major bleeding - Thrombus aspiration[294]												
1	No evidence available	Serious ¥	No serious inconsistency	No serious indirectness	Very serious (d)	None	20/529(3.8%)	18/531(3.4%)	RR 1.21 (0.6 to 2.08)	4 more per 1000 (from 14 fewer to 37 more	VERY LOW	IMPORTANT
Major bleeding - Mechanical thrombus extraction												
3	Randomised trial	Very serious (€)	No serious inconsistency	No serious indirectness	Very serious (d)	None	11/352 (3.1%)	6/341 (1.8%)	RR 1.71 (0.66 to 4.44)	12 more per 1000 (from 6 fewer to 61 more)	VERY LOW	IMPORTANT

a) 7 out of 13 studies no detail of randomisation, 4 out of 13 studies if outcome assessors blinded.
b) CI of estimate of effect size crosses line of no effect and 1 default MID (1.25).
c) 3 out of 7 studies no detail of randomisation, 2 out of 6 studies unclear if outcome assessors blinded.
d) CI of estimate of effect size crosses line of no effect and 2 default MIDs (0.75 and 1.25).
e) 4 out of 6 studies no detail of randomisation, 1 out of 6 studies unclear if outcome assessors blinded.
f) 8 out of 9 studies no detail of randomisation, 4 out of 9 studies unclear if outcome assessors blinded.
g) 6 out of 7 studies no detail of randomisation, 4 out of 7 studies unclear if outcome assessors blinded.
h) 1 out of 2 studies no detail of randomisation and unclear if outcome assessors blinded in studies.
i) 5 out of 11 studies no detail of randomisation, 4 out of 11 studies unclear if outcome assessors blinded.
j) 4 out of 7 studies no detail of randomisation, 2 out of 7 studies unclear if outcome assessors blinded.
k) 2 out of 4 studies no detail of randomisation, 2 out of 4 studies unclear if outcome assessors blinded.
l) 8 out of 10 studies no detail of randomisation, 4 out of 10 studies unclear if outcome assessors blinded.
m) 6 out of 8 studies no detail of randomisation, 4 out of 8 studies unclear if outcome assessors blinded.
n) 3 out of 7 studies no detail of randomisation, 3 out of 7 studies unclear if outcome assessors blinded.
o) 3 out of 5 studies no detail of randomisation, 1 out of 5 studies unclear if outcome assessors blinded.
p) 3 out of 4 studies no detail of randomisation, 2 out of 4 studies unclear if outcome assessors blinded.

q) 2 out of 2 studies no detail of randomisation, 1 out of 2 studies unclear if outcome assessors blinded.
r) 3 out of 3 studies no detail of randomisation, 1 out of 3 studies unclear if outcome assessors blinded.
s) CI of the estimate of the effect size crosses and line of no effect and 1 default MID (0.75).
t) 1 out of 2 studies no detail of randomisation, 1 out of 2 studies unclear if outcome assessors blinded.
u) 1 out of 1 study no detail of randomisation.
v) 7 out of 10 studies no detail of randomisation, 4 out of 10 studies unclear if outcome assessors blinded.
w) 3 out of 5 studies no detail of randomisation, 2 out of 5 studies unclear if outcome assessors blinded.
x) 4 out of 5 studies no detail of randomisation, 4 out of 5 studies unclear if outcome assessors blinded.
y) 5 out of 7 studies no detail of randomisation, 3 out of 7 studies unclear if outcome assessors blinded.
z) 1 out of 4 studies no detail of randomisation, 3 out of 4 studies unclear if outcome assessors blinded.
¥) Unclear if outcome assessors blinded.
€) 1 out of 3 studies no detail of randomisation, 2 out of 3 studies unclear if outcome assessors blinded.

8.4 Economic evidence

No relevant economic evaluations were identified that compared PPCI with and without the use of thrombus extraction devices in people with STEMI.

Two economic evaluations relating to this review question were selectively excluded due to a combination of limited applicability and methodological limitations.[8,297] These are summarised in Appendix K, with reasons for exclusion given. See also the economic article selection flow diagram in Appendix E.

A comparative cost analysis was undertaken for this question, which can be found in Appendix M.

8.5 Evidence statements

Clinical

All-cause mortality

Very low quality evidence suggested that there:

- may be no clinical difference between thrombus aspiration PPCI and standard PPCI at reducing all-cause mortality at ≤ 30 days, but the direction of the estimate of effect could favour either intervention [7 studies, n = 2516].
- may be no clinical difference between mechanical thrombus extraction PPCI and standard PPCI at reducing all-cause mortality at ≤ 30 days [6 studies, n = 1439].
- may be no clinical difference between mechanical thrombus extraction PPCI and standard PPCI at reducing all-cause mortality 6 months, but the direction of the estimate of effect favoured mechanical thrombus extraction [2 studies, n = 701].
- Low quality evidence showed that thrombus aspiration PPCI is more effective when compared to standard PPCI at reducing all-cause mortality at up to 2 years, but the effect size is too small to be clinically important [7 studies, n = 1950].

Reinfarction

- Very low quality evidence suggested that thrombus aspiration PPCI is potentially more effective when compared to standard PPCI at reducing reinfarction at ≤ 30 days, but the direction of the estimate of effect could favour either intervention [7 studies, n = 2626].
- Very low quality evidence suggested that mechanical thrombus extraction PPCI is potentially more clinically effective when compared to standard PPCI at reducing reinfarction at ≤ 30 days, but the direction of the estimate of effect could favour either intervention [4 studies, n = 893].
- Low quality evidence showed that thrombus aspiration PPCI is more effective when compared to standard PPCI at reducing reinfarction at up to 2 years, but the effect size is too small to be clinically important [8 studies, n = 2082].
- Very low quality evidence suggested that mechanical thrombus extraction PPCI is potentially more clinically effective when compared to standard PPCI at reducing reinfarction at 6 months, but the direction of the estimate of effect could favour either intervention [2 studies, n = 701].

Stroke

Very low quality evidence suggested that:

- thrombus aspiration PPCI is potentially more clinically effective when compared to standard PPCI at reducing stroke at ≤ 30 days, but the direction of the estimate of effect could favour either intervention [2 studies, n = 548].

- standard PPCI is potentially more clinically effective when compared to mechanical thrombus extraction PPCI at reducing stroke at ≤ 30 days, but the direction of the estimate of effect could favour either intervention [5 studies, n = 1373].
- standard PPCI is potentially more clinically effective when compared to thrombus aspiration PPCI and mechanical thrombus extraction PPCI at reducing stroke at 6 months, but the direction of the estimate of effect could favour either intervention [2 studies, n = 107 and 2 studies, n = 701].

Heart failure

Very low quality evidence suggested that:

- thrombus aspiration PPCI is potentially more clinically effective when compared to standard PPCI at reducing heart failure at ≤ 30 days [3 studies, n = 648].
- mechanical thrombus extraction PPCI is potentially more clinically effective when compared to standard PPCI at reducing heart failure at ≤ 30 days, but the direction of the estimate of effect could favour either intervention [1 study, n = 92].
- thrombus aspiration PPCI is potentially more clinically effective when compared to standard PPCI at reducing heart failure at 6 months, but the direction of the estimate of effect could favour either intervention [2 studies, n = 184].

Unplanned target vessel revascularisation

Very low quality evidence suggested that:

- there may be no clinical difference between thrombus aspiration PPCI and standard PPCI at reducing unplanned target vessel revascularisation ≤ 30 days, but the direction of the estimate of effect could favour either intervention [5 studies, n = 1849].
- mechanical thrombus extraction PPCI is potentially more clinically effective when compared to standard PPCI at reducing unplanned target vessel revascularisation at ≤ 30 days, but the direction of the estimate of effect could favour either intervention [5 studies, n = 959].
- there may be no clinical difference between thrombus aspiration PPCI when compared to standard PPCI at reducing unplanned target vessel revascularisation at up to 2 years, but the direction of the estimate of effect favoured thrombus aspiration [5 studies, n = 1767].
- Low quality evidence showed that mechanical thrombus extraction PPCI is more effective when compared to standard PPCI at reducing unplanned target vessel revascularisation at 6 months, but the effect size is too small to be clinically important [2 studies, n = 701].

Major bleeding

- Very low quality evidence suggested thrombus aspiration PPCI is potentially more clinically effective when compared to standard PPCI at reducing major bleeding at ≤ 30 days, but the direction of the estimate of effect could favour either intervention [1 study, n = 1060].
- Very low quality evidence suggested that there may be no clinical difference between mechanical thrombus extraction PPCI and no thrombus aspiration PPCI at reducing major bleeding at ≤ 30 days, but the direction of the estimate of effect could favour either intervention [3 studies, n = 693].

Economic

- One original comparative cost analysis found that PPCI carried out using a thrombus extraction device was more costly than PPCI carried out without a thrombus extraction device (cost difference: £110–£125 for PPCI using a thrombus aspiration device, £1200 for PPCI using a mechanical thrombus extraction device). This analysis was assessed as directly applicable with minor limitations.

8.6 Recommendations and link to evidence

Recommendations	**The current recommendations can be found at: www.nice.org.uk/guidance/ng185**
Relative values of different outcomes	For this review question the GDG considered the outcome of mortality (all-cause and cardiovascular) as critical to decision-making. Stroke, myocardial reinfarction, heart failure, quality of life, and major bleeding were considered important, and unplanned urgent target vessel revascularisation, minor bleeding, and length of hospital stay as less important to decision-making. No data were found for quality of life, minor bleeding or length of hospital stay.
Trade-off between clinical benefits and harms	This review provides evidence that thrombus aspiration during PPCI for acute STEMI is associated with lower rates of longer-term mortality and reinfarction, relative to PPCI without thrombus aspiration. There was no evidence that thrombus aspiration affected short-term outcomes or longer-term risk of stroke, heart failure or target vessel revascularisation. There was no evidence of harm associated with the use of thrombus aspiration devices. There was no evidence that mechanical thrombus extraction versus standard PPCI influenced short-term or longer-term outcomes, apart from a reduction in the longer-term rate of unplanned revascularisation, which was based on very low quality evidence. The GDG did not consider this potential advantage of mechanical thrombus extraction to be clinically important. The GDG noted that longer-term all-cause mortality was reduced by the use of thrombus aspiration devices while 30-day all-cause mortality was not significantly affected. The GDG noted that the reduction in longer-term mortality associated with use of thrombus aspiration was driven mainly by the TAPAS trial. TAPAS reported a 2.2% absolute and 39% relative reduction in mortality.[319] The GDG considered that the mechanism of benefit in TAPAS is unclear, and although the use of thrombus aspiration devices might reduce mortality by reducing infarct size and the late development of heart failure, enzyme release (a surrogate for infarct size) was not reduced by thrombus aspiration.[319] TAPAS was a single centre trial and had relatively short ischaemia and door-to-balloon times, which might reduce the relevance of the trial to the wider population of people undergoing PPCI. The median ischaemia times in the thrombus aspiration and conventional PPCI groups were 190 and 185 minutes, respectively. Hence the majority of people in this trial may have been treated before the development of extensive intra-coronary thrombus, and this may have resulted in better outcomes. The GDG's recommendation that PPCI operators should consider using thrombus aspiration devices was made on the basis that there was some evidence of benefit, and no evidence of harm. A stronger recommendation, stating that thrombus aspiration devices should be used routinely in people with STEMI, was discussed but it was felt that the evidence from the available trials was insufficient for such a firm recommendation. The GDG agreed that mechanical extraction devices should not be used routinely as there is no evidence that these devices confer clinically important benefit or are likely to be cost effective.
Economic considerations	No health economic evidence was found for this question. A comparative costing analysis was therefore undertaken to investigate the costs of using thrombus

	extraction devices in PPCI, based on the resources used (thrombus aspiration or mechanical extraction devices, stents and balloon catheters) and the duration of the procedure. No other equipment was considered to be likely to give rise to a difference in costs. This analysis concluded that there was unlikely to be any cost difference due to stent usage or, for thrombus aspiration devices, due to procedure duration. For mechanical extraction devices there was an increase in procedure duration of 14 minutes, which might lead to increased costs in specific circumstances (such as a very busy PCI centre), but which would be less important than the cost of the device. Only 1 study[23] reported the number of balloon catheters used. The GDG believed that the main effect of the use of thrombus extraction devices on resource use would be to reduce the use of balloon catheters as a first device prior to stenting and that the use of balloon catheters could be inferred from reported data on the frequency of direct stenting. The clinical evidence showed a reduction in use of balloon catheters in people treated with both thrombus aspiration devices and mechanical thrombus extraction devices, leading to a modest decrease in costs. The GDG agreed that there is variation in balloon usage according to operator preferences, and that reductions in balloon usage in current UK practice may not be the same as seen in the clinical evidence, but agreed that there would be some reduction in balloon catheter usage in people treated with thrombus extraction devices. The largest difference in costs between PPCI with either thrombus aspiration or mechanical extraction and conventional PPCI without thrombectomy was found to be the cost of the thrombus extraction devices. Thrombus aspiration devices cost around £150 and mechanical thrombus extraction devices around £1240. The costing analysis concluded that PPCI using mechanical thrombus extraction devices is likely to cost around £1200 more than not using any thrombus extraction device. The clinical evidence showed no benefit but evidence of harm for these devices, and therefore they will not be cost effective. The costing analysis concluded that using thrombus aspiration devices will cost more than not using any thrombus extraction device, and that the cost difference is most likely to be around £110–£125. No data were available on quality of life, and so it is not possible to judge the cost effectiveness of the interventions in terms of QALYs gained. However, the GDG has found evidence that thrombus aspiration devices may be more clinically effective than no thrombus extraction. There is some uncertainty about this evidence (see below). If the use of thrombus aspiration devices is more effective, as indicated by the clinical evidence, then it is likely to be cost effective due to the amount of clinical benefit seen and the relatively modest increased cost.
Quality of evidence	The evidence in this review was of low to very low quality. The trials were relatively small and lacked statistical power to detect clinically important differences in outcomes. Other potential methodological limitations include insufficient detail about randomisation processes and unblinded adjudication of outcomes.[142] Outcome definitions and use of conjunctive medications also varied between the trials. The available data do not allow meaningful conclusions regarding stroke to be drawn.
Other considerations	There is concern that aspiration of thrombus from a coronary artery may cause thrombus to enter the systemic circulation and result in systemic embolism. In a

	meta-analysis that included data from both published and unpublished trials, use of aspiration thrombectomy, mechanical thrombus extraction, or distal embolic protection devices was associated with a strong trend towards an increased risk of stroke relative to PPCI alone.[19] The GDG noted that the use of direct stenting in the TAPAS trial was higher in the thrombus aspiration arm than in the standard PPCI arm, but it is unclear whether this contribute d to the differences in outcome between the two treatment groups.[293,319] The GDG noted 2 large trials of thrombus aspiration are ongoing at present (ClinicalTrials.gov identifiers NCT01093404 and NCT01149044). If these trials are positive, then the argument for routine use of thrombus aspiration devices will become stronger.

9 Culprit versus complete revascularisation

The section was updated and replaced in 2020.

See www.nice.org.uk/guidance/ng185 for the 2020 evidence review.

10 Cardiogenic shock

10.1 Introduction

Cardiogenic shock is a state of reduced end-organ perfusion due to low cardiac output. In people with acute STEMI cardiogenic shock usually results from ischaemic myocardial damage, but may also be caused by mechanical complications (including acute severe mitral regurgitation and ventricular septal rupture) or by malignant arrhythmia. Cardiogenic shock is characterised by hypotension, oliguria or alteration in mental status. Cardiogenic shock has been reported in around 5% to 8% of people who are admitted to hospital with STEMI and is associated with high in-hospital mortality rates (around 50% to 80%).[16,104,117] In a large registry study mortality from cardiogenic shock fell over time, but it is unclear whether this improved outcome is due to advances in therapy or to changes in definitions or case ascertainment.[16]

As discussed elsewhere in this guideline, early reperfusion therapy is a treatment priority for people with STEMI, but the presence of cardiogenic shock may necessitate immediate medical stabilisation and this may take precedence over interventions to restore myocardial blood supply. The GDG agreed that there is variation in current practice and some people with acute STEMI complicated by cardiogenic shock are not offered reperfusion therapy until their condition has been stabilised. The relative advantages of early revascularisation over medical stabilisation in people with acute STEMI complicated by cardiogenic shock are unclear. This question reviews the evidence for early revascularisation versus medical stabilisation of any person with acute STEMI complicated by cardiogenic shock.

10.2 Review question: In people with cardiogenic shock due to STEMI what is the clinical and cost effectiveness of early revascularisation compared with medical stabilisation?

10.3 Clinical evidence

A literature search identified 2 RCTs (the SHOCK and SMASH trials)[135,309] published after 1990 that addressed the review question. See review protocol in Appendix C.

An additional 8 follow-up papers from the SHOCK trial were also included in this review.[91,101,131,136,137,144,277,279] Non-randomised registry data reported in both the SHOCK and SMASH trials was not included in this review.

An individual patient-level data (IPD) meta-analysis was performed by Jeger et al. on the SHOCK and SMASH trial data sets.[144] Because this type of analysis better captures the variability within the results, individual patient data is used in preference to carrying out an original meta-analysis. For this reason, results on all-cause mortality for people who underwent early revascularisation or medical treatment over and under the age of 75 were extracted from the IPD meta-analysis by Jeger et al.[144]

The results are reported for both short-term (≤ 30 days) and longer-term (≤ 1 year) follow-ups. Data was also captured for the following relevant subgroups: people without diabetes; people < 75 or > 75 years of age; those with renal failure.

Evidence is reported in the GRADE tables below. See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

Table 36: Summary of studies used in this review

Study	Intervention/Control	Population	Outcomes Follow-up	Definitions	Treatments
SHOCK trial [135]	Within < 12 hours: Emergency revascularisation (CABG or angioplasty) (< 6 hours) versus initial medical stabilisation (intra-aortic balloon counter-pulsation and fibrinolytic therapy were recommended) Note: Delayed revascularisation in the medical stabilisation group after 54 hours was recommended if clinically appropriate	n = 302 Developed cardiogenic shock due to left ventricular failure within 36 hours of an acute myocardial infarction.	All-cause mortality Cardiac mortality Emergency PCI/CABG NYHA Class 30 days 1 year	Cardiogenic shock was defined as having a systolic blood pressure of < 90 mmHg for at least 30 minutes or the need for supportive measures to maintain systolic blood pressure of ≥ 90 mmHg and end-organ hypoperfusion (cool extremities or a urine output of < 30 ml/h and a heart rate of ≥ 60 beats per minute).	<u>Revascularisation group</u> (n = 152) CABG = 37.5% Angioplasty = 55% (stents were placed in 35.7%) Fibrinolytic therapy = 49.3% Platelet glyocoprotein IIb/IIa receptor antagonist = 16%. <u>Medical therapy</u> (n = 150) CABG = 11.3% Angioplasty = 14% (stents were placed in 52.3%) Fibrinolytic therapy = 63.3% Platelet glyocoprotein IIb/IIa receptor antagonist = 3%.
SMASH trial [309]	Emergency angiography + immediate revascularisation versus medical management (without angiography) Note: For PPCI, investigators were	n = 55 Developed cardiogenic shock due to primary pump failure within the first 48 hours of an acute myocardial infarction	All-cause mortality Quality of life NYHA Class Renal failure Major/minor bleeding Intracranial bleeding IABP	Eligibility: cardiogenic shock for 30 minutes or more, with compatible clinical presentation associated with a systolic blood pressure of ≤ 90 mmHg despite inotropic support and intravenous volume administration as	<u>Invasive group</u> (n = 32) Fibrinolysis = 34% (n = 11) PPCI = 84% (n = 27) Stent = 13% (n = 4) Successful = 85% (n = 23/27) <u>Conservative treatment group</u> (n = 23)

Study	Intervention/Control	Population	Outcomes Follow-up	Definitions	Treatments
	free to prescribe antiplatelet agents if deemed appropriate. No data was provided on the number of people who used concomitant therapies.		30 days, 6 months 1 year 6 years	needed	Fibrinolysis = 39% (n = 9) PCI at up to 30-day follow-up = late 4% (n = 1)

10.3.1 Clinical evidence profiles: early revascularisation versus initial medical stabilisation

Table 37: Clinical evidence profile: all-cause mortality

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Early revascularisation	Initial medical stabilisation	Relative (95% CI)	Absolute	Quality	Importance
All-cause mortality hazard ratio [137]												
1	Randomised trials	No serious risk of bias	No serious inconsistency (a)	No serious indirectness	No serious imprecision	None	107/152 (70.4%)	119/150 (79.3%)	HR 0.74 (0.56 to 0.97)	105 fewer per 1000 (from 10 fewer to 207 fewer)	HIGH	CRITICAL
All-cause mortality short-term ≤30 days [137,309]												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious (c)	None	93/184 (50.5%)	102/173 (59%)	RR 0.84 (0.7 to 1.02)	94 fewer per 1000 (from 177 fewer to 12 more)	MODERATE	CRITICAL
All-cause mortality short-term ≤30 days - IPD age > 75 years [144]												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious (d)	None	-	-	RR 0.93 (0.39 to 2.25)	-	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Early revascularisation	Initial medical stabilisation	Relative (95% CI)	Absolute	Quality	Importance
All-cause mortality short-term ≤30 days - IPD age < 75 years [144]												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious (e)	None	-	-	RR 0.83 (0.62 to 1.11)	-	MODERATE	CRITICAL
All-cause mortality 1-year follow-up – IPD age > 75 years [144]												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious (d)	None	-	-	RR 0.93 (0.56 to 1.54)	-	LOW	CRITICAL
All-cause mortality 1-year follow-up – IPD age < 75 years [144]												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious (b)	none	-	-	RR 0.79 (0.63 to 0.99)	-	MODERATE	CRITICAL
Survival 1-year follow-up – People with diabetes [101]												
1	Randomised trials	No serious risk of bias	No serious inconsistency (a)	No serious indirectness	Serious (c)	None			HR 0.62 (0.36 to 1.08)	-	MODERATE	CRITICAL
Survival 1-year follow-up – People without diabetes [101]												
1	Randomised trials	No serious risk of bias	No serious inconsistency (a)	No serious indirectness	Serious (c)	None			HR 0.75 (0.52 to 1.09)	-	MODERATE	CRITICAL

(a) Only 1 study so no test of heterogeneity.
(b) Confidence interval crosses default minimum important difference (0.75).
(c) Confidence interval crosses default minimum important difference (0.75) and line of no effect.
(d) 95% CI crosses the line of no effect and 2 minimum important differences (0.75 and 1.25).
(e) 95% CI crosses line of no effect and 1 minimum important difference (0.75).

Table 38: Clinical evidence profile: quality of life (multidimensional index of life quality)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Early revascularisation	Initial medical stabilisation	Relative (95% CI)	Absolute	Quality	Importance
Quality of life short-term ≤ 30 days (2 weeks) – measured with: Multidimensional Index of Life Quality (MILQ); range of scores: 35–245; better indicated by higher values [279]												
1	Randomised trials	No serious risk of bias	No serious inconsistency (a)	No serious indirectness	Serious (b)	None	41	23	-	MD 1.2 higher (2.4 lower to 4.8 higher)	MODERATE	CRITICAL
Quality of life longer-term (6 months) – measured with: Multidimensional Index of Life Quality (MILQ); range of scores: 35–245; better indicated by higher values [279]												
1	Randomised trials	No serious risk of bias	No serious inconsistency (a)	No serious indirectness	Serious (c)	None	41	23	-	MD 2.6 higher (0.44 lower to 5.64 higher)	MODERATE	CRITICAL

(a) Only 1 study so no test of heterogeneity.
(b) Confidence interval crosses 1 minimum important difference (3.9) and line of no effect (0).
(c) Confidence interval crosses 1 default minimum important difference (2.85) and line of no effect (0).

Table 39: Clinical evidence profile: short-term (≤30 days) stroke and renal failure

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Early revascularisation	Initial medical stabilisation	Relative (95% CI)	Absolute	Quality	Importance
Stroke short-term ≤30 days [309]												
1	Randomised trials	No serious risk of bias	No serious inconsistency (a)	No serious indirectness	Very serious (b)	None	0/32 (0%)	2/23 (8.7%)	RR 0.15 (0.01 to 2.89)	74 fewer per 1000 (from 86 fewer to 164 more)	LOW	IMPORTANT
Renal failure short-term ≤30 days [137]												
1	Randomised trials	No serious risk of bias	No serious inconsistency (a)	No serious indirectness	No serious imprecision	None	17/152 (11.2%)	32/150 (21.3%)	RR 0.55 (0.3 to 0.9)	96 fewer per 1000 (from 21 fewer to 149 fewer)	HIGH	IMPORTANT

(a) Only 1 study so no test of heterogeneity.

(b) Crosses line of no effect and 2 minimum important differences.

Table 40: Clinical evidence profile: reinfarction

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Early revascularisation	Initial medical stabilisation	Relative (95% CI)	Absolute	Quality	Importance
Non-fatal and all (fatal and non-fatal) myocardial infarction short-term ≤30 days [309]												
1	Randomised trials	No serious risk of bias	No serious inconsistency (a)	No serious indirectness	Very serious (b)	None	1/32 (3.1%)	1/23 (4.3%)	RR 0.72 (0.05 to 10.91)	12 fewer per 1000 (from 41 fewer to 431 more)	LOW	IMPORTANT
Reinfarction longer-term [309]												
1	Randomised trials	No serious risk of bias	No serious inconsistency (a)	No serious indirectness	No serious imprecision (c)	None	0/10 (0%)	0/5 (0%)	(c)	(d)	HIGH	IMPORTANT

(a) Only 1 study so no test of heterogeneity.
(b) Crosses line of no effect and 2 minimum important differences.
(c) Relative risk was not estimable.
(d) Absolute effect not estimable.

Table 41: Clinical evidence profile: unplanned early revascularisation

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	revascularisation	Control	Relative (95% CI)	Absolute	Quality	Importance
Unplanned revascularisation short-term ≤ 30 days [309]												
1	Randomised trials	No serious risk of bias	No serious inconsistency (a)	No serious indirectness	Very serious (b)	None	2/32 (6.3%)	1/23 (4.3%)	RR 1.44 (0.14 to 14.92)	19 more per 1000 (from 37 fewer to 605 more)	LOW	IMPORTANT
Unplanned revascularisation longer-term [309]												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious (b)	None	1/10 (10%)	0/5 (0%)	RR 1.64 (0.08 to	(c)	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	revascularisation	Control	Relative (95% CI)	Absolute		
			(a)						34.28)			

(a) Only 1 study so no test of heterogeneity.
(b) Crosses line of no effect and 2 minimum important differences.
(c)Not estimable.

Table 42: Clinical evidence profile: intracranial bleeding

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Early revascularisation	Initial medical stabilisation	Relative (95% CI)	Absolute		
Intracranial bleeding [137]												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious (a)	None	0/152 (0%)	2/150 (1.3%)	RR 0.20 (0.01 to 4.08)	11 fewer per 1000 (from 13 fewer to 41 more)	LOW	IMPORTANT

(a) Crosses line of no effect and 2 minimum important differences (0.75 to 1.26).

Table 43: Clinical evidence profile: heart failure

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Early revascularisation	Initial medical stabilisation	Relative (95% CI)	Absolute		
Heart failure Class I short-term ≤ 30 days [279]												
1	Randomised trials	No serious risk of bias	No serious inconsistency (a)	No serious indirectness	Very serious (a)	None	27/58 (46.6%)	18/48 (37.5%)	RR 1.24 (0.79 to 1.96)	90 more per 1000 (from 79 fewer to 360 more)	LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Early revascularisation	Initial medical stabilisation	Relative (95% CI)	Absolute	Quality	Importance
Heart failure Class I longer-term (6 months) [279]												
1	Randomised trials	No serious risk of bias	No serious inconsistency (a)	No serious indirectness	Very serious (b)	None	30/55 (54.5%)	20/37 (54.1%)	RR 1.01 (0.69 to 1.48)	5 more per 1000 (from 168 fewer to 259 more)	LOW	IMPORTANT
Heart failure Class II short-term ≤ 30 days (2 weeks) [279]												
1	Randomised trials	No serious risk of bias	No serious inconsistency (a)	No serious indirectness	Very serious (b)	None	17/58 (29.3%)	12/48 (25%)	RR 1.17 (0.62 to 2.21)	42 more per 1000 (from 95 fewer to 303 more)	LOW	IMPORTANT
Heart failure Class II longer-term (6 months) [279]												
1	Randomised trials	No serious risk of bias	No serious inconsistency (a)	No serious indirectness	Very serious (b)	None	9/55 (16.4%)	6/37 (16.2%)	RR 1.01 (0.39 to 2.6)	2 more per 1000 (from 99 fewer to 259 more)	LOW	IMPORTANT
Heart failure Class III short-term ≤ 30 days (2 weeks) [279]												
1	Randomised trials	No serious risk of bias	No serious inconsistency (a)	No serious indirectness	Very serious (b)	None	6/58 (10.3%)	6/48 (12.5%)	RR 0.83 (0.29 to 2.4)	21 fewer per 1000 (from 89 fewer to 175 more)	LOW	IMPORTANT
Heart failure Class III longer-term (6 months) [279]												
1	Randomised trials	No serious risk of bias	No serious inconsistency (a)	No serious indirectness	Very serious (b)	None	7/55 (12.7%)	3/37 (8.1%)	RR 1.57 (0.43 to 5.68)	46 more per 1000 (from 46 fewer to 379 more)	LOW	IMPORTANT
Heart failure Class IV short-term ≤ 30 days (2 weeks) [279]												
1	Randomised trials	No serious risk of bias	No serious inconsistency (a)	No serious indirectness	Very serious (b)	None	8/58 (13.8%)	12/48 (25%)	RR 0.55 (0.25 to 1.24)	112 fewer per 1000 (from 188 fewer to 60 more)	LOW	IMPORTANT
Heart failure Class IV longer-term (6 months) [279]												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Early revascularisation	Initial medical stabilisation	Relative (95% CI)	Absolute		
1	Randomised trials	No serious risk of bias	No serious inconsistency (a)	No serious indirectness	Very serious (b)	None	9/55 (16.4%)	8/37 (21.6%)	RR 0.76 (0.32 to 1.78)	52 fewer per 1000 (from 147 fewer to 169 more)	LOW	IMPORTANT

(a) Only 1 study so heterogeneity could not be calculated.
(b) Confidence interval crosses 2 minimum important differences (0.75 and 1.25) and line of no effect.

10.3.2 Results that are incongruent with GRADE profile presentation

The following data were not meta-analysed because either no raw numbers were provided or hazard ratio data was available and presented in preference to relative risk data.

Short-term (30 days)

- An individual patient data meta-analysis derived from the SHOCK and SMASH trials reported early revascularisation had no effect on the relative risk of short-term mortality (RR) for: all people and when analysing as subgroups: 71–75 years, 66–70 years, 56–65 years, ≤ 55 years.[144].

Longer-term (1 year)

- There is no apparent effect of early revascularisation on all-cause mortality amongst people of different gender or presence/absence of diabetes mellitus.[136]
- An individual patient data meta-analysis on the SHOCK and SMASH trials reported early revascularisation decreased longer-term mortality (RR) on all participants. No benefit of early revascularisation was reported in subgroup analysis (underpowered) amongst people aged: 71–75 years, 66–70 years, 56–65 years, ≤ 55 years.[144]

Longer-term (6 years)

- Longer-term survival analysis identified no interactions between treatment assignment and age (≤ 75 versus ≥ 75 years), gender or diabetes. [137]

10.4 Economic evidence

No relevant economic evaluations were identified that compared early revascularisation with medical stabilisation in people with cardiogenic shock due to STEMI. See also the economic article selection flow diagram in Appendix E.

10.5 Evidence statements

Clinical

All-cause mortality

- High quality evidence suggested that early revascularisation potentially has a greater clinically effective association, when compared to initial medical stabilisation, with reduced longer-term all-cause mortality [1 study, n = 301].
- Moderate quality evidence suggested that there may be no clinically important difference between the association between early revascularisation or initial medical stabilisation with reduced all-cause mortality at ≤30 days, but the direction of the estimate of effect favoured early revascularisation [2 studies, n = 357].
- Low quality evidence suggested that there may be no clinically important difference between the association with early revascularisation or initial medical stabilisation with reduced all-cause mortality in people aged over 75 years at ≤30 days, but the direction of the estimate of effect could favour either intervention [1 study, n = 357].
- Moderate quality evidence suggested that there may be no clinically important difference in the association between early revascularisation or initial medical stabilisation with reduced all-cause mortality in people aged under 75 years at ≤30 days, but the direction of the estimate of effect favoured early revascularisation [1 study, n = 357].
- Low quality evidence suggested that there may be no clinically important difference in the association between early revascularisation or initial medical stabilisation with reduced longer-

term all-cause mortality in people aged over 75 years, but the direction of the estimate of effect could favour either intervention [1 study, n = 357].

- Moderate quality evidence suggested that there may be no clinically important difference in the association between early revascularisation or initial medical stabilisation with reduced all-cause mortality in people aged under 75 years in the longer term , but the direction of the estimate of effect favoured early revascularisation [1 study, n = 357].
- Moderate quality evidence suggested that early revascularisation potentially has a greater clinically effective association than initial medical stabilisation with reduced all-cause mortality in people with diabetes in the longer term [1 study, n = 198].
- Moderate quality evidence suggested that early revascularisation potentially has a greater clinically effective association than initial medical stabilisation with reduced all-cause mortality in people with without diabetes, [1 study, n = 90].

Quality of life

- Moderate quality evidence suggested that initial medical stabilisation is potentially more clinically effective when compared to early revascularisation at improving quality of life at ≤30 days, but the direction of the estimate of effect could favour either intervention [1 study, n = 64].
- Moderate quality evidence suggested that initial medical stabilisation is potentially more clinically effective when compared to early revascularisation at improving quality of life in the longer term [1 study, n = 64].

Stroke

- Low quality evidence suggested that early revascularisation potentially has a greater clinically effective association than initial medical stabilisation with reduced incidence of stroke at ≤30 days, but the direction of the estimate of effect could favour either intervention [1 study, n = 55].

Renal failure

- High quality evidence suggested that early revascularisation potentially has a greater clinically effective association than initial medical stabilisation with reduced incidence of renal failure at ≤30 days [1 study, n = 302].

Reinfarction

- Low quality evidence suggested that early revascularisation potentially has a greater clinically effective association than initial medical stabilisation with reduced incidence of reinfarction at ≤30 days but the direction of the estimate of effect could favour either intervention [1 study, n = 55].
- High quality evidence suggested that the difference in the association between early revascularisation and initial medical stabilisation with reduced incidence of reinfarction in the longer term is uncertain as there were no events in either arm and no comparative analysis could be carried out [1 study, n = 15).

Unplanned revascularisation

- Low quality evidence suggested that initial medical stabilisation potentially has a greater clinically effective association than early revascularisation with reduced incidence of unplanned revascularisation at ≤30 days, but the direction of the estimate of effect could favour either intervention [1 study, n = 55].
- Low quality evidence suggested that initial medical stabilisation potentially has a greater clinically effective association than early revascularisation with reduced incidence of longer-term unplanned revascularisation, but the direction of the estimate of effect could favour either intervention [1 study, n = 15].

Intracranial bleeding

- Low quality evidence suggested that early revascularisation potentially has a greater clinically effective association than initial medical stabilisation with reduced incidence of intracranial bleeding at ≤30 days, but the direction of the estimate of effect could favour either intervention [1 study, n = 302].

Heart failure (Class I)

- Low quality evidence suggested that there may be no clinical difference in the association between early revascularisation or initial medical stabilisation with reduced incidence of Class I heart failure at ≤30 days, but the direction of the estimate of effect favoured initial medical stabilisation [1 study, n = 106].
- Low quality evidence showed that there is no clinically important difference in the association between early revascularisation or initial medical stabilisation with reduced incidence of Class I heart failure in the longer term [1 study, n = 92].

Heart failure (Class II)

- Low quality evidence suggested that there may be no clinically important difference in the association between early revascularisation or initial medical stabilisation with reduced incidence of Class II heart failure at ≤30 days, but the direction of the estimate of effect could favour either intervention [1 study, n = 106].
- Low quality evidence suggested that there may be no clinically important difference in the association between early revascularisation or initial medical stabilisation with reduced incidence of Class II heart failure (Class II) in the longer term, but the direction of the estimate of effect could favour either intervention [1 study, n = 92].

Heart failure (Class III)

- Low quality evidence suggested that there may be no clinically important difference in the association between early revascularisation or initial medical stabilisation with reduced incidence of Class III heart failure at ≤30 days, but the direction of the estimate of effect could favour either intervention [1 study, n = 106].
- Low quality evidence suggested that initial medical stabilisation is potentially has a greater clinically effective association than early revascularisation with reduced incidence of Class III heart failure in the longer term, but the direction of the estimate of effect could favour either intervention [1 study, n = 92].

Heart failure (Class IV)

- Low quality evidence suggested that early revascularisation potentially has a greater clinically effective association than initial medical stabilisation with reduced incidence of Class IV heart failure at ≤30 days [1 study, n = 106].
- Low quality evidence suggested that there may be no clinically important difference in the association between early revascularisation and initial medical stabilisation reduced incidence of Class IV heart failure in the longer term, but the direction of the estimate of effect could favour either intervention [1 study, n = 92].

Economic

- No relevant economic evaluations were identified that compared early revascularisation with medical stabilisation in people with cardiogenic shock due to STEMI.

10.6 Recommendations and link to evidence

Recommendations	**The current recommendations can be found at: www.nice.org.uk/guidance/ng185**
Relative values of different outcomes	For this review question the GDG considered the outcomes of all-cause mortality, stroke, intracranial bleeding and quality of life as critical to decision-making. Myocardial reinfarction, heart failure, unplanned revascularisation, major bleeding and renal failure were considered important, and minor bleeding and length of hospital stay as less important to decision-making. No data were found for cardiovascular mortality, minor bleeding, length of hospital stay or use of IABP.
Trade-off between clinical benefits and harms	The GDG acknowledged that it is difficult to conduct RCTs in people with acute STEMI complicated by cardiogenic shock and consequently there is a paucity of contemporary data to address this review question. The GDG agreed that data from 2 relatively old RCTs generally favoured early myocardial revascularisation over initial medical stabilisation in people with acute STEMI complicated by cardiogenic shock. The available evidence suggests that early revascularisation is associated with a reduction in mortality when compared with medical stabilisation. One high quality RCT reported time to event data demonstrating a 26% relative reduction (95% confidence interval 3% to 44%) in all-cause mortality with early revascularisation. The rates of stroke and myocardial reinfarction in the trials were low with wide confidence intervals and high uncertainty about the direction of treatment effect on these outcomes. There was no evidence that a strategy of early revascularisation was associated with harm when compared with a strategy of medical stabilisation. The GDG consensus was that early intervention may salvage myocardium and thereby improve outcome and hence this should be the over-riding priority. In addition, in modern practice other supporting 'medical' interventions can be delivered in the cardiac catheter laboratory (for example insertion of an IABP, mechanical ventilation, administration of inotropes). The GDG concluded that people with cardiogenic shock should not be treated any differently from other people with acute STEMI. The GDG therefore recommended that people who present with cardiogenic shock who present within 12 hours after the onset of STEMI (which is not due to acute mechanical complications) should be offered coronary angiography with PPCI coronary revascularisation if indicated. The GDG debated the management of people who present in cardiogenic shock more than 12 hours after the onset of STEMI. The potential to salvage myocardium by revascularisation in people with acute STEMI who present more than 12 hours after the onset of symptoms is limited. On the other hand, the GDG agreed that the time from onset of STEMI to the development of cardiogenic shock may vary widely. In the SHOCK trial participants were randomised within 48 hours of the onset of myocardial infarction and within 36 hours of the diagnosis of cardiogenic shock. In the early revascularisation group the median time from the onset of myocardial infarction to randomisation was 11.0 hours (IQR 5.9–19.4 hours) and the median time from randomisation to revascularisation was 0.9 hours for coronary angioplasty and 2.7 hours for coronary bypass surgery. Hence a substantial proportion of participants in SHOCK were revascularised more than 12 hours after the onset of myocardial infarction. On this basis the GDG agreed that coronary angiography (with

	coronary revascularisation if indicated) should be considered for people with cardiogenic shock who present more than 12 hours after the onset of STEMI.
Economic considerations	No health economic evidence was found for this question. More revascularisation procedures were carried out in the early revascularisation treatment groups in the RCTs included in the clinical review, making it likely that early revascularisation is a more expensive strategy. As discussed above, the GDG considered that the clinical evidence favoured a strategy of early revascularisation, which may make it cost effective to carry out these additional procedures. PPCI has been found to be cost effective in a general STEMI population. The GDG did not identify any reason for people with cardiogenic shock to be treated differently from other people with acute STEMI. As people with cardiogenic shock are at high absolute risk of adverse outcomes it is plausible that the absolute benefit in terms of clinical events avoided and QALYs gained may also be higher than in the general STEMI population, in which case PPCI would be at least as cost effective in people with cardiogenic shock as in the general STEMI population.
Quality of evidence	The GDG noted that definitions of cardiogenic shock differed between the trials in this review. The RCTs in this review enrolled people with cardiogenic shock over 20 years ago, which reduces their applicability to modern practice. The trials were conducted before the availability of intra-coronary stents, which likely explains the high use of coronary artery bypass graft surgery (36%) in the early revascularisation arm of the SHOCK trial.
Other considerations	The GDG noted that a high percentage of people were given fibrinolysis before randomisation and intra-aortic balloon pumps were inserted in 86% of people in both arms of the SHOCK trial.[135]

11 People who remain unconscious after a cardiac arrest

11.1 Introduction

A considerable number of people with STEMI present as out-of-hospital cardiac arrest. The global incidence of adult out-of-hospital cardiac arrest has been estimated at 95.9 cases per 100,000 person-years.[24] The proportion who have acute STEMI is not known but studies conducted around 2 decades ago reported that one-third of people with an acute coronary syndrome die before arrival in hospital.[181,244]

Resuscitation by emergency medical services is attempted in up to two-thirds of out-of-hospital cardiac arrests.[24] Although return of spontaneous circulation is achieved in only the minority of such people, of those who reach hospital, approximately two-thirds remain unconscious (unresponsive or responsive only to pain) in the immediate period following resuscitation (London Ambulance Service: unpublished evidence 2012). During this period, a variety of investigations and treatments may be indicated and may compete for priority, such as prompt admission to an intensive care unit for haemodynamic and metabolic stabilisation, tracheal intubation, therapeutic hypothermia,[240] as well as the potential need for PPCI. Some emergency services and receiving hospitals, have felt it more important to take such people to the nearest hospital with an intensive care unit, whereas others have admitted only to centres capable of undertaking PPCI. It has therefore been unclear as to whether delaying intensive care unit stabilisation to perform immediate PCI is or is not the optimal strategy.

The GDG reviewed the evidence as to whether people with evolving STEMI who remain unconscious after cardiac arrest should undergo immediate coronary angiography, with follow-on PPCI if indicated (as would be the case for their conscious counterparts), or whether there is evidence that initial stabilisation on an intensive care unit prior to PPCI is a more beneficial strategy.

11.2 Review question: Does immediate angiography followed by PPCI where indicated improve outcomes of people with presumed STEMI who are resuscitated but remain unconscious after a cardiac arrest?

For full details see review protocol in Appendix C.

11.3 Clinical evidence

Three cohort studies were included in the review.[46,178,252] No RCT studies were identified. A summary of the included cohorts is given in Table 44. The participants either underwent immediate angiography followed by PPCI or they transferred to ITU and received standard care. A summary of the baseline patient characteristics, GPI use and stents used during PPCI is given in Table 45. Evidence from the cohort studies are summarised in the clinical GRADE evidence profile below (Table 48). See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

The population of interest for the review question was patients who are resuscitated but remain unconscious after an out-of-hospital cardiac arrest due to STEMI. All of the cohort studies identified have a mixed population of conscious and unconscious people in the PPCI study arm. One study states that the PPCI subgroup is a mixed population.[46] One study reports the degree of consciousness using the Glasgow coma score, where eye opening, verbal response, and motor ability are assessed

in response to stimuli.[252] One study reports the degree of consciousness using the Glasgow coma scale for a single cut-off value.[178] Details of the Glasgow coma scale are given in Table 46.

Neurological outcome is assessed using the Cerebral Performance Categories (CPC) of the Glasgow-Pittsburgh Outcome Categorisation in 1 cohort study.[252] Details of this cerebral performance scale are also given in Table 46. Nine case series were identified and excluded from formal analyses as the studies had no usual care comparator for the PPCI STEMI group. However data from these studies are detailed in Table 47 in order to demonstrate the feasibility of coronary angiography followed by PPCI in unconscious people after cardiac arrests from STEMI.

Table 44: Summary of studies included in the review

Study	Intervention/comparison	Population	Outcomes	Comments
Bulut 2000[46]	Immediate angiography followed by PPCI versus usual care	n = 30	In-hospital all-cause mortality	Retrospective cohort study
Liu 2012[178]	Immediate angiography followed by PPCI versus usual care	n = 81	In-hospital all-cause mortality, stroke, acute renal failure	Retrospective cohort study
Pleskot 2008[252]	Immediate angiography followed by PPCI versus usual care	n = 26	In-hospital and 12-month all-cause mortality In-hospital and 12-month good performance on Glasgow-Pittsburgh Outcome Categorisation (CPS)	Retrospective cohort study

Table 45: Summary of baseline characteristics

Study	STEMI definition	Cardiac arrest to needle time	Glasgow coma scale (GCS) score at admission			Conscious, n/total (%)		GPI, n/total (%)		Stenting, n/total (%)	
						PPCI	Usual care	PPCI	Usual care	PPCI	Usual care
Bulut 2000[46]	Electrographic and enzymatic evidence of acute MI	NA	NA (data provided on cohort of STEMI and non-STEMI cardiac arrest patients)			6/10 (60)	NA	NA	NA	NA	-
Liu 2012[178]	Typical chest pain with ST-segment elevation ≥ 1 mm in at least 2 consecutive precordial or inferior limbs, or chest pain with new onset of complete bundle branch block	NA	GCS ≤ 7 = 24/81 (29.6%)			NA	NA	46/49 (93.9)	NA	44/49 (89.8)	-
Pleskot 2008[252]	Acute STEMI defined as dynamic ST-segment elevation on ECG plus typical rise (minimum 3 times above the upper border of normal values) and fall in biochemical markers of myocardial necrosis (serum creatine kinase and its MB fraction) with the consequent development of a pathologic Q wave on the ECG	N/A but states; for all PPCI patients the interval from the symptom onset to hospital admission did not exceed 180 minutes	GCS	PPCI, n/total (%)	Usual care, n/total (%)	2/20 (10)	0/6 (0)	NA	NA	17/19 (85)	-
			3–5	17/20 (85%)	6/6 (100%)						
			6–10	1/20 (5%)	0						
			11–15	2/20 (10%)	0						

NA = Not applicable

Table 46: Descriptions of neurological scales included in cohort studies

NA; not availableScale	Category	Description
Glasgow coma scale (GCS)	13–15	Mild disability
	9–12	Moderate disability • loss of consciousness longer than 30 minutes • physical or cognitive impairments which may or may not resolve • benefit from rehabilitation
	3–8	Severe disability • coma: unconscious state • no meaningful response, no voluntary activities
	< 3	Vegetative state • sleep wake cycles • arousal, but no interaction with environment no localised response to pain
Cerebral Performance Categories (CPC) of the Glasgow-Pittsburgh Outcome Categorisation	CPC 1	Good cerebral performance; conscious and alert with normal neurological function or only slight cerebral disability
	CPC 2	Moderate cerebral disability; conscious and sufficient cerebral function for part-time work in sheltered environment or independent activities of daily life
	CPC 3	Severe cerebral disability; conscious and dependent on others for daily support because of impaired brain function
	CPC 4	Coma, vegetative state
	CPC 5	Dead or brain dead

Table 47: Case series studies of immediate angiography followed by PPCI for resuscitated people that remain unconscious after an out-of-hospital cardiac arrest due to STEMI

Study	STEMI definition	CAG, n	PPCI, n (%)	Conscious, n (%)	GPI, n (%)	Stenting, n (%)	PPCI success, n (%)	Survival, n (%)	CPC 1–2, n (%)
Bendz 2004[22]	Electrocardiographic evidence of ST-elevation	40	40 (100)	4 (10)	15 (38)	39 (95)	38 (95)	29 (73)	NR
Dumas 2010[90]	An ST-segment elevation was defined as an elevation of > 1 mm in 2 contiguous leads in standard leads and > 2 mm in precordial leads	134	110 (75)	NR	NR	NR	99 (90)	56 (51)	NR

Study	STEMI definition	CAG, n	PPCI, n (%)	Conscious, n (%)	GPI, n (%)	Stenting, n (%)	PPCI success, n (%)	Survival, n (%)	CPC 1–2, n (%)
Garot 2007[112]	Resuscitated from cardiac arrest, with > 2 mm ST-segment elevation in > 2 contiguous leads or a left bundle branch block or at least 1 culprit lesion on angiography. Emergency PCI of the infarct-related artery was performed in all people with the use of standard balloon and stent techniques.	168	168 (100)	NR	31 (17)	168 (90)	161 (87)	103 (55)	100 (54)
Gorjup 2007[121]	STEMI not defined	117	108 (80)	48 (44)	60 (55)	85 (79)	102 (94)	88 (81)	75 (69)
Kahn 1995[151]	ST-segment elevation including cardiogenic shock (systolic BP < 90 mmHg)	11	11 (100)	4 (36)	0 (0)	0 (0)	7 (64)	6 (55)	4 (36)
Keelan 2003[156]	STEMI not defined	16	16 (100)	2 (18)	0 (0)	2 (13)	14 (88)	11 (69)	9 (56)
Lettieri 2009 [174]	12-lead ECG finding > 2 mm ST-segment elevation in > 2 contiguous leads or the new appearance of left bundle-branch block in the presence of at least 1 culprit lesion on angiography	99	99 (100)	NR	68 (69)	90 (91)	80 (81)	77 (78)	69 (89)
Markusohn 2007[189]	STEMI not defined	25	25 (100)	7 (28)	13 (52)	23 (92)	22 (88)	19 (76)	17 (68)
Wolfrum 2008[334]	ST-segment elevation 0.1 m ST-segment elevation in > 2 contiguous leads in at least 2 contiguous leads, retrospectively confirmed by troponin T	16	16 (100)	NR	15 (94)	16 (100)	16 (100)	12 (75)	11 (69)

(a) CAG: immediate coronary angiography.

(b) CPC 1–2: Cerebral Performance Categories 1–2 of the Glasgow-Pittsburgh Outcome Categories where CPC 1 equates to good cerebral performance (conscious and alert with normal neurological function or only slight cerebral disability) and CPC 2 equates to moderate cerebral disability (conscious and sufficient cerebral function for part-time work in sheltered environment or independent activities of daily life).

(c) NR: not reported.

Table 48: Clinical evidence profile: immediate coronary angiography followed by PPCI versus usual care

No. of studies	Design	Results	Limitations	Inconsistency	Indirectness	Imprecision	Quality	Importance
Outcome: All-cause mortality ≤ 30 days [46,178,252]								
3	Retrospective cohort Retrospective cohort Retrospective cohort	RR (95%CI); 0.92 (0.51, 1.68) RR (95%); 0.44 (0.29, 0.65) RR (95%CI); 0.38 (0.18, 0.80)	Very serious (a)	Serious (b)	Serious (c)	Very serious (d)	VERY LOW	CRITICAL
Outcome: All-cause mortality longer-term [252]								
1	Retrospective cohort	HR (95%CI); 0.32 (0.12, 0.90)	Very serious (a)	No serious inconsistency	Serious (e)	Serious (f)	VERY LOW	CRITICAL
Outcome: Good performance on CPS ≤ 30 days [252]								
1	Retrospective cohort	RR (95%CI); 3.07 (0.27, 34.37)	Very serious (a)	No serious inconsistency	Serious (e)	Very serious (g)	VERY LOW	IMPORTANT
Outcome: Good performance on CPS 1 year [252]								
1	Retrospective cohort	RR (95%CI); 3.60 (0.32, 39.94)	Very serious (a)	No serious inconsistency	Serious (e)	Very serious (g)	VERY LOW	IMPORTANT
Outcome: Stroke ≤ 30 days [178]								
1	Retrospective cohort	RR (95%CI); 0.50 (0.28, 0.88)	Very serious (a)	No serious inconsistency	Serious (e)	Serious (f)	VERY LOW	CRITICAL
Outcome: Renal failure ≤ 30 days [178]								
1	Retrospective cohort	RR (95%CI); 0.22 (0.02, 2.00)	Very serious (a)	No serious inconsistency	Serious (e)	Very serious (g)	VERY LOW	IMPORTANT

(a) Retrospective cohort(s).
(b) 1 study effect size and confidence intervals not equivalent to 2 other studies.
(c) Mixed population of unconscious and conscious people in PPCI group in 3 studies.
(d) Very wide confidence interval in 1 study.
(e) Mixed population of unconscious and conscious people in PPCI group.
(f) Wide confidence interval.
(g) Very wide confidence interval.

11.4 Economic evidence

No relevant economic evaluations were identified that compared immediate angiography followed by PPCI with no immediate angiography in people with presumed STEMI who are resuscitated but remain unconscious after a cardiac arrest. See also the economic article selection flow diagram in Appendix E.

11.5 Evidence statements

Clinical

Very low quality evidence suggested that there may be no clinical difference between PPCI and usual care at:

- reducing in-hospital all-cause mortality, but the direction of the estimate of effect could favour either intervention [3 cohort studies, n = 137].
- reducing in-hospital renal failure, but the direction of the estimate of effect could favour either intervention [1 cohort study, n = 81].

Very low quality evidence suggested that PPCI is potentially more clinically effective when compared to usual care at:

- reducing all-cause mortality at 12 months [1 cohort study, n = 30].
- improving in-hospital performance on CPS overall and at 1 year but the direction of the estimate of effect could favour either intervention [1 cohort study, n = 30].
- at reducing in-hospital stroke [1 cohort study, n = 81].

Economic

- No relevant economic evaluations were identified that compared immediate angiography followed by PPCI with no immediate angiography in people with presumed STEMI who are resuscitated but remain unconscious after a cardiac arrest.

11.6 Recommendations and link to evidence

Recommendations	The current recommendations can be found at: www.nice.org.uk/guidance/ng185
Relative values of different outcomes	For this review question the GDG considered the outcomes of short-term and longer-term all-cause mortality and stroke as critical to decision-making. Neurological outcomes and renal failure were considered important to decision-making. No data were found for myocardial reinfarction, heart failure, unplanned urgent target vessel revascularisation, major bleeding, minor bleeding, length of hospital stay or quality of life. Because there were so few studies, the GDG also reviewed data reported from case series that presented survival rates, to consider whether PPCI is feasible in unconscious people.
Trade-off between clinical benefits and harms	From the evidence base the GDG were unable to say whether immediate coronary angiography (with follow-on PPCI if indicated) versus usual care was of benefit in people with evolving STEMI who remain unconscious after cardiac arrest.

	The GDG debated the potential benefits of coronary angiography and follow-on PPCI (restoration of coronary artery flow, preservation of myocardial function, and prevention of recurrent ventricular arrhythmia) versus the potential benefits of early admission to an intensive care unit (for haemodynamic and metabolic stabilisation). The GDG considered that the need for therapeutic hypothermia [240] should not determine management as this therapy can be delivered in a cardiac catheter laboratory or in an intensive care unit. The GDG also noted evidence that PPCI confers a mortality advantage in conscious people, as discussed in chapter 11. The GDG agreed that while there was generally a lack of good data, there was no evidence to suggest that people with STEMI who remain unconscious after cardiac arrest should be treated any differently from conscious people with STEMI in terms of timing of angiography and PPCI. From a clinical perspective likelihood of harm from coronary angiography was judged to be low. The GDG felt that this tipped the balance in favour of a consensus recommendation for considering coronary angiography with follow-on PPCI if indicated in people with a suspected STEMI and who remain unconscious after cardiac arrest.
Economic considerations	No health economic evidence was found for this question. The GDG noted that a PPCI procedure in an unconscious person would be largely similar to a standard PPCI procedure but that there would be increased costs in transferring the person into the cardiac catheter laboratory and in having a dedicated anaesthetist attending during the procedure. There may also be an increased need for haemodynamic support, such as an intra-aortic balloon pump, which is expensive. Usual care for an unconscious person not given PPCI would be admission to intensive care. In contrast to this, PPCI would be an additional procedure, generally being followed by the same intensive care treatment, and would thus give rise to an additional cost. This would be partially offset by a proportion of people admitted directly to intensive care without PPCI instead receiving an elective PCI or CABG procedure at a later date after they had recovered consciousness. The GDG noted that carrying out immediate PPCI, if successful, will stabilise the person's heart and so could reduce the risk of further complications, such as heart failure, occurring later during admission compared to intensive care only. This could reduce later treatment costs for complications, and could also reduce the length of time spent in hospital, in particular in intensive care, which is very expensive. The GDG also noted that salvaged myocardium improves left ventricular function, which is a powerful determinant of longer-term outcome and future treatment cost. It is not possible to cost these possible savings. The GDG noted that it was not possible to establish the cost effectiveness of treating unconscious people with PPCI, but agreed that there was no evidence to suggest a different clinical effectiveness and therefore no reason for expecting a significant difference in the cost effectiveness of PPCI compared to people who are conscious.
Quality of evidence	The GDG found little data for angiography (with follow-on PPCI if indicated) in people with evolving STEMI who remain unconscious after cardiac arrest. No RCTs were identified to help answer the question but the GDG reviewed 3 retrospective cohort studies with low event numbers. No reliable data were available on all-cause mortality, stroke, intracranial bleeding, quality of life, myocardial reinfarction, heart failure, unplanned revascularisation, major/minor bleeding, and hospital stay.

	The 2 retrospective cohort studies were of very low quality and 1 was relatively old (2000). Most of the studies in this review report level of consciousness using either the Glasgow Coma Scale or AVPU (A = Alert; V = responding to verbal stimuli; P = responding to painful stimuli; U = unresponsive). The GDG discussed the definition of 'unconscious' and agreed that although there were no clear boundaries in these scales, a GCS ≤ 8 or P/U could be considered as 'unconscious'. The GDG could not be certain from the data reported in the studies that all of the people were unconscious, although it was inferred that the majority were unconscious from the GCS and AVPU scale. The studies included mixed populations with conscious and unconscious patients. The GDG considered these to be relevant despite some indirectness because no other data were available. The evidence has been downgraded accordingly. The GDG noted that 'usual care' (anything other than coronary angiography) in these studies is not the same as 'usual care' in contemporary practice. The studies reported very few details on what constituted usual care and whether this included cooling or ventilation.
Other considerations	The GDG were aware that a number of PPCI centres in the UK do not accept people with STEMI who remain unconscious after cardiac arrest, because of uncertainty about the neurological prognosis. The GDG agreed that whilst predicting neurological outcome in an unconscious person is not possible, these people should be assessed at a PPCI centre and should not be denied PPCI because they are unconscious. The GDG considered that coronary angiography and revascularisation if indicated should be carried out in parallel with ICU interventions and that angiography should not delay commencing therapeutic hypothermia.

12 Hospital volumes of primary percutaneous coronary intervention

12.1 Introduction

Provision of an elective PCI service requires appropriate facilities, a complement of trained staff, and an ongoing volume of activity to attain and sustain performance. Most PCI services in the UK participate in local and national audit, but there are no easily monitored or widely accepted measures for assessing and comparing service quality. Risk-adjusted outcomes, plotted using statistical process control techniques such as funnel plots, have been used to provide both a comparative index of service performance and a means of monitoring variations in performance over time.[182] Such analyses are critically dependent on the risk-adjustment model employed, and when the number of procedures is low and event rates are very low their comparative value may be limited. An alternative and less sophisticated approach has been to use the number of procedures performed by a service (or by an individual operator) as a crude surrogate for quality[161], and professional societies have defined minimum numbers of PCI procedures for training and maintenance of individual and institutional competence.[66,280]

Effective provision of a PPCI service is a more complex process that requires integrated working across emergency care, interventional cardiology, and other clinical and non-clinical services. Ambulance services must correctly identify people with acute STEMI, assess eligibility for reperfusion, and arrange direct and expeditious transfer of appropriate people to a PPCI facility. A multidisciplinary catheter laboratory team must be available to receive the patient at any time of day or night, and to ensure the timely and efficient delivery of PPCI to all who may benefit from the procedure. The intervention requires a skilled operator and supporting clinical staff, who must make rapid knowledge-based decisions to optimise procedural outcome. Following PPCI, people require appropriate post-procedural care, including rehabilitation and secondary prevention measures. Defining measures of quality for this complex process is problematic, although in the UK call-to-balloon and door-to-balloon times provide information about some aspects of the care pathway (see chapter 5). The extent to which procedural outcomes are influenced by the PPCI service volume has also been the focus of debate. The GDG was therefore interested to know whether PPCI service volume influences outcome of PPCI procedures.

12.2 Review question: What is the impact of high volume versus low volume PPCI services on patient outcomes?

For full details see review protocol in Appendix C.

12.3 Clinical evidence

Five studies were included in the review.[49,100,165,185,282] Evidence from these are summarised in Table 49 and the clinical evidence profile in Table 50. See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

Table 49: Characteristics of included studies

Study	Population	Data	Inclusion	Exclusion
KUMBHANI 2009[165]	American Heart Association's get with the guidelines – coronary artery disease national database	n = 29,513 July 2001 to December 2007	ECG evidence of new ST-segment elevation or new left bundle branch block. Cardiac diagnosis of STEMI	People without STEMI, no PPCI, people receiving fibrinolytic therapy, people with 25% or more missing data, people treated at hospitals that submitted less than 30 PPCI cases over 6-year duration of study
MAGID 2000[185]	National registry of myocardial infarction (NRMI) (voluntary database), USA	n = 62,299 June 1994 to July 1999	Arrival at hospital within 12 hours of AMI onset; initial ECG ST-segment elevation or left bundle branch block; absence of cardiogenic shock; no contraindications to fibrinolytic therapy	Hospitals that did not regularly report data to the NRMI registry and those who had participated < 6 months; people who did not complete their hospital stay at a single hospital
SRINIVAS 2009[282]	New York State PCI reporting system	n = 7321 2000 to 2002	AMI presenting within 12 hours of chest pain, excluding those receiving fibrinolytics	
CANTO 2000 [49]	National Registry of Myocardial Infarction (voluntary registry on people hospitalised with confirmed MI)	n = 36,535 June 1994 to March 1998	All primary angioplasty procedures (including procedures performed in those transferred from other hospital)	Hospitals without onsite availability of cardiac surgery as back-up
EVERY 2000[100]	The Cooperative Cardiovascular Project (CCP) database – mandated quality improvement project, USA	n = 6124 February 1994 and July 1995	Medicare patients ≥ 65 years) with confirmed AMI who underwent coronary angioplasty within 12 hours of hospital admission	People admitted with cardiogenic shock or who received fibrinolytic therapy prior to the performance of angioplasty; people without data for the first 12 hours of treatment

Table 50: Clinical evidence profile: hospital volumes of PPCI

Study	Design	Results			Limitations	Inconsistency	Indirectness	Imprecision	Quality	Importance
Outcome: All-cause mortality in-hospital										
KUMBHANI 2009[165]	Registry Model for in-hospital mortality Adjusted for demographics, hospital characteristics, past medical history, and acute use of aspirin and beta blockers.	Low versus high volume hospital (< 36 versus 36–70 PPCI/year) OR = 1.22 (0.78–1.91), p = 0.38	Medium versus high volume hospitals (36–70 versus > 70 PPCI/year) OR = 1.14 (0.78–1.66), p = 0.49	Volume as a continuous variable (For every decrease in 50 procedures per year) 1.13 (0.93–1.37), p = 0.23	Serious (f)	No serious inconsistency	No serious indirectness	Very serious (d)	VERY LOW	CRITICAL
MAGID 2000[185]	Registry	Low volume: ≤ 16 PPCI/year, n = 1423 6.2 %	Intermediate volume: 17–48 PPCI/year, n = 8817 4.5 %	High volume: ≥ 49 PPCI/year, n = 1733 3.4 %	Very serious (a)(b)(f)	No serious inconsistency	No serious indirectness	Very serious (e)	VERY LOW	CRITICAL
SRINIVAS 2009[282]	Registry	Annual hospital volume threshold for PPCI (per year)	Mortality (%)	OR risk adjusted in-hospital mortality (g)	Serious (f)	No serious inconsistency	No serious indirectness	Very serious (d)	VERY LOW	CRITICAL
		≤ 25	5.37	Reference						
		> 25	3.62	0.61 (0.34–1.10)						
		≤ 50	5.40	Reference						
		> 50	3.40	0.58 (0.38–0.88)						
		≤ 75	4.24	Reference						
		> 75	3.32	0.82 (0.57–1.17)						
CANTO 2000[49]	Registry Model Adjusted for demographic characteristics, medical history, clinical	Quartile 2 (12–20 PPCI/year) RR in-hospital mortality (a) OR = 0.87 (0.71–1.07)	Quartile 3 (21–33 PPCI/year) RR in-hospital mortality OR = 0.83 (0.69–1.01)	Quartile 4 (> 33 PPCI/year) RR in-hospital mortality OR = 0.72 (0.60–0.87)	Very serious (b) (f)	No serious inconsistency	No serious imprecision	Very serious (d)	VERY LOW	CRITICAL

Study	Design	Results			Limitations	Inconsistency	Indirectness	Imprecision	Quality	Importance
	presentation, medications within 24 hours, year, and volume of people with MI. The odds ratio for all 3 quartiles is compared with the first quartile.									
Outcome: All-cause mortality ≤ 30 days										
EVERY 2000[100]	Registry	OR = 0.95 per quartile, 95% CI 0.91–1.00, NS			Serious (f)	No serious inconsistency	Very serious (c)	No serious imprecision	VERY LOW	CRITICAL
Outcome: Non-fatal stroke in-hospital										
MAGID 2000[185]	Registry	Low volume (<16 PPCI/year) 0.4 %	Intermediate volume (16–47) 0.5 %	High volume (< 49) 0.4 %	Very serious (a) (b) (f)	No serious inconsistency	No serious imprecision	Very serious (e)	VERY LOW	CRITICAL
Outcome: Major bleeding in-hospital										
MAGID 2000[185]	Registry	Low volume (<16 PPCI/ year) 4.2 %	Intermediate volume (16–47) 3.8 %	High volume (< 49) 3.6 %	Very serious (a) (b) (f)	No serious inconsistency	No serious imprecision	Very serious (e)	VERY LOW	IMPORTANT

(a) Data not adjusted for possible confounders.
(b) Possible selection bias - voluntary registry participation.
(c) Total PPCI volumes estimated from second database that includes all AMI people regardless of Medicare status.
(d) Very wide confidence interval.
(e) No confidence interval given.
(f) Retrospective data.
(g) Rate of observed mortality to predicted mortality multiplied by state-wide mortality rate of 3.75% (95% CI).

12.4 Economic evidence

No relevant economic evaluations were identified that compared the impact of high volume and low volume PPCI services on people with STEMI. See also the economic article selection flow diagram in Appendix E.

12.5 Evidence statements

Clinical

Very low quality evidence comparing hospitals with higher volume PPCI service to lower volume PPCI services:

Suggested that hospitals with higher volume PPCI services potentially have a reduced in hospital:

- all-cause mortality, but the direction of the estimate of effect could favour either group [4 studies, n = 135,668].
- major bleeding but the difference is uncertain as no comparative analysis could be carried out [1 study, n = 62,299].

Showed that there is no clinical difference in:

- all-cause mortality at 30 days [1 study, n = 6124].
- in-hospital non-fatal stroke, but the difference is uncertain as no comparative analysis could be carried out [1 study, n = 62,299].

Economic

- No relevant economic evaluations were identified that compared the impact of high volume and low volume PPCI services on people with STEMI.

12.6 Recommendations and link to evidence

Recommendations	**The current recommendations can be found at: www.nice.org.uk/guidance/ng185**
Relative values of different outcomes	For this review question the GDG considered the outcomes of mortality (both all-cause and cardiovascular) and stroke as critical to decision-making. Major and minor bleeding were considered important to decision-making. No data were found for cardiovascular mortality, minor bleeding, myocardial reinfarction, heart failure, unplanned revascularisation, length of hospital stay or quality of life.
Trade-off between clinical benefits and harms	The GDG were interested to know whether there is a relationship between PPCI service volume and procedural outcome, and whether there are particular volume thresholds above which additional volume has no impact on outcome. Understanding whether there are specific PPCI service volume thresholds with regard to procedural outcomes is critical for healthcare planning and commissioning of services. The evidence in this review suggests that low PPCI service procedural volume is associated with worse clinical outcomes, including a higher risk of death, stroke, and bleeding. The available data only extend up to PPCI service volumes of around 70 procedures per annum and the relationship with outcome at higher volumes is uncertain. 2010 UK audit data reports that of 69 PPCI centres offering a routine service 22 carried out fewer than 70 procedures (17 did fewer than 50, and 28 did

	fewer than 100).[182] The data in the review were of limited quality and interpretation is confounded by potential differences in baseline characteristics of people treated at low and high volume centres. For example, high risk people might have been preferentially referred for PPCI at low volume centres, or at centres that use fibrinolysis as the preferred reperfusion strategy, and such imbalances could contribute to the reported differences in outcome. The GDG concluded that there is some evidence of an inverse relationship between PPCI service volume and outcome for procedural volumes up to around 70 per annum. The GDG considered that commissioners of PPCI services should be aware that outcomes are strongly related to how quickly PPCI can be delivered and can be influenced by procedural volumes of the PPCI centre.
Economic considerations	No health economic evidence was found for this question. The GDG agreed that it is not possible to make generalisations about the cost effectiveness of PPCI service provision based on volume of PPCI cases alone. Hospitals that carry out PPCI also use the same facilities (cardiac catheter laboratories) and staff members to carry out other PCI and angiography procedures. The time, and hence the cost, of staff and facilities will be divided between PPCI and other PCI procedures. A PPCI service may increase costs per procedure because of differences in use of consumables and length of hospital stay, and because of the need to provide and sustain the service 24 hours per day, 365 days per year. At low volume centres cost per procedure would increase if the total number of angiography, PCI and PPCI procedures are too low to fully utilise a single cardiac catheter laboratory and staff team. Centres that carry out high volumes of PCI procedures may also make more efficient use of catheter laboratory time and have somewhat lower costs for interventional equipment due to bulk purchasing discounts. There is little reason to think that there would be any other substantial economies of scale and the overall effect of providing a PPCI service on cost is therefore likely to depend on the relative sizes of the PPCI and PCI services. Consequently, the GDG concluded that the cost of providing PPCI is highly dependent on the local context and is unlikely to vary systematically with PPCI volume. The clinical evidence suggests that centres with very low volumes of PPCI may have decreased effectiveness. If this is the case in the UK, and assuming that costs are similar regardless of service volume, very low volume centres could be somewhat less cost effective than larger volume centres. Elsewhere in this guideline the GDG recommended that PPCI should be delivered as quickly as possible, and within 120 minutes of the time when fibrinolysis could have been given (see chapter 5). Fibrinolysis may therefore be the preferred reperfusion strategy for people who present with acute STEMI in areas where travel times to the nearest PPCI service are relatively long. Commissioners of healthcare will need to balance the requirement for timely access to the preferred reperfusion strategy (PPCI) against the need to commission services with sufficient volume to sustain effective PPCI service delivery, especially in geographically remote or sparsely populated regions. If the population is already well-served by existing 24-hour PPCI services cost effectiveness would need to be considered before additional low volume PPCI services could be justified.
Quality of evidence	Evidence supporting a relationship between service volume and outcome of PPCI is derived from 5 registry studies conducted in the USA.[49,100,165,185,282]. Data from the UK MINAP registry were not included in this review as there were no outcomes reported relevant to the review protocol.[326] All studies were graded as very low quality. Magid, Canto and Every all published data in 2000 (from data collection periods predating this period) and treatment strategies have evolved since then (for example, with the widespread use of bare metal and drug-eluting stents[72]). Two of the studies, Magid

	and Canto, are based on data from the National Registry of Myocardial Infarction (NRMI) with dates for data collection covering the same period 1994–98 and 1994–99 and written by many of the same authors. It is not clear whether some of the same data are included in both papers. A third paper by Every is also written by many of the same authors but involves a different, smaller American registry based on Medicare for the period 1994–95. The GDG noted that Magid et al reported data that is unadjusted for potential confounders and that both Magid and Canto include people from voluntary registry participation and hence have potential selection bias. Only Kumbhani, Srinivas and Canto had data suitable for meta-analysis, Magid and Every reporting descriptive data in the form of percentages only. The number of PPCIs in the low volume centres in the NRMI registries was between 5 and 16 per annum, but Every et al[100] point out that at that time 82% of US hospitals performed fewer than 3 PPCIs per annum. Many hospitals in the studies used both fibrinolysis and primary angioplasty as treatment for STEMI. In the low volume hospitals fibrinolysis was the main treatment modality but the ratio was reversed in the high volume hospitals. The definitions of high and low volume varied across studies, but were substantially lower than volumes at most current UK PPCI centres. In 2011 PPCI was carried out at 99 UK hospitals, of which 81 did over 100 procedures and 91 did over 50 procedures.[182]
Other considerations	Data from the British Cardiovascular Intervention Society (BCIS) audit [182] show that 25% of all PCI in England and Wales in 2011 was PPCI, equivalent to rates of 362 per million population for England and 175 per million for Wales. Data from MINAP suggest that 31% of people presenting with acute STEMI in 2011/12 did not receive any reperfusion therapy.[204]

13 Pre-hospital versus in-hospital fibrinolysis

13.1 Introduction

Fibrinolytic drugs are administered to people with acute STEMI to dissipate occlusive coronary artery thrombus (blood clot), restore coronary artery blood flow, and limit the extent of heart muscle damage. Fibrinolytic drugs act by converting the pro-enzyme plasminogen to active plasmin, which digests the fibrin molecules that provide blood clots with structural integrity. Because of these actions, fibrinolytic drugs are also called are 'plasminogen activators' or 'thrombolytic drugs'.

Streptokinase was the first fibrinolytic agent to be used for the treatment of STEMI. Streptokinase is a non-fibrin-selective drug that activates plasminogen bound to fibrin in clot but also in the circulating blood. Streptokinase is therefore associated with transient systemic plasminogen depletion and a fibrinolytic state associated with a risk of bleeding. Fibrin-specific fibrinolytic agents (alteplase, reteplase, tenecteplase) preferentially activate plasminogen bound to fibrin with less effect on circulating plasminogen. Fibrin-specific agents have advantages over streptokinase,[300] and have largely replaced streptokinase in the UK.

Fibrinolysis has been the mainstay of reperfusion therapy for STEMI for several decades, but recently PPCI has emerged as the reperfusion strategy of choice provided it can be delivered in a timely fashion. The roll-out of PPCI services in the UK has led to a rapid decline in the use of fibrinolytic therapy and it is likely that a small and diminishing number of people will be offered fibrinolysis in the future.[204,242] Nevertheless, fibrinolysis is likely to remain the reperfusion strategy of choice for a small proportion of the population in whom PPCI cannot be delivered within recommended timescales.

Pooled data from RCTs suggest a curvilinear relationship between the early mortality benefit of fibrinolysis and the delay from symptom onset to treatment of acute STEMI, with much greater benefit in people with short delays to treatment. Over 60 deaths per 1000 treated are prevented if fibrinolysis is delivered within 1 hour of symptom onset, but this declines to fewer than 20 deaths prevented with delays greater than 6 hours.[32] Systems to reduce delays in the administration of fibrinolysis have therefore been developed, including the delivery of fibrinolysis by bolus injection (reteplase and tenecteplase) to people with acute STEMI in the pre-hospital setting ('pre-hospital fibrinolysis').[301] According to the latest report from the Myocardial Ischaemia National Audit Project (MINAP), in 2011/12 only 1625 people were given fibrinolysis in England and Wales (5% of all people presenting with acute STEMI), of which 24% was administered in the pre-hospital setting and 74% in the in-hospital setting (location of treatment was unknown in 2%).[204]

Pre-hospital administration of a fibrinolytic may shorten the time to treatment and potentially improve outcome. On the other hand, in the UK pre-hospital care of people with acute STEMI is delivered almost exclusively by paramedics, who require appropriate training to ensure that pre-hospital fibrinolysis can be administered safely and effectively to people with acute STEMI.[255] This chapter reviews the evidence to establish the clinical and cost effectiveness of pre-hospital fibrinolysis relative to in-hospital fibrinolysis.

13.2 Review question: What is the clinical and cost effectiveness of pre-hospital versus in-hospital fibrinolysis?

For full details see review protocol in Appendix C.

13.3 Clinical evidence

Six studies, reported in 9 papers, were identified.[18,36,43,53,164,190,263,269,324] These are summarised in Table 51 and the clinical GRADE evidence profile in Table 52. See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

Table 51: Summary of studies included in the review

Study	Intervention/comparison	Population	Outcomes	Angiography/ angioplasty	Timing
Barbash et al 1990[18]; Roth et al 1990[263]	120 mg recombinant tissue plasminogen activator (rt-PA) administered pre-hospital by mobile intensive care unit staffed by physician and paramedic or following admission to a coronary care unit.	n = 191 Mean age, male: 161; female: 62 years	• In-hospital mortality • Mortality at 60 days • Mortality at 24 months • In-hospital bleeding • Myocardial reinfarction • Length of stay • Heart failure	Angiography at 72 hours after treatment unless necessitated earlier.	Median time from symptoms to treatment: • Pre-hospital group 96 minutes ± 36 minutes • In-hospital group 132 minutes ± 42 minutes ($p < 0.0001$)
McAleer at al 2006[190]	1.5 million units streptokinase in 100ml of N saline either pre-hospital (administered by SHO level physician) or in coronary care unit.	n = 248 Mean age, male: 61 years; female: 60.5 years	• Mortality at 30 days, 1 year, 2 years, 5 years. • Minor bleeding • Major bleeding	Not reported.	Mean delay time to treatment: • Pre-hospital 136 minutes • In-hospital 196 minutes ($p < 0.00001$)
Schofer et al 1990[269]	Urokinase (2 million units intravenous) administered by ambulance doctor pre-hospital or following hospital admission. 1000 U/hour heparin followed second injection.	n = 78 Mean age, pre-hospital: 57 years, in-hospital: 55 years	• Bleeding • Pre-hospital mortality • In-hospital bleeding • In-hospital death • Reinfarction	Angiography before discharge unless clinically necessitated earlier.	Mean time to treatment: • Pre-hospital group 85.1 minutes • In-hospital 137 ± 50 minutes ($p < 0.0005$)
Weaver 1993[324]; Brouwer 1996[43] MITI trial	350 mg aspirin and 100 mg alteplase administered either pre-hospital by paramedic (suitability discussed by phone/radio with physician at hospital), or on arrival at hospital.	n = 360 Mean age, pre-hospital: 57 years, in-hospital: 59 years	• Mortality • Heart failure	Angiography and angioplasty numbers reported.	Median time to treatment: • Pre-hospital group 77 minutes (56 and 101; 25th and 75th percentiles) • In-hospital group 110 minutes (85 and 140; 25th and 75th percentiles) for hospital group ($p < 0.0001$).
Castaigne 1989[53]	30 units anisoylated plasminogen streptokinase activator complex (APSAC) pre-hospital by mobile care unit	n = 100 Mean age, male: 55 years; female: 63	• Mortality pre-hospital and in-hospital	n = 30 between 1 and 10 days. n = 18 CABG between 1 and	Median time from symptoms to treatment • Pre-hospital group 131 minutes

Study	Intervention/comparison	Population	Outcomes	Angiography/ angioplasty	Timing
	physician or at hospital	years		15 days.	• In-hospital 180 minutes
Kuhn et al 1993[164]; Boissel, J. 1995[36] EMIP	30 units of anistreplase administered by emergency medical physician pre-hospital, or after hospital admission.	n = 5469 87% STEMI	• Mortality at 30 days • Stroke • Cardiac mortality (30 days)	Not reported.	Median time from symptoms to treatment: • Pre-hospital group 130 minutes • In-hospital 190 minutes
Note; where there is more than 1 reference for an included study, this is because it included a published study protocols, or, studies have reported separate outcomes in different publications.					

Table 52: Clinical evidence profile: pre-hospital versus in-hospital fibrinolysis

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Pre-hospital fibrinolysis	In-hospital fibrinolysis	Relative (95% CI)	Absolute	Quality	Importance
Pre-hospital mortality[36,53,164,269]												
3	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Serious (b)	None	37/2847 (1.3%)	25/2793 (0.9%)	RR 1.44 (0.87 to 2.39)	4 more per 1000 (from 1 fewer to 12 more)	LOW	CRITICAL
All-cause mortality (short-term) (follow-up 30 days) [18,36,43,53,164,190,263,269,324]												
6	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Serious (c)	None	287/3176 (9%)	350/3188 (11%)	RR 0.83 (0.72 to 0.97)	19 fewer per 1000 (from 3 fewer to 31 fewer)	LOW	CRITICAL
All-cause mortality (longer-term) (follow-up 6 months) [43,190,324]												
2	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision	None	18/257 (7%)	54/351 (15.4%)	RR 0.52 (0.31 to 0.88)	74 fewer per 1000 (from 18 fewer to 106 fewer)	MODERATE	CRITICAL
Cardiac mortality (short-term) (follow-up 30 days) [36,164]												
1	Randomised	Serious	No serious	No serious	Serious (c)	None	228/2750	267/2719	RR 0.84	16 fewer	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Pre-hospital fibrinolysis**	**In-hospital fibrinolysis**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
	trials	(a)	inconsistency	indirectness			(8.3%)	(9.8%)	(0.71 to 1)	per 1000 (from 28 fewer to 0 more)		
Stroke (short-term) (follow-up 30 days) [36,43,164,324]												
2	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Serious (d)	None	90/2925 (3.1%)	86/2904 (3%)	RR 1.04 (0.78 to 1.39)	1 more per 1000 (from 7 fewer to 12 more)	LOW	CRITICAL
Intracranial bleeding												
0	No evidence available					None	-	-	-	-		CRITICAL
Quality of life												
0	No evidence available					None	-	-	-	-		CRITICAL
Myocardial reinfarction (short-term) (follow-up 30 days) [18,263,269]												
2	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Very serious (d)	None	14/112 (12.5%)	11/82 (13.4%)	RR 0.91 (0.43 to 1.93)	12 fewer per 1000 (from 76 fewer to 125 more)	VERY LOW	IMPORTANT
Heart failure (short-term) (follow-up 30 days)[18,43,263,324]												
2	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Very serious (d)	None	17/247 (6.9%)	20/229 (8.7%)	RR 0.76 (0.41 to 1.39)	21 fewer per 1000 (from 52 fewer to 34 more)	VERY LOW	IMPORTANT
Unplanned revascularisation												
0	No evidence available					None	-	-	-	-		IMPORTANT
Bleeding – major and minor (short-term) (follow-up 30 days) [18,190,269]												

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Pre-hospital fibrinolysis**	**In-hospital fibrinolysis**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
3	Randomised trials	Serious (a)	Serious (e)	No serious indirectness	No serious imprecision	None	31/194 (16%)	15/258 (5.8%)	RR 2.78 (1.58 to 4.9)	103 more per 1000 (from 34 more to 227 more)	LOW	IMPORTANT
Subsequent revascularisation												
0	No evidence available					None	-	-	-	-		IMPORTANT
Length of hospital stay, days (better indicated by lower values) [18,263]												
1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision	None	0	-	-	MD 3 higher (0 to 0 higher)	MODERATE	IMPORTANT

a)Unclear allocation concealment in >50% of evidence.
b) Confidence interval crosses default minimum important difference of 1.25 and line of no effect.
c) Confidence interval crosses default minimum important difference of 0.75 and line of no effect.
d) Confidence interval crosses default minimum important differences of 0.75 and 1.25 and line of no effect .
e) Unexplained heterogeneity (I2 >50%).

13.4 Economic evidence

No relevant economic evaluations were identified that compared pre-hospital fibrinolysis with in-hospital fibrinolysis in people with STEMI.

Two economic evaluations relating to this review question were selectively excluded due to a combination of limited applicability and methodological limitations.[310,311] These are summarised in Appendix K, with reasons for exclusion given. See also the economic article selection flow diagram in Appendix E.

13.5 Evidence statements

Clinical

- Low quality evidence suggested that in-hospital fibrinolysis is potentially more clinically effective when compared to pre-hospital fibrinolysis at reducing incidence of pre-hospital mortality [3 studies, n = 5640].
- Low quality evidence suggested that there may be no clinical difference between in-hospital fibrinolysis when compared to pre-hospital fibrinolysis at reducing short-term mortality, but the direction of the estimate of effect favoured pre-hospital fibrinolysis [6 studies, n = 6364].
- Moderate quality evidence showed that that pre-hospital fibrinolysis is more effective when compared to in-hospital fibrinolysis at reducing longer-term all-cause mortality, but the effect size is too small to be clinically important [2 studies, n = 608].
- Low quality evidence suggested that there may be no clinical difference between pre-hospital fibrinolysis when compared to in-hospital fibrinolysis at reducing short-term cardiac mortality, but the direction of the estimate of effect favoured pre-hospital fibrinolysis [1 study, n = 5469].
- Very low quality evidence suggested that there may be no clinical difference between pre-hospital fibrinolysis and in-hospital fibrinolysis at reducing short-term myocardial reinfarction, but the direction of the estimate of effect could favour either intervention [2 studies, n = 194].
- Very low quality evidence suggested that there may be no clinical difference between pre-hospital fibrinolysis and in-hospital fibrinolysis at reducing short-term heart failure, but the direction of the estimate of effect could favour either intervention [2 studies, n = 476].
- Low quality evidence suggested that there may be no clinical difference between pre-hospital fibrinolysis when compared to in-hospital fibrinolysis at short-term stroke, but the direction of the estimate of effect favoured in-hospital fibrinolysis [2 studies, n = 5829].
- Low quality evidence showed that in-hospital fibrinolysis is more clinically effective when compared to pre-hospital fibrinolysis at reducing short-term bleeding [3 studies, n = 452].

Economic

- No relevant economic evaluations were identified that compared pre-hospital fibrinolysis with in-hospital fibrinolysis in people with STEMI.

13.6 Recommendations and link to evidence

Recommendations	The current recommendations can be found at: www.nice.org.uk/guidance/ng185
Relative values of different outcomes	For this review question the GDG considered the outcomes of all-cause mortality, cardiovascular mortality, stroke, intracranial bleeding, and quality of life as critical to decision-making. Myocardial reinfarction, heart failure, and major and minor bleeding were considered important, and length of hospital stay as less important to decision-making. No data were found for intracranial bleeding, subsequent revascularisation and quality of life.
Trade-off between clinical benefits and harms	The available evidence suggests that pre-hospital fibrinolysis is associated with lower all-cause and cardiac mortality at 30 days and lower all-cause mortality at 6 months, when compared with in-hospital fibrinolysis. There was no difference in the rates of pre-hospital mortality, stroke, reinfarction, or heart failure between the 2 treatment strategies. Pre-hospital fibrinolysis was associated with a significant increase in the combined rate of major and minor bleeding but no evidence was available for intracranial bleeding. Overall there was a 1.9% absolute reduction in 30-day all-cause mortality and an 8.4% reduction in 6-month all-cause mortality, but these benefits were partially offset by an absolute increase in short-term major and minor bleeding of 10.2%. The GDG noted that 6-month mortality data were available for less than 10% of the total number of participants enrolled in the trials in this review, and the confidence intervals for the estimate of treatment effect for this outcome were very wide. Nevertheless, in the trials in this review pre-hospital fibrinolysis was administered around 30–60 minutes earlier than in-hospital fibrinolysis, and the GDG considered that this difference in the time to treatment is a plausible explanation for the mortality advantage associated with pre-hospital treatment. The GDG also noted that the evidence for major or minor bleeding was based on a relatively small number of participants and the confidence intervals for this treatment effect were very wide. The GDG was uncertain why pre-hospital administration of a fibrinolytic agent might increase the risk of bleeding and questioned the biological plausibility of this finding. The GDG agreed that the most important factor in determining the outcome of fibrinolysis is the delay to treatment. The location of treatment was considered less important, provided that systems are in place to ensure that fibrinolysis is administered appropriately and safely to people with acute STEMI. The GDG concluded that reperfusion services that include a fibrinolytic strategy should develop systems to minimise treatment delays. These systems should include pre-hospital fibrinolysis where feasible, supported by continuous audit to ensure that the service operates safely and effectively.
Economic considerations	No health economic evidence was found for this question. The GDG considered that the additional resource use associated with pre-hospital fibrinolysis relative to in-hospital fibrinolysis will depend on how reperfusion services are configured. The delivery of pre-hospital fibrinolysis will be associated with ongoing ambulance service training costs. An optimal pre-hospital fibrinolysis service might also require equipment to allow transmission of electrocardiograms from ambulances to hospital clinicians for decision support (if this facility is not already available in ambulances for other reasons). Such equipment costs would include a modem in each ambulance and an annual subscription for use.

	The costs of delivering pre-hospital fibrinolysis relative to in-hospital fibrinolysis will depend on the service configuration. A service that requires telemetry of the ECG and in-hospital decision support by an experienced clinician before pre-hospital fibrinolysis can be delivered by a paramedic will have high equipment costs, but comparatively low paramedic training costs. If the relevant technology (a modem for telemetry) is installed in an ambulance, it can also be used for other conditions and so the equipment costs may not all be attributable to pre-hospital fibrinolysis alone. On the other hand, if paramedics are trained to make a diagnosis of acute STEMI and deliver pre-hospital fibrinolysis independently, training costs will be higher but additional equipment would not be needed. There are examples of both of these approaches in the UK. While clinical evidence suggests that pre-hospital fibrinolysis will have a net health benefit over in-hospital fibrinolysis, the costs, and therefore cost effectiveness, of this strategy will vary depending on specific local circumstances. For example, the ambulance service training and equipment costs are likely to be constant irrespective of the number of people treated. The cost per person of providing a pre-hospital fibrinolysis service will therefore be lower, the greater the proportion of the STEMI population that is treated with pre-hospital fibrinolysis. As the number of cases treated with pre-hospital fibrinolysis diminishes, the cost per person will increase and the cost effectiveness of pre-hospital fibrinolysis will reduce. Fibrinolysis should only be used where it is not feasible to carry out PPCI within 120 minutes of the time fibrinolysis could have been given (see chapter 5). In an area where a significant proportion of people may need to receive fibrinolysis, pre-hospital administration may be cost effective; however in an area where only a very small proportion of people are likely to be potentially eligible for fibrinolysis it may not be cost effective to implement a pre-hospital treatment system. In-hospital fibrinolysis will only be cost effective compared to PPCI if a hospital providing fibrinolysis can be reached rapidly, but travel time to the nearest hospital providing PPCI is relatively long. To deliver PPCI within 120 minutes of when fibrinolysis could have been given, the transport time to reach the nearest PPCI centre could be around 105 minutes longer than the transport time to reach the nearest hospital capable of delivering in-hospital fibrinolysis. Transport times of this length between hospitals with and without PPCI services are uncommon in England and Wales, and are most likely to be found in areas where provision of a pre-hospital fibrinolysis service is likely to be cost effective. The GDG therefore expects the situations where in-hospital fibrinolysis is appropriate to be very rare. The GDG were unable to conclude whether pre-hospital fibrinolysis is cost effective in all situations, but agreed that cost effectiveness must be considered locally.
Quality of evidence	The trials included in this review are all relatively old, with publication dates ranging from 1989 to 2006. The EMIP trial was relatively large with 5469 participants but the other trials in this review are relatively small and underpowered for clinically important outcomes. Several of the trials did not report outcomes that the GDG considered to be critical to decision-making. The trials used a number of different fibrinolytic treatments (see chapter 17), some of which are no longer available and some of which are not recommended by NICE.[210] None of the trials used reteplase or tenecteplase, which are fibrin-specific fibrinolytic agents that are administered by bolus injection and are recommended for use in the pre-hospital setting.[210,301] The healthcare professionals responsible for administering fibrinolysis varied (between paramedics, physicians and general practitioners) across trials reflecting practice in different parts of the world. In the UK, pre-hospital fibrinolysis is generally

	delivered by paramedics. The potential risks and benefits of pre-hospital fibrinolysis may be influenced by the varying clinical skills of the staff responsible for initiating treatment. Consistent with current practice, all trials included in this review used an electrocardiographic diagnosis of STEMI to confirm entry into the trial. The GREAT trial did not require an electrocardiographic diagnosis[257] and only 55% of the people subsequently had a confirmed diagnosis of STEMI. For this reason GREAT was excluded from the evidence review. Two economic analyses were identified relevant to pre-hospital versus in-hospital fibrinolysis but both of these related to the GREAT trial and were therefore also excluded.[310,311]
Other considerations	The recommendation based on the evidence review in this chapter impacts a small and diminishing number of people who receive fibrinolysis.

14 Use of antithrombin as an adjunct to fibrinolysis

14.1 Introduction

Treatment of people with acute STEMI aims to rapidly restore normal coronary blood flow to the infarct-related artery, thus preserving left ventricular function and improving early survival. Infarct-related artery patency may be achieved and sustained by reperfusion therapy (fibrinolysis or PPCI) and a combination of conjunctive antiplatelet and antithrombin medication. However, combinations of antithrombotic agents increase the risk of bleeding, including intracranial bleeding.

Fibrinolytic agents act by converting plasminogen to active plasmin, which lyses fibrin within the blood clot. Non-specific fibrinolytic agents (streptokinase) also cause systemic depletion of fibrinogen and other clotting factors, and production of fibrinogen degradation products that cause a systemic coagulopathy. Fibrin-specific agents (alteplase, reteplase, tenecteplase) are relatively inactive in the absence of fibrin, with less effect on systemic fibrinogen and the coagulation system. On the other hand, fibrinolytic agents also have procoagulant effects mediated by activation of platelets and thrombin. In particular, exposure of clot-bound thrombin may act as a focus platelet activation, thrombin generation and further thrombosis. For these reasons there has been considerable research interest in the role of conjunctive antithrombotic medication in people with acute STEMI who are treated with fibrinolysis.

The benefits of aspirin in people with acute myocardial infarction who are treated with fibrinolysis were recognised several decades ago[143] and in current practice aspirin is administered routinely to all people with STEMI. Conjunctive administration of heparin in the hours and days after fibrinolysis promotes coronary artery patency,[69,308] but evidence of long-term clinical benefit is not compelling and has to be balanced against an increase in risk of bleeding.[60,186] Nevertheless, use of heparin in conjunction with fibrin-specific fibrinolytic agents is part of established clinical practice.

NICE technology appraisal 52 (Guidance on the use of drugs for early fibrinolysis in the treatment of acute myocardial infarction) was published in 2002, and states that heparin should be given with all fibrin-specific fibrinolytic drugs. TA52 did not recommend use of heparin with streptokinase because of the systemic anticoagulant effects of non-specific fibrinolytic drugs.[210] Streptokinase is not recommended for pre-hospital fibrinolysis and in the UK is rarely used in contemporary practice.

This guideline emphasises the importance of delivering reperfusion therapy as soon as possible after the onset of symptoms of STEMI and the relative benefits of pre-hospital versus in-hospital fibrinolysis are discussed in chapter 13. The GDG were concerned that people receiving pre-hospital fibrinolytic therapy may not be given an antithrombin until after arrival in hospital, and that this may adversely affect patient outcomes. This chapter therefore looked for evidence comparing pre-hospital and in-hospital administration of conjunctive antithrombin therapy in people with acute STEMI treated by pre-hospital fibrinolysis.

14.2 Review question: Does administration of antithrombin treatment at the same time as pre-hospital fibrinolysis improve outcomes compared to administration of pre-hospital fibrinolysis alone?

14.3 Clinical evidence

A literature search identified 956 papers; none of these were RCTs that met the inclusion criteria of the review protocol. The search was not limited by publication date.

14.4 Economic evidence

No relevant economic evaluations were identified that compared the administration of antithrombin treatment at the same time as pre-hospital fibrinolysis with administration of pre-hospital fibrinolysis alone in people with STEMI. See also the economic article selection flow diagram in Appendix E.

14.5 Evidence statements

Clinical

- No RCTs were identified that compared the administration of antithrombin treatment at the same time as pre-hospital fibrinolysis with administration of pre-hospital fibrinolysis alone.

Economic

- No relevant economic evaluations were identified that compared the administration of antithrombin treatment at the same time as pre-hospital fibrinolysis with administration of pre-hospital fibrinolysis alone in people with STEMI.

14.6 Recommendations and link to evidence

Recommendations	**The current recommendations can be found at: www.nice.org.uk/guidance/ng185**
Relative values of different outcomes	For this review question the GDG considered the outcomes of mortality, stroke, intracranial bleeding and major bleeding as critical to decision-making. Minor bleeding was considered less importance. However, no evidence was identified for any outcome.
Trade-off between clinical benefits and harms	No clinical or health economic evidence was found for this review. TA52 was published in 2002 and recommends administration of heparin with all fibrin-specific fibrinolytic agents, but not with streptokinase. TA52 also recommends the use of bolus fibrinolytic drugs (reteplase or tenecteplase) as the preferred option for people with acute STEMI who are treated by pre-hospital fibrinolysis. Since TA52 was published several randomised trials have compared the use of unfractionated heparin with alternative anticoagulants as conjunctive therapy in people treated with streptokinase or fibrin-specific fibrinolytic agents. These trials did not consider the use of pre-hospital fibrinolysis.[116,327,335] Moreover, the GDG noted that the roll-out of PPCI services across the UK has been associated with a rapid decrease in the number of people who are treated with fibrinolysis. In England in 2011/12 only 1625 people with acute STEMI were given fibrinolytic therapy, of whom 398 (24%) were treated in the ambulance.[204] This chapter therefore relates to small and diminishing proportion of the acute STEMI population, and early in the development of this guideline the GDG agreed that the choice of antithrombin as conjunctive therapy in people treated with fibrinolysis was not a high priority question. The GDG were therefore not able to comment on the choice of antithrombin as conjunctive therapy with a fibrin-specific, bolus fibrinolytic drug. The GDG considered that the benefits of antithrombin in people treated with reteplase or tenecteplase are likely to accrue, regardless of whether the fibrinolytic drug is delivered in the pre-hospital setting or in-hospital. The GDG

	agreed that delay in administration of an antithrombin until a person treated by pre-hospital fibrinolysis arrives in hospital may have deleterious effects. The GDG therefore made a consensus recommendation that people given a fibrin-specific fibrinolytic agent in the pre-hospital setting should also be given an antithrombin at the same time.
Economic considerations	No health economic evidence was found for this question. Additional resource use associated with pre-hospital antithrombin administration may include some additional drug costs and potentially ambulance service training costs. However, if ambulance services are already being trained to administer pre-hospital fibrinolysis the additional cost of training to administer an antithrombin is likely to be minimal. If antithrombin is more effective when given pre-hospital, any additional costs of delivering the intervention are likely to be offset in part or in full by reductions in downstream management costs. It was noted that there would be practical implementation costs of stocking ambulances with an antithrombin, but this was not considered likely to increase costs per person as appropriate stock rotation should minimise wastage. While acknowledging the lack of clinical and cost-effectiveness evidence to inform a judgement, the GDG concluded it likely that administration of antithrombin pre-hospital would be cost effective because the small additional cost of giving antithrombin pre-hospital is likely to be offset by reduced costs associated with reduced clinical events and improved health outcomes for the individual concerned.
Quality of evidence	No clinical or health economic evidence was found for this review and therefore the recommendation was based on GDG informal consensus opinion.
Other considerations	The Joint Royal Colleges Ambulance Liaison Committee (JRCALC) recommends pre-hospital fibrinolysis with reteplase or tenecteplase for eligible people with acute STEMI who are aged 80 years or less and present within 12 hours of symptom onset. People with left bundle branch block (LBBB) are considered eligible if the clinical picture strongly suggests acute myocardial infarction and preferably after senior clinical advice has been obtained via telemetry or telephone discussion. JRCALC recommends concomitant pre-hospital administration of an intravenous bolus of adjunctive unfractionated heparin.[301] While the GDG were not able to recommend a particular adjunctive antithrombin, they did consider the importance of offering the same drug in-hospital as had been given pre-hospital.

15 Rescue percutaneous coronary intervention

15.1 Introduction

ST-segment-elevation myocardial infarction (STEMI) is most often caused by thrombotic occlusion of a coronary artery, which results in irreversible heart muscle injury. Restoration of normal coronary blood flow by pharmacological intervention (fibrinolysis) or mechanical intervention (PPCI) limits the extent of heart muscle damage, improves clinical outcomes, and is the principal objective of reperfusion therapy.

Fibrinolytic agents and conjunctive aspirin have been shown to improve survival in people with STEMI.[32,143] The National Service Framework (NSF) for Coronary Heart Disease, published by the Department of Health (England) in 2000[78] set standards for the administration of fibrinolytic therapy to people with STEMI. At that time fibrinolysis was the reperfusion treatment of choice, but PPCI subsequently replaced fibrinolysis as the preferred reperfusion treatment with the proviso that it could be delivered in a timely fashion.[79,80]

As discussed elsewhere in this guideline (chapter 5), fibrinolysis may still be the preferred reperfusion strategy for individuals who present with STEMI in geographically remote areas and in whom reperfusion therapy will otherwise be delayed by transfer to a hospital capable of carrying out PPCI. Consequently, it is estimated that up to 5% of the population may still require fibrinolysis.[242] In the cardiac catheter laboratory coronary blood flow can be assessed angiographically as Thrombolysis In Myocardial Infarction (TIMI) Grade Flow 0–3[305]:

Grade	Definition
TIMI 0	No forward flow beyond a coronary occlusion
TIMI 1	Faint forward flow beyond the occlusion, and incomplete filling of the distal coronary territory
TIMI 2	Delayed or sluggish forward flow, but with complete filling of the distal coronary territory
TIMI 3	Normal forward flow which fills the distal coronary territory

Coronary artery patency (TIMI 2–3) is restored in up to 75% of people within 90 minutes of administration of fibrinolysis, but normal (TIMI 3) coronary blood flow is only achieved in around 50% of cases. Restoration of normal (TIMI 3) flow after fibrinolytic therapy is associated with a mortality benefit but lesser degrees of coronary reperfusion after (TIMI 0–2) do not improve survival.[300,320] Failed fibrinolysis, defined as < 50% ST-segment resolution on a follow-up electrocardiogram 60–90 minutes after fibrinolysis has been reported in 40.3% of people.[162]

In clinical practice identification of people with infarct artery patency (reperfusion) after fibrinolysis is problematic. Complete or partial (> 50%) resolution of ST-segment elevation on an electrocardiogram recorded 60–90 minutes after the start of treatment is a relatively reliable non-invasive surrogate marker of reperfusion but persistent ST-segment elevation is a poor predictor of infarct artery patency.[70,118] Optimal management of people in whom ECG evidence of reperfusion is not achieved has been controversial. Options that have been proposed include conservative management, a further dose of fibrinolysis, or immediate referral for coronary angiography and PCI to restore coronary blood flow ('rescue PCI'). PCI undertaken for failed coronary reperfusion after fibrinolysis requires emergency transfer of the patient to an interventional cardiac catheter laboratory. This chapter reviews evidence for the use of these strategies in people who have electrocardiographic evidence of failed fibrinolytic therapy 60–90 minutes after treatment.

15.2 Review question: What is the clinical and cost effectiveness of rescue PCI, repeated fibrinolysis or conservative management compared to each other in people with STEMI who fail to reperfuse after fibrinolytic therapy?

15.3 Clinical evidence

A literature search identified 7 RCTs which addressed the review question and were consequently included in this review (Table 53). Since only 2 RCTs deployed ≥ 50% stents in eligible participants (REACT 2005[52,113] and MERLIN[166,290,291]) and only 2 began recruiting after 1996 (REACT 2005[52,113] and MERLIN[166,290,291]) all studies published after 1990 were considered.

No study assessed the relative benefits of rescue PCI, conservative therapy and repeat fibrinolysis exclusively among people with renal dysfunction or diabetes, or in participants aged > 70 years. In addition, none of the included studies stratified participants according to age, or the presence of diabetes or renal dysfunction, or stated in advance that they would analyse any of these subgroups separately.

Bleeding rates were recorded according to their original study definition. Bleeding episodes were categorised by the GDG as major or minor on a case by case basis when studies did not define major and minor bleeding and sufficient information was recorded within the study to make this distinction. It was unclear whether bleeding episodes in the MERLIN,[166,290,291] Belenkie[20] and Mounsey[203] studies were major or minor, but the GDG agreed that these studies should be included; consequently a sensitivity analysis was undertaken, investigating each scenario. Evidence is reported in the GRADE profiles below. See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

Table 53: Summary of included RCTs

Study	Enrolment	Study design	n	Inclusion criteria	Stents Rescue PCI patients	GPIs Rescue PCI patients	Symptom onset to rescue PCI (minutes)
REACT (2005)[52,113]	Dec 1999 – Mar 2004	Rescue PCI vs CT vs RF	427	< 50% ST-segment resolution at 90 minutes and < TIMI 3	68.5%	43.4%	414 (350–505) (a)
MERLIN (2004)[166,290,291]	Feb 1999 – June 2002	Rescue PCI vs CT	307	< 50% ST-segment resolution at 60 minutes	50.3%	3.3%	327 ± 121
RESCUE II (2000)[96]	Sep 1995 – Jan 1998	Rescue PCI vs CT	29	TIMI 2	29%	7%	294 ± 252
RESCUE I (1994)[95]	Jan 1990 – Mar 1993	Rescue PCI vs CT	151	TIMI 0/1	0%*	0%*	270 ± 110
Belenkie et al. (1992)[20]	Aug 1986 – Oct 1988	Rescue PCI vs CT	28	TIMI 0	0%*	0%*	257 ± 57
Sarullo et al. (2000)[266]	Jan 1995– Dec 1997	RF vs CT	90	< 50% ST-segment resolution at 120 minutes	_	_	–

Study	Enrolment	Study design	n	Inclusion criteria	Stents Rescue PCI patients	GPIs Rescue PCI patients	Symptom onset to rescue PCI (minutes)
Mounsey et al. (1995) [203]	No details	RF vs CT	37	< 25% ST-segment resolution at 90 minutes	_	_	–

CT: conservative therapy; RF: repeated fibrinolysis.
(a) Interquartile range.
**Although the proportion of stents deployed wasn't documented in these studies, the GDG concluded that these were balloon angiography studies based on their enrolment dates.*

Table 54: Summary of subgroups

Study	Age (mean years)	Male	Diabetes mellitus	Renal dysfunction
REACT[52,113]	61 Exclusion criteria: Participants aged > 85 years	79%	14%	No details
MERLIN[166,290,291]	63	73%	13%	No details
RESCUE II[96]	63	93%	21%	No details
RESCUE I[95]	59	82%	14%	No details
Belenkie et al[20]	60 Exclusion criteria: Participants aged ≥ 76 years	47%	No details	No details
Sarullo et al[266]	57 Exclusion criteria: Participants aged ≥ 70 years	77%	31%	No details
Mounsey et al[203]	63	65%	No details	No details

Table 55: RCTs and outcomes included in the review

Study	Study design	Outcomes	Follow-up period
REACT*[52,113]	Rescue PCI vs CT	Mortality	30 days, 6 months, 12 months†, 4.4 years
		Reinfarction	30 days, 6 months
		Heart failure	30 days, 6 months, 12 months†
		Stroke	30 days, 6 months, 12 months†
		Bleeding	In-hospital
		Revascularisation§	6 months, 12 months
MERLIN[166,290,291]	Rescue PCI vs CT	Mortality	30 days, 6 months, 12 months†, 3 years
		Reinfarction	30 days, 6 months, 12 months†, 3 years†
		Heart failure	30 days, 6 months, 12 months†, 3 years†
		Stroke	30 days, 6 months, 12 months†, 3 years†
		Bleeding	In-hospital
			30 days, 6 months, 12 months†, 3

Study	Study design	Outcomes	Follow-up period
		Revascularisation§	years†
			In-hospital
		Hospital stay	
RESCUE II[96]	Rescue PCI vs CT	Mortality	30 days, 12 months
		Reinfarction	In-hospital
		Revascularisation§	In-hospital, 12 months
		Hospital stay	In-hospital
RESCUE I[95]	Rescue PCI vs CT	Mortality	30 days
		Heart failure	30 days
Belenkie et al[20]	Rescue PCI vs CT	Mortality	In-hospital
REACT*[52,113]	CT vs RF	Mortality	6 months†, 12 months†, 4.4 years
			6 months
		Reinfarction	6 months, 12 months†
		Heart failure	6 months, 12 months†
		Stroke	In-hospital
		Bleeding	6 months†, 12 months
		Revascularisation§	
Sarullo et al[266]	RF vs CT	Mortality	In-hospital
		Reinfarction	In-hospital
		Revascularisation§	In-hospital
		Bleeding	In-hospital
Mounsey et al[203]	RF vs CT	Mortality	6 weeks
REACT*[52,113]	Rescue PCI vs CT	Mortality	6 months†, 12 months†, 4.4 years
			6 months
		Reinfarction	6 months, 12 months†
		Heart failure	6 months, 12 months†
		Stroke	In-hospital
		Bleeding	6 months†, 12 months
		Revascularisation§	

CT; conservative therapy, RF; repeated fibrinolysis.
**REACT is a 3-way comparator study: rescue PCI versus RT versus CT. †Data reported in evidence tables but not included in meta-analysis §Unplanned revascularisation.*

Table 56: Summary of end point definitions

End point	Study	Definition
Reinfarction	REACT[52,113]	During index admission: further chest pain lasting more than 30 minutes and accompanied by new electrocardiographic changes (new Q waves above 0.04 second or ST-segment elevation above 0.1 mV in 2 leads for more than 30 minutes), further enzyme rise, or both Late chest pain lasting more than 30 minutes and accompanied by new electrocardiographic changes, enzyme rise, or both
	MERLIN[166,290,291]	Repeat episode of ischaemic chest pain after recovery from the initial event, associated with typical ST-segment re-elevation on the ECG and lasting for more than 30 minutes despite opiate and nitrate therapy.
	RESCUE II[96]	Not defined
	Sarullo et al[266]	Not defined; recorded in this review as non-fatal events
Heart	REACT[52,1	Early heart failure: any new-onset cardiogenic shock or heart failure with

End point	Study	Definition
failure	[13]	pulmonary oedema that is resistant to medical therapy and that occurs during the index admission and after randomisation Late heart failure: admission to hospital for treatment of heart failure (New York Heart Association class III or IV)
	MERLIN[1] [66,290,291]	Requirement for diuretic treatment in the presence of typical chest X-ray characteristics, or auscultatory crackles extending at least one-third of the way up the lung fields without a previous history of chronic pulmonary disease, or A third heart sound with persistent tachycardia
	RESCUE I[95]	New York Heart Association functional class III or IV
Stroke	REACT[52,1] [13]	A new focal neurologic deficit of presumed vascular cause persisting for more than 24 hours and without evidence of a nonvascular cause according to a neurologic imaging study
	MERLIN[1] [66,290,291]	Any new neurologic deficit lasting more than 24 hours; computed axial tomography was performed when possible
Unplanned revascularisation	REACT[52,1] [13]	Not defined; with no mandated angiography (except for the rescue procedure) all revascularisation was clinically driven
	MERLIN[1] [66,290,291]	Any catheter-based or surgical intervention in the conservative group and any additional revascularisation procedure in the rescue group that was not planned after the initial coronary angiogram
	RESCUE II[96]	Not defined; recorded in this review as further intervention (CABG or PCI)
	Sarullo et al[266]	Not defined; recorded in this review as urgent PCI or CABG
Major bleed	REACT[52,1] [13]	Modified TIMI: Decrease in haemoglobin of at least 5 g/dl during index admission, severe bleeding event (for example intracranial haemorrhage, haemopericardium, or haemodynamic compromise, with or without transfusion), or both
	Sarullo et al[266]	Not defined
Minor bleed	REACT[52,1] [13]	Modified TIMI: Observed bleeding during index admission, with or without a decrease in haemoglobin of at least 5 g/dl, with or without transfusion
	MERLIN[1] [66,290,291]	Did not define bleeding or distinguish between major and minor bleeding. Recorded in this review as transfusions. Transfusion was reserved for those with a fall in haemoglobin of ≥ 2 g/dl, and only if this took the total haemoglobin to < 10 g/dl.
	Sarullo et al[266]	Not defined

Table 57: Clinical evidence profile: rescue PCI versus conservative therapy

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Rescue PCI	Conservative therapy	Relative (95% CI)	Absolute	Quality	Importance
All-cause mortality (short-term) Belenkie 1992[20], MERLIN[166,290,291], REACT[52,113], RESCUE I[95], RESCUE II[96]												
5 (a)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious (b)	None	28/405 (6.9%)	43/395 (10.9%)	RR 0.64 (0.41 to 1)	39 fewer per 1000 (from 64 fewer to 0 more)	MODERATE	CRITICAL
All-cause mortality (longer-term) MERLIN[166,290,291], REACT[52,113], RESCUE II[96]												
3 (c)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious (b)	None	27/311 (8.7%)	38/310 (12.3%)	RR 0.71 (0.44 to 1.13)	36 fewer per 1000 (from 69 fewer to 16 more)	MODERATE	CRITICAL
All-cause mortality (time to event) MERLIN[166,290,291], REACT[52,113]												
2 (d)	Randomised trials	No serious risk of bias	Serious (e)	No serious indirectness	Serious (b)	None	43/297 (14.5%)	56/295 (19%)	HR 0.68 (0.46 to 1.02)	56 fewer per 1000 (from 98 fewer to 3 more)	LOW	CRITICAL
Cardiovascular mortality (short-term) MERLIN[166,290,291]												
1 (f)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious (g)	None	13/153 (8.5%)	17/154 (11%)	RR 0.77 (0.39 to 1.53)	25 fewer per 1000 (from 67 fewer to 59 more)	LOW	CRITICAL
Cardiovascular mortality (time to event) REACT[52,113]												
1 (h)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious (b)	None	13/144 (9%)	23/141 (16.3%)	HR 0.52 (0.27 to 1.02)	75 fewer per 1000 (from 116 fewer to 3 more)	MODERATE	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Rescue PCI	Conservative therapy	Relative (95% CI)	Absolute	Quality	Importance
Stroke (short-term) MERLIN[166,290,291], REACT[52,113]												
2 (f)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious (i)	None	9/297 (3%)	2/295 (0.68%)	RR 4.48 (0.98 to 20.52)	24 more per 1000 (from 0 fewer to 132 more)	MODERATE	CRITICAL
Stroke (longer-term) MERLIN[166,290,291], REACT[52,113]												
2 (j)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious (i)	None	10/297 (3.4%)	3/295 (1%)	RR 3.33 (0.93 to 11.95)	24 more per 1000 (from 1 fewer to 111 more)	MODERATE	CRITICAL
Health-related quality of life (any follow-up period) – not measured												
0	-	-	-	-	-	None	-	-	-	-		CRITICAL
Reinfarction (short-term) MERLIN[166,290,291], REACT[52,113], RESCUE II[96]												
3 (k)	Randomised trials	No serious risk of bias	Serious (e)	No serious indirectness	No serious imprecision	None	12/311 (3.9%)	25/310 (8.1%)	RR 0.48 (0.25 to 0.93)	42 fewer per 1000 (from 6 fewer to 60 fewer)	MODERATE	IMPORTANT
Reinfarction (longer-term) MERLIN[166,290,291], REACT[52,113]												
2 (j)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	15/297 (5.1%)	32/295 (10.8%)	RR 0.47 (0.26 to 0.84)	57 fewer per 1000 (from 17 fewer to 80 fewer)	HIGH	IMPORTANT
Reinfarction (time to event) REACT[52,113]												
1 (j)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	3/144 (2.1%)	12/141 (8.5%)	HR 0.33 (0.12 to 0.91)	56 fewer per 1000 (from 7 fewer to 74 fewer)	HIGH	IMPORTANT
Heart failure (short-term) MERLIN[166,290,291], REACT[52,113], RESCUE I[95]												

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Rescue PCI**	**Conservative therapy**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
3 (f)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious (b)	None	44/375 (11.7%)	61/368 (16.6%)	RR 0.72 (0.51 to 1.01)	46 fewer per 1000 (from 81 fewer to 2 more)	MODERATE	IMPORTANT
Heart failure (longer-term) MERLIN[166,290,291], REACT[52,113]												
2 (j)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious (b)	None	46/297 (15.5%)	59/295 (20%)	RR 0.78 (0.56 to 1.09)	44 fewer per 1000 (from 88 fewer to 18 more)	MODERATE	IMPORTANT
Unplanned revascularisation (short-term) MERLIN[166,290,291], RESCUE II[96]												
2 (l)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	10/167 (6%)	36/169 (21.3%)	RR 0.29 (0.15 to 0.56)	151 fewer per 1000 (from 94 fewer to 181 fewer)	HIGH	IMPORTANT
Unplanned revascularisation (longer-term) MERLIN[166,290,291], REACT[52,113], RESCUE II[96]												
3 (m)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	42/311 (13.5%)	76/310 (24.5%)	RR 0.55 (0.39 to 0.78)	110 fewer per 1000 (from 54 fewer to 150 fewer)	HIGH	IMPORTANT
Unplanned revascularisation (time to event) REACT[52,113]												
1 (n)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	25/144 (17.4%)	40/141 (28.4%)	HR 0.50 (0.3 to 0.83)	130 fewer per 1000 (from 42 fewer to 188 fewer)	HIGH	IMPORTANT
Major bleeding (short-term) REACT[52,113]												
1 (o)	Randomised trials	No serious risk of	No serious inconsistency	No serious indirectness	Very serious (g)	None	4/144 (2.8%)	5/141 (3.5%)	RR 0.78 (0.21 to	8 fewer per 1000 (from 28 fewer to	LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Rescue PCI	Conservative therapy	Relative (95% CI)	Absolute	Quality	Importance
		bias							2.86)	66 more)		
Minor bleeding (short-term) MERLIN[166,290,291], REACT[52,113]												
2 (o)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	50/297 (16.8%)	10/295 (3.4%)	RR 4.93 (2.56 to 9.49)	133 more per 1000 (from 53 more to 288 more)	HIGH	LESS IMPORTANT
Hospital stay (index admission) (better indicated by lower values) RESCUE II[96]												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious (p)	None	14	15	-	MD 1.2 higher (0.57 lower to 2.97 higher)	MODERATE	IMPORTANT
Hospital stay (index admission) (better indicated by lower values) MERLIN[166,290,291]												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious (q)	None	153	154	-	Rescue PCI: median 7 (2–23); CT: median 7 (2–46)	LOW	IMPORTANT

(a) Belenkie 1992[20]: in-hospital follow-up; rest: 30-day follow-up.
(b) Confidence interval crosses 1 default minimum important difference (0.75) and line of no effect.
(c) MERLIN[166,290,291] and REACT[52,113]: 6-month follow-up; RESCUE II[96]: 12-month follow-up.
(d) MERLIN[166,290,291]: 3 year follow-up; REACT[52,113]: median follow-up of 4.4 years.
(e) Unexplained heterogeneity $I^2 > 50\%$.
(f) 30-days follow-up.
(g) Confidence interval crosses both default minimum important difference (0.75 and 1.25) and line of no effect.
(h) At a median follow-up of 4.4 years.
(i) Confidence interval crosses 1 default minimum important difference (1.25) and line of no effect.
(j) At 6-month follow-up.
(k) RESCUE II[96]: in-hospital follow-up; rest 30-day follow-up.
(l) RESCUE II[96]: in-hospital follow-up; MERLIN[166,290,291] 30-day follow-up.
(m) RESCUE II[96]: 12-month follow-up; rest 6-months follow-up.
(n) At 12-month follow-up.
(o) In-hospital follow-up.
(p) Confidence interval crosses 1 default minimum important difference (2 days) and line of no effect.

(q) Results reported as median (range), which unlike results reported as mean (SD) cannot be pooled and analysed together.

Table 58: Clinical evidence profile: repeat fibrinolysis versus conservative therapy

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Repeated fibrinolysis	Conservative therapy	Relative (95% CI)	Absolute	Quality	Importance
All-cause mortality (short-term) Mounsey 1995[203], Sarullo 2000[266]												
2 (a)	Randomised trials	Serious (b)	No serious inconsistency	No serious indirectness	No serious imprecision	None	4/64 (6.3%)	14/63 (22.2%)	RR 0.28 (0.1 to 0.81)	160 fewer per 1000 (from 42 fewer to 200 fewer)	MODERATE	CRITICAL
All-cause mortality (time to event) REACT[52,113]												
1 (c)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious (d)	None	31/142 (21.8%)	30/141 (21.3%)	HR 1.04 (0.63 to 1.73)	7 more per 1000 (from 73 fewer to 126 more)	LOW	CRITICAL
Cardiovascular mortality (time to event) REACT[52,113]												
1 (c)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious (d)	None	28/142 (19.7%)	23/141 (16.3%)	HR 0.82 (0.47 to 1.42)	27 fewer per 1000 (from 83 fewer to 60 more)	LOW	CRITICAL
Stroke (longer-term) REACT[52,113]												
1 (e)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious (d)	None	1/142 (0.7%)	1/141 (0.71%)	RR 0.99 (0.06 to 15.72)	0 fewer per 1000 (from 7 fewer to 104 more)	LOW	CRITICAL
Health-related quality of life (any follow-up period) - not measured												
0	-	-	-	-	-	None	-	-	-	-		CRITICAL
Reinfarction (short-term) Sarullo 2000[266]												
1 (f)	Randomised trials	Serious (g)	No serious inconsistency	No serious indirectness	Serious (h)	None	7/45 (15.6%)	0/45 (0%)	RR 15 (0.88 to 255.04)	-	LOW	IMPORTANT
Reinfarction (longer-term) REACT[52,113]												
1 (e)	Randomised	No	No serious	No serious	Very serious	None	15/142	12/141	RR 1.24	20 more per	LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Repeated fibrinolysis**	**Conservative therapy**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
	trials	serious risk of bias	inconsistency	indirectness	(d)		(10.6%)	(8.5%)	(0.6 to 2.56)	1000 (from 34 fewer to 133 more)		
Heart failure (longer-term) REACT[52,113]												
1 (e)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious (d)	None	10/142 (7%)	11/141 (7.8%)	RR 0.9 (0.4 to 2.06)	8 fewer per 1000 (from 47 fewer to 83 more)	LOW	IMPORTANT
Unplanned revascularisation (short-term) Sarullo 2000[266]												
1 (f)	Randomised trials	Serious (g)	No serious inconsistency	No serious indirectness	No serious imprecision	None	14/45 (31.1%)	1/45 (2.2%)	RR 14 (1.92 to 102.03)	289 more per 1000 (from 20 more to 1000 more)	MODERATE	IMPORTANT
Unplanned revascularisation (time to event) REACT[52,113]												
1 (i)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious (d)	None	41/142 (28.9%)	40/141 (28.4%)	HR 1.05 (0.68 to 1.62)	12 more per 1000 (from 81 fewer to 134 more)	LOW	IMPORTANT
Major bleeding (short-term) REACT[52,113], Sarullo 2000[266]												
2 (f)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious (d)	None	8/187 (4.3%)	5/186 (2.7%)	RR 1.54 (0.54 to 4.4)	15 more per 1000 (from 12 fewer to 91 more)	LOW	IMPORTANT
Minor bleeding (short-term) REACT[52,113], Sarullo 2000[266]												
2 (f)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	30/187 (16%)	15/186 (8.1%)	RR 1.99 (1.13 to 3.51)	80 more per 1000 (from 10 more to 202 more)	HIGH	IMPORTANT

(a) Mounsey 1995[203]: 6 week follow-up; Sarullo 2000[266]: in-hospital follow-up.
(b) 2/2 studies: unclear allocation concealment.
(c) At a median follow-up of 4.4 years.
(d) Confidence interval crosses both default minimum important differences (0.75 and 1.25) and line of no effect.

(e) At 6-month follow-up.
(f) In-hospital follow-up.
(g) Unclear allocation concealment.
(h) Confidence interval crosses default minimum important difference (1.25) and line of no effect.
(i) At 12-month follow-up.

Table 59: Clinical evidence profile: rescue PCI versus repeat fibrinolysis

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Rescue PCI	Repeated fibrinolysis	Relative (95% CI)	Absolute	Quality	Importance
All-cause mortality (time to event) REACT[52,113]												
1 (a)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	16/144 (11.1%)	31/142 (21.8%)	HR 0.41 (0.22 to 0.75)	122 fewer per 1000 (from 50 fewer to 166 fewer)	HIGH	CRITICAL
Cardiovascular mortality (time to event) REACT[52,113]												
1 (a)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	13/144 (9%)	28/142 (19.7%)	HR 0.43 (0.22 to 0.84)	107 fewer per 1000 (from 29 fewer to 150 fewer)	HIGH	CRITICAL
Stroke (longer-term) REACT[52,113]												
1 (b)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious (c)	None	3/144 (2.1%)	1/142 (0.7%)	RR 2.96 (0.31 to 28.1)	14 more per 1000 (from 5 fewer to 191 more)	LOW	CRITICAL
Health-related quality of life (any follow-up period) - not measured												
0	-	-	-	-	-	None	-	-	-	-		CRITICAL
Reinfarction (time to event) REACT[52,113]												
1 (b)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	3/144 (2.1%)	15/142 (10.6%)	HR 0.23 (0.09 to 0.6)	80 fewer per 1000 (from 41 fewer to 96 fewer)	HIGH	IMPORTANT
Heart failure (longer-term) REACT[52,113]												
1 (b)	Randomised	No serious risk of	No serious	No serious	Very serious	None	7/144	10/142	RR 0.69 (0.27 to	22 fewer per 1000 (from 51	LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Rescue PCI	Repeated fibrinolysis	Relative (95% CI)	Absolute	Quality	Importance
	trials	bias	inconsistency	indirectness	(c)		(4.9%)	(7%)	1.76)	fewer to 54 more)		
Unplanned revascularisation (time to event) REACT[52,113]												
1 (d)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	25/144 (17.4%)	41/142 (28.9%)	HR 0.53 (0.33 to 0.87)	124 fewer per 1000 (from 32 fewer to 182 fewer)	HIGH	IMPORTANT
Major bleeding (short-term) REACT[52,113]												
1 (e)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious (c)	None	4/144 (2.8%)	7/142 (4.9%)	RR 0.56 (0.17 to 1.88)	22 fewer per 1000 (from 41 fewer to 43 more)	LOW	IMPORTANT
Minor bleeding (short-term) REACT[52,113]												
1 (e)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	33/144 (22.9%)	10/142 (7%)	RR 3.25 (1.67 to 6.35)	158 more per 1000 (from 47 more to 377 more)	HIGH	IMPORTANT

(a) At a median follow-up of 4.4 years.
(b) At 6-month follow-up.
(c) Confidence interval crosses both default minimum important differences (0.75 and 1.25) and line of no effect.
(d) At 12-month follow-up.
(e) In-hospital follow-up.

15.4 Economic evidence

No relevant economic evaluations were identified that compared rescue PCI, repeat fibrinolysis or conservative management with each other in people with STEMI who failed to reperfuse after fibrinolytic therapy. See also the economic article selection flow diagram in Appendix E.

15.5 Evidence statements

Clinical

Rescue PCI versus conservative therapy

All-cause mortality

- Evidence suggested that rescue PCI is potentially more clinically effective when compared to conservative therapy at reducing all-cause mortality at ≤ 30 days and in the longer term (both moderate quality) and at improving time to all-cause mortality (low quality) [5 studies, n = 800; 3 studies, n = 621; and 2 studies, n = 592 respectively].

Cardiovascular mortality

- Low quality evidence suggested that there may be no clinical difference between rescue PCI and conservative therapy at reducing cardiovascular mortality at ≤ 30 days, but the direction of the estimate of effect could favour either intervention [1 study, n = 307].
- Moderate quality evidence suggested that rescue PCI is potentially more clinically effective when compared to conservative therapy at improving time to cardiovascular mortality [1 study, n = 144].

Stroke

- Moderate quality evidence suggested that conservative therapy is potentially more clinically effective when compared to rescue PCI at reducing the incidence of stroke at ≤ 30 days and in the longer term [2 studies, n = 592].

Reinfarction

- Evidence suggested that rescue PCI is potentially more clinically effective when compared to conservative therapy at reducing the incidence of reinfarction at ≤ 30 days (moderate quality) and in the longer term as well as improving the time to reinfarction (both high quality) [3 studies, n = 621; 2 studies, n = 592; and 1 study, n = 144 respectively].

Heart failure

Moderate quality evidence suggested that:

- rescue PCI is potentially more clinically effective when compared to conservative therapy at reducing the incidence of heart failure at ≤ 30 days [3 studies, n = 743].
- There may be no clinical difference between rescue PCI when compared to conservative therapy at reducing the incidence of heart failure in the longer term, but the direction of the estimate of effect favoured rescue PCI [2 studies, n = 592].

Unplanned revascularisation

- High quality evidence showed that rescue PCI is more clinically effective when compared to conservative therapy at reducing the incidence of unplanned revascularisation at ≤ 30 days [2 studies, n = 336].

- High quality evidence suggested that rescue PCI is potentially more clinically effective when compared to conservative therapy reducing the incidence of unplanned revascularisation in the longer term and at improving the time to incidence of unplanned revascularisation [3 studies, n = 621; 1 study, n = 144 respectively].

Major bleeding

- Low quality evidence suggested that there may be no clinical difference between rescue PCI and conservative therapy at reducing the incidence of major bleeding at ≤ 30 days, but the direction of the estimate of effect could favour either intervention [1 study, n = 285].

Minor bleeding

- High quality evidence showed that conservative therapy is more clinically effective when compared to rescue PCI at reducing the incidence of minor bleeding at ≤ 30 days [2 studies, n = 592].

Hospital stay

- Moderate quality evidence suggested that conservative therapy is potentially more clinically effective when compared to rescue PCI at reducing hospital stay, but the direction of the estimate of effect could favour either intervention [1 study, n = 29].
- Low quality evidence suggested that the difference between rescue PCI and conservative therapy is uncertain as no comparative analysis could be carried out [1 study, n = 307].

Repeat fibrinolysis versus conservative therapy

All-cause mortality

- Moderate quality evidence showed that repeated fibrinolysis is more clinically effective when compared to conservative therapy at improving all-cause mortality at ≤ 6 weeks [2 studies, n = 127].
- Low quality evidence suggested that there may be no clinical difference between repeated fibrinolysis and conservative therapy at improving all-cause mortality calculated as time to event, but the direction of the estimate of effect could favour either intervention [1 study, n = 283].

Cardiovascular mortality

- Low quality evidence suggested that there may be no clinical difference between repeated fibrinolysis and conservative therapy at improving cardiovascular mortality calculated as time to event, but the direction of the estimate of effect could favour either intervention [1 study, n = 283].

Stroke

- Low quality evidence suggested that there may be no clinical difference between repeated fibrinolysis and conservative therapy at reducing the incidence of stroke in the longer term, but the direction of the estimate of effect could favour either intervention [1 study, n = 283].

Reinfarction

Low quality evidence suggested that:

- conservative therapy is potentially more clinically effective when compared to repeated fibrinolysis at reducing the incidence of reinfarction at ≤ 6 weeks [1 study, n = 90].
- there may be no clinical difference between repeated fibrinolysis and conservative therapy at reducing the incidence of reinfarction in the longer term, but the direction of the estimate of effect could favour either intervention [1 study, n = 283].

Heart failure

- Low quality evidence suggested that there may be no clinical difference between repeated fibrinolysis and conservative therapy at reducing the incidence of heart failure in the longer term, but the direction of the estimate of effect could favour either intervention [1 study, n = 283].

Unplanned revascularisation

- Moderate quality evidence showed that conservative therapy is clinically more effective when compared to repeated fibrinolysis at reducing unplanned revascularisation rate at ≤ 6 weeks [1 study, n = 90].
- Low quality evidence suggested that there may be no clinical difference between repeated fibrinolysis and conservative therapy at reducing unplanned revascularisation rate calculated as time to event , but the direction of the estimate of effect could favour either intervention [1 study, n = 283].

Major bleed

- Low quality evidence suggested that conservative therapy is potentially more clinically effective when compared to repeated fibrinolysis at reducing the incidence of major bleeding at ≤ 6 weeks, but the estimate of the effect could favour either intervention [2 studies, n = 373].

Minor bleed

- High quality evidence showed that conservative therapy is more clinically effective when compared to repeated fibrinolysis at reducing the incidence of minor bleeding at ≤ 6 weeks [2 studies, n = 373].

Rescue PCI versus repeat fibrinolysis

All-cause mortality

- High quality evidence showed that rescue PCI is more clinically effective when compared to repeated fibrinolysis at improving all-cause mortality calculated as time to event [1 study, n = 286].

Cardiovascular mortality

- High quality evidence showed that rescue PCI is more clinically effective when compared to repeated fibrinolysis at improving cardiovascular mortality calculated as time to event [1 study, n = 286].

Stroke

- Low quality evidence suggested that repeated fibrinolysis is potentially more clinically effective when compared to rescue PCI at reducing the incidence of stroke in the longer term, but the direction of the estimate of effect could favour either intervention [1 study, n = 286].

Reinfarction

- High quality evidence showed that rescue PCI is more clinically effective when compared to repeated fibrinolysis at reducing the incidence of reinfarction calculated as time to event [1 study, n = 286].

Heart failure

- Low quality evidence suggested that rescue PCI is potentially more clinically effective when compared to repeated fibrinolysis at reducing the incidence of heart failure in the longer term, but the direction of the estimate of effect could favour either intervention [1 study, n = 286].

Unplanned revascularisation

- High quality evidence showed that rescue PCI is more clinically effective when compared to repeated fibrinolysis at reducing the incidence of reinfarction calculated as time to event [1 study, n = 286].

Major bleeding

- Low quality evidence suggested that rescue PCI is potentially more clinically effective when compared to repeated fibrinolysis at reducing the incidence of major bleeding at ≤ 6 weeks, but the direction of the estimate of effect could favour either intervention [1 study, n = 286].

Minor bleeding

- High quality evidence showed that repeated fibrinolysis is more clinically effective when compared to rescue PCI at reducing the incidence of minor bleeding at ≤ 6 weeks [1 study, n = 286].

No studies reported data on quality of life.

Economic

- No relevant economic evaluations were identified that compared rescue PCI, repeat fibrinolysis or conservative management with each other in people with STEMI who failed to reperfuse after fibrinolytic therapy.

15.6 Recommendations and link to evidence

Recommendation	The current recommendations can be found at: www.nice.org.uk/guidance/ng185
Relative values of different outcomes	For this review question the GDG considered the outcomes of all-cause and cardiovascular mortality, stroke (especially haemorrhagic stroke) and quality of life as critical to decision-making. Myocardial reinfarction, major bleeding, heart failure and unplanned revascularisation were considered important, and minor bleeding and length of hospital stay as less important to decision-making. No data were found for quality of life.
Trade-off between clinical benefits and harms	**Rescue PCI versus conservative therapy:** Rescue PCI reduced the incidence of myocardial reinfarction and unplanned revascularisation at short- and longer-term follow-up compared to conservative therapy. Rescue PCI reduced all-cause mortality, which was statistically significant in the short-term but not in the longer term. The reduction in the incidence of heart failure did not reach statistical significance and different definitions for this outcome between studies complicated interpretation of the results. The incidence of stroke in the trials was too low to draw meaningful conclusions Conservative therapy was associated with a lower incidence of minor but not major bleeding, relative to rescue PCI. The interpretation of bleeding results was complicated by use of different definitions of major and minor bleeding between studies. REACT[52,113] used separate definitions for major and minor bleeding and reported no difference in major bleeding between rescue PCI and conservative therapy. MERLIN[166,290,291] and Belenkie et al. [20] did not categorise bleeding as major or minor events. In a sensitivity analysis, in which all of the reported bleeds in MERLIN[166,290,291] and Belenkie et al. [20] were assumed to be major, conservative therapy reduced the incidence of major bleeding compared to rescue PCI. The GDG considered this scenario to be unlikely, however, and agreed that the quality of the evidence was insufficient to allow a definite conclusion about the overall incidence of major bleeding associated

	with rescue PCI and conservative therapy. Conservative therapy was associated with a lower incidence of minor bleeds compared to rescue PCI, irrespective of whether REACT[52,113] was analysed alone or if all of the bleeding events in MERLIN[166,290,291]and Belenkie et al.[20] were assumed to be minor bleeds. **Repeat fibrinolysis versus conservative therapy:** Repeat fibrinolysis was associated with a reduction in all-cause mortality at short-term follow-up compared with conservative therapy, but this finding is based on 2 small trials with only 127 participants. Moreover, the analysis is dominated by a single trial in which the mortality in the conservative arm was relatively high (29%).[266] Short-term data from the REACT trial[52,113] were not available but in the time to event analysis of this trial there was no difference in mortality between repeat fibrinolysis and conservative care. Repeat fibrinolysis was associated with increased rates of unplanned revascularisation and minor bleeding at short-term follow-up relative to conservative care. Repeat fibrinolysis increased the incidence of minor bleeding irrespective of whether all bleeding events reported in Mounsey et al. [203] were combined with minor bleeding reported in REACT[52,113] and Sarullo et al. [266] It was not possible to draw meaningful conclusions regarding the effect of repeat fibrinolysis on stroke, unplanned revascularisation, myocardial reinfarction, heart failure and major bleeding. **Rescue PCI versus repeat fibrinolysis:** Rescue PCI reduced the incidence of all-cause mortality, myocardial reinfarction, and unplanned revascularisation at longer-term follow-up compared to repeat fibrinolysis. Rescue PCI increased the incidence of minor bleeding. The available data do not allow meaningful conclusions regarding heart failure, stroke and major bleeding. The GDG concluded that the benefits of rescue PCI relative to repeat fibrinolysis or conservative care (including reduced all-cause mortality, and incidences of reinfarction, heart failure and unplanned revascularisation) outweigh any potential increase in risk of major bleeding. The GDG considered that minor bleeding was not a sufficiently important outcome to alter the net benefit of rescue PCI compared to conservative therapy and that the incidence of stroke in the trials was too low to draw meaningful conclusions. Hence the GDG agreed that rescue PCI should be offered to people with acute STEMI and electrocardiographic evidence of failed reperfusion after fibrinolysis. The GDG agreed that there is no compelling evidence of benefit from repeat fibrinolysis, but as this therapy may be associated with harm the GDG recommended that repeat fibrinolysis should not be used in people with failed reperfusion after fibrinolysis.
Economic considerations	No health economic evidence was found comparing any combination of rescue PCI, repeat fibrinolysis and conservative therapy in people with STEMI who fail to reperfuse after fibrinolytic therapy. The GDG considered it likely that in terms of the cost of the interventions (initial procedures and drugs) rescue PCI would be the most costly option, followed by repeat fibrinolysis, and then conservative management. In addition to the cost of a PCI procedure, it was highlighted that undertaking rescue PCI would mean that people requiring the intervention (estimated at

	around 30% of people treated with fibrinolysis) would need to be transferred to a PCI-capable hospital, and potentially this is also a significant cost. However, the recommendation to offer rescue PCI overlaps with other areas in the guideline (for example, with the role of routine early angiography after fibrinolysis, see chapter 16) and so these costs may not be attributable only to this question. In addition, it is likely that the health gains resulting from rescue PCI would decrease future management costs. The GDG concluded that the health benefits of rescue PCI were likely to justify any additional costs over repeat fibrinolysis or conservative management. The GDG considered that the probable higher cost of repeat fibrinolysis compared to conservative management, and the lack of convincing evidence of clinical benefit justified a recommendation that repeat fibrinolytic therapy should not be given where rescue PCI is not possible.
Quality of evidence	The GDG noted that the dates of publication of the trials ranged from 1992 through to 2005 and of the 7 RCTs, 3 were conducted in the UK (REACT[52,113], MERLIN[166,290,291] and Mounsey et al[203]). The inclusion criteria differed between trials. The MERLIN[166,290,291] and REACT[52,113] trials enrolled people with acute STEMI and evidence of failed reperfusion on an electrocardiogram recorded 60 and 90 minutes, respectively, after fibrinolysis. RESCUE I[95] and RESCUE II[96] enrolled people with acute STEMI and angiographic evidence of impaired flow in the infarct-related artery at least 90 minutes after fibrinolysis. MERLIN[166,290,291] was a locally confined study that recruited people from 3 sites in North-East England, while REACT[52,113] was a UK-wide study that recruited people from 35 sites. The median time from symptom onset to rescue PCI was 327 minutes in MERLIN[166,290,291] and 414 minutes in REACT[52,113], but shorter times were reported in the RESCUE I[95] and RESCUE II[96] trials. REACT[52,113] and MERLIN[166,290,291] recruited patients at non-interventional hospitals and those assigned to rescue PCI required transfer to facilities capable of carrying out these procedures. The GDG debated whether people with acute STEMI who are treated by pre-hospital fibrinolysis should be transferred directly to a PCI-capable hospital, but concluded that there is insufficient evidence to make a specific recommendation about this aspect of care. Management of people with acute STEMI following administration of fibrinolytic therapy should therefore be determined by local policy. The GDG noted differences in stent and GPI use between the studies included in this review. The older studies (Belenkie et al. [20] and RESCUE 1[95]) were conducted before the availability of coronary stents. In the 2 largest and most recent trials (MERLIN[166,290,291] and REACT[52,113]) stents were used in more than 50% of eligible participants. REACT[52,113] was the only study to use GPIs in >10% of participants. Other differences included: use of streptokinase as the initial fibrinolytic agent, full details are provided in the Evidence tables in Appendix G. The robustness and clinical relevance of end point definitions were taken into account. In several studies unplanned revascularisation, myocardial reinfarction and bleeding events were recorded but not defined, thereby complicating interpretation. Definitions of reinfarction varied between trials and adjudication of this outcome may be particularly problematic in people who have electrocardiographic evidence of failed reperfusion after fibrinolysis, and these issues reduced the GDG's confidence in the validity of this outcome. The definition of heart failure in MERLIN[166,290,291] was much broader than in

	REACT[52,113] and included people with clinical signs but no other confirmatory evidence of heart failure. The GDG also noted that many of the studies in this review were not powered to detect differences in individual end points, although this was improved by pooling data where possible. It was noted that length of hospital stay has reduced over time and so older studies may not be representative of current practice.
Other considerations	The GDG considered the time interval between symptom onset and admission to a PCI capable hospital an important consideration but noted that study results were not stratified according to time to rescue PCI or whether or not inter-hospital transfer was required. The GDG noted that failed fibrinolysis was defined differently in the studies in this review. The GDG agreed that electrocardiographic evidence of failed coronary reperfusion fibrinolysis should be defined as residual ST-segment elevation (less than 50% resolution of the ST-segment elevation) recorded 60 minutes to 90 minutes after initiation of fibrinolytic therapy in the electrocardiographic lead that had the greatest ST-segment elevation at presentation. The GDG thought it likely that incidences of haemorrhagic stroke were counted as both major bleeding and all-cause stroke in the REACT[52,113] study and that this might also be the case in other studies that did not define bleeding. The recommendations in this chapter impact a small and diminishing number of people who are treated by fibrinolysis. In 2011/12 7.5% (1625) of STEMI people in England and Wales that had reperfusion therapy were given fibrinolysis.[204] Around a third of people that receive fibrinolysis will be eligible for rescue PCI. In 2011 in the UK it was reported that 1032 people were treated by rescue PCI (4.6% of all PCI procedures carried out for STEMI)[183] – this suggests that rescue PCI is current practice for those who fail to reperfuse.

16 Routine early angiography following fibrinolysis

16.1 Introduction

The objectives of fibrinolytic therapy in people with acute STEMI are to restore coronary artery blood flow as quickly as possible to preserve myocardial function and reduce mortality. Angiographic studies show that fibrinolysis restores coronary artery patency within 90 minutes in around 75% of people with acute STEMI, but complete reperfusion with normal flow in the infarct-related coronary artery is observed in around 50%.[71,118,300] Identification of people who fail to reperfuse after fibrinolysis is difficult and the role of emergency coronary arteriography and 'rescue' PCI in people with persistent ST-segment elevation after fibrinolysis is discussed elsewhere in this guideline (see chapter 15). Following apparently successful fibrinolysis there may be residual narrowing at the site of a ruptured coronary plaque, which may predispose the vessel to re-occlusion in around 18% to 32% of people within 3 months.[125,316] Consequently, people with acute STEMI treated by fibrinolysis may develop recurrent ischaemia and further myocardial injury because of re-occlusion. In addition, people with STEMI may have multivessel disease and disease in non-infarct-related arteries can also be responsible for further episodes of myocardial ischaemia.

For these reasons people with acute STEMI who have been treated by fibrinolysis may be referred for coronary angiography to assess the patency of the infarct-related artery and the extent of disease in other coronary arteries, and to consider the need for myocardial revascularisation. The role and optimal timing of coronary angiography in these circumstances are unclear. Early coronary angiography carried out routinely within 24 hours of administration of fibrinolysis is likely to be associated with a risk of bleeding or thrombotic complications associated with the effects of recent fibrinolysis. On the other hand, people treated by fibrinolysis are at particularly high risk of adverse ischaemic events during the hours after treatment and might therefore benefit from an early routine invasive strategy. This guideline addresses the evidence for a strategy of routine early (within 24 hours) angiography after fibrinolysis for acute STEMI compared to either routine deferred angiography (angiography more than 24 hours after fibrinolysis) or selective angiography (angiography carried out only for clinical indications).

16.2 Review question: What is the clinical and cost effectiveness of routine early angiography following STEMI successfully treated by fibrinolysis compared to routine deferred or selective angiography?

For full details see review protocol in Appendix C.

16.3 Clinical evidence

Seven studies were included in the review. Three studies compared routine early angiography (and PCI where indicated) versus routine deferred coronary angiography (and PCI where indicated) in people who had prior fibrinolysis.[34,35,50,268] Study details and intervention definitions are given in Table 60. Four studies compared routine early angiography (and PCI were indicated) versus selective angiography (and PCI were indicated) in people who had prior fibrinolysis.[1,12,103,168] Study details and intervention definitions are given in Table 61. Evidence from the 7 included studies are summarised in the clinical GRADE evidence profile below (Table 67). See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

Our initial analyses categorised the studies into 2 groups according to the management strategy employed in the comparator group (routine deferred angiography versus selective angiography). All

7 studies were then analysed together to increase the power the power to detect differences in early angiography versus a more conservative approach. Analysing the 7 studies together showed that there was heterogeneity for the 2 outcomes of recurrent ischaemia and unplanned revascularisation. This heterogeneity for these outcomes of unplanned revascularisation may be explained by a subgroup effect of the comparator arms of routine deferred angiography versus selective angiography. Further details are given in the clinical GRADE evidence profiles (Table 67 and Table 68) and the forest plots in Appendix I.

Details of study populations, fibrinolytic agent and time from symptom onset to are given in Table 62. Procedural and angiographic information from the routine early versus routine deferred angiography studies is given in Table 63. Procedural and angiographic information from the routine early versus selective angiography studies is given in Table 64. Details of adjuvant pharmacotherapies in the included studies are given in Table 65. Definitions of outcomes for the included studies are given in Table 66.

Table 60: Summary of studies included in the review; routine early angiography versus routine deferred angiography

Study	Study definition of routine angiography	Study definition of routine deferred angiography	Population	Outcomes
NORDISTEMI[34,35]	Immediate transfer for angiography and PCI where indicated after randomisation	Conservative management and angiography 2 to 4 weeks after discharge recommended, with referral for early angiography if spontaneous recurrent ischaemia with or without ECG changes	n = 266	Short term (≤ 30 days): all-cause mortality, stroke, revascularisation, major bleeding, minor bleeding, recurrent ischaemia, HRQoL Longer term (7 months): HRQoL Longer term (12 months): all-cause mortality, stroke, revascularisation, reinfarction, recurrent ischaemia Hospital stay
SIAM III[268]	Transfer within 6 hours for immediate angiography and PCI were indicated after randomisation	Elective coronary angiography after 2 weeks or earlier in case of ongoing ischaemia	n = 163	Short term (≤ 30 days): all-cause mortality, reinfarction, unplanned revascularisation, major bleeding, recurrent ischaemia Longer term (6 months): all-cause mortality, stroke, reinfarction, unplanned revascularisation, major bleeding, recurrent ischaemia
TRANSFER- AMI[50]	Transfer within 6 hours for immediate angiography and conventional stenting after randomisation	Standard treatment angiography recommended within 2 weeks, unless failed FT and PCI required	n = 1059	Short term (≤ 30 days): all-cause mortality, stroke, reinfarction, heart failure, major bleeding, minor bleeding, recurrent ischaemia Longer term (6 months): all-cause mortality, reinfarction, intracranial bleeding

Table 61: Summary of studies included in review; routine early angiography versus routine selective angiography

Study	Study definition of routine angiography	Study definition of elective angiography study definition	Population	Follow-up period
Agati et al[1]	PCI within 24 hours after randomisation	Conservative management, enoxaparin repeated every 12 hours up to 7 days	n = 60	In-hospital: major bleeding
WEST[12]	Weight-adjusted tenecteplase followed by mandatory invasive management within 24 hours after randomisation	Weight-adjusted tenecteplase followed by usual care	n = 204	Short term (≤ 30 day): all-cause mortality, reinfarction, heart failure, recurrent ischaemia, stroke, bleeding
CAPITAL-AMI[168]	Randomised and given weight-adjusted tenecteplase followed by immediate transfer for angiography and PCI if indicated (time limit not reported)	Weight-adjusted tenecteplase alone	n = 170	Short term (≤ 30 day): all-cause mortality, reinfarction, stroke, heart failure, unplanned revascularisation, major bleeding, minor bleeding, recurrent ischaemia Longer term (6 months): all-cause mortality, reinfarction, stroke, heart failure, unplanned revascularisation, recurrent ischaemia Hospital stay
GRACIA-1[103]	Routine angiography and PCI where indicated within 24 hours after randomisation	Ischaemia-driven conservative approach	n = 500	Short term (≤ 30 day): all-cause mortality, reinfarction, stroke, unplanned revascularisation, major bleeding, minor bleeding, recurrent ischaemia Longer term (1 year): all-cause mortality, reinfarction, unplanned revascularisation, recurrent ischaemia Hospital stay

Table 62: Summary of population details, fibrinolytic agent and time and time from symptom onset to fibrinolysis

Study	Population inclusion criteria	Population exclusion criteria	Fibrinolytic agent [where administered]	Time from symptom onset to FT in study population
NORDISTEMI (2010)[34] Bøhmer 2011[35]	Age 18–75 years, symptoms MI present < 6 h, ≥ 2 mm ST-segment elevation in 2 contiguous precordial leads or ≥1 mm ST-segment elevation in 2 contiguous extremity leads or new left bundle branch block, expected time delay from first medical contact to PCI > 90 min, receiving FT with tenecteplase	Standard exclusion criteria for tenecteplase, cardiogenic shock or serious arrhythmias at randomisation, renal failure, pregnancy, other diseases with life expectancy < 12 months, psychiatric disease, learning disability, dementia, drug abuse, alcoholism, or conditions that can severely reduce compliance	Tenecteplase (weight adjusted) [57% pre-hospital]	2 hours (median)
TRANSFER-AMI (2009)[50]	ST-segment elevation < 12 hours of symptom onset, treated with tenecteplase, ST-segment elevation of ≥2 mm in 2 anterior leads, or, one of the following had to be present if ST-segment elevation of ≥ 1 mm in 2 inferior leads; systolic blood pressure < 100 mm Hg, heart rate of > 100 bpm, Killip class II or III, ST-segment depression of ≥ 2 mm in anterior leads, or ST-segment elevation of ≥ 1 mm or more in right-sided lead V_4 (V_4R)	Cardiogenic shock before randomisation, PCI within previous month, prior CABG, availability of PPCI with an anticipated door-to-balloon < 60 min	Tenecteplase [In-hospital]	1.9 hours (median)
SIAM III (2003) [268]	Aged >18 years, presenting within < 12 hours symptoms, ST-segment elevation of ≥ 1 mm in ≥ 2 limb leads or ST-segment elevation of ≥ 2 mm in the precordial leads, or new LBBB, eligible for FT, indication for angioplasty independent of the study, infarct-related lesion in a native coronary artery > 2.5 mm, diameter stenosis of ≥70% or TIMI flow < grade 3	Chronic renal insufficiency requiring dialysis, secondary or iatrogenic infarction, coronary anatomy unsuitable for stent placement, scheduled surgical coronary revascularisation within 6 months, previous MI in the area of the infarct-related vessel, infarct-related lesion not clearly defined	Reteplase [In-hospital]	3.4 hours (mean)
Agati et al. (2007) [1]	Presentation within 3 hours of symptom onset	Aged ≥ 80 years, revascularisation procedure as a result of failed fibrinolysis, early reinfarction, or ischaemia after the initial treatment (lysis or PCI), prior MI, cardiomyopathy, prior CABG	Tenecteplase [In-hospital]	2.1 hours (median)

Study	Population inclusion criteria	Population exclusion criteria	Fibrinolytic agent [where administered]	Time from symptom onset to FT in study population
		contraindications to GPIs, PCI, or lysis		
WEST (2006) [12]	Aged > 18 years, symptoms presumed secondary to STEMI lasting at least 20 min accompanied by ECG evidence of high risk including ≥ 2 mm of ST-elevation in 2 or more contiguous precordial leads or limb leads; or ≥1 mm ST-elevation in 2 or more limb leads coupled with ≥ 1 mm ST-depression in 2 or more contiguous precordial leads (total ST-deviation ≥4 mm) or presumed new left bundle branch block, reperfusion therapy feasible within 3 hours randomisation	PPCI was deemed to be available within 1 hour of diagnosis, prior CABG, pregnancy, contraindications to FT GPI use < 7 days	Tenecteplase (weight adjusted) [41% pre-hospital]	2 hours (median)
CAPITAL- AMI (2005) [168]	Presentation ≤6 hours of onset of chest discomfort of ≥ 30 minutes and ≥ 1 mm ST-segment elevation in 2 or more contiguous leads or left bundle branch block on a 12-lead electrocardiogram; and people were eligible if they had 1 of the following high-risk criteria; (1) anterior infarction with ST-segment elevation ≥2 mm in each of 2 contiguous precordial leads, (2) extensive non-anterior infarction 8 or more leads with ≥ 1 mm ST-segment elevation or depression or both, or the sum of ST-segment elevation > 20 mm, (3) Killip class 3, (4) systolic blood pressure <100 mm Hg	Active bleeding , cardiogenic shock, prior stroke, prior CABG, PCI within 6 months, CNS damage, major surgery or trauma within 3 months, uncontrolled hypertension, prolonged (> 10 min) cardiopulmonary resuscitation, blood coagulation disorder, current warfarin treatment, GPIs within 7 days ≥ 5,000 IU of unfractionated heparin < 6 hours, LMW heparin < 6 hours, expected survival < 12 months for other illness, pregnancy, creatine > 300 micromol/l (3.40 mg/dl), severe contrast allergy	Tenecteplase (weight adjusted) [In-hospital]	2 hours (median)
GRACIA-1 (2004) [102]	Aged > 18 years, chest pain lasting 30 minutes – 12 hours unresponsive to nitroglycerin with ST-segment elevation ≥ 1 mm in ≥ 2 contiguous leads or a non-diagnostic ECG due to LBBB or paced rhythm, received FT with accelerated dose of	Cardiogenic shock, PAD, renal failure, prior stroke, pregnancy, suspicion/evidence of mechanical complication, survival < 1 year, current use anticoagulant, active bleeding or major surgery < 2 weeks,	Alteplase (accelerated dose) [In-hospital]	3.1 hours (mean)

Study	Population inclusion criteria	Population exclusion criteria	Fibrinolytic agent [where administered]	Time from symptom onset to FT in study population
	alteplase within 12 hours of pain onset	aspirin, ticlopidine, clopidogrel or heparin contraindication, CAD not amenable to revascularisation, surgery in pending year		

Table 63: Procedural and angiographic details of routine early angiography versus routine deferred angiography

Study	Time from FT to angiography in routine early angiography arm	Stent usage in routine early angiography arm	Time from FT to angiography in routine deferred angiography arm	Stent usage in routine deferred angiography arm	Indication for urgent angiography in routine deferred angiography arm	Percentage of people in routine deferred angiography group who had urgent angiography and PCI where indicated
NORDISTEMI (2010)[34] Bøhmer 2011[35]	163 min (median)	86%	5.5 days (median)	68%	Persistent chest pain and <50% reduction of ST-segment elevation 60 minutes after fibrinolysis initiation; haemodynamic instability.	26%
TRANSFER-AMI (2009) [50]	3.9 hours (median)	98%	22.7 hours (median)	99%	Decrease in ST-segment elevation of >50% and chest pain or with haemodynamic instability	34% (<12 hours after FT)
SIAM III (2003) [268]	3.5 hours (mean)	100%	Mean (SD) of 11.7(6.8) days	100%	Ongoing electrocardiographic ischaemia, postinfarction angina pectoris, haemodynamic instability	23.5% (mean (SD) = 3.1(4.2) days after FT)

Table 64: Procedural and angiographic details of routine early angiography versus selective angiography

Study	Time from FT to angiography in routine early angiography arm	Stent usage in routine early angiography arm	Indication for urgent angiography and PCI where indicated in selective angiography group	Percentage of people in selective angiography group who had urgent angiography and PCI where indicated
Agati et al. (2007) [1]	20 hours (mean)	100%	No details	No details
CAPITAL- AMI (2005)	1.4 hours (median	89%	Persistent chest pain and ST-segment elevation ≥ 90	67% during hospital admission

Study	Time from FT to angiography in routine early angiography arm	Stent usage in routine early angiography arm	Indication for urgent angiography and PCI where indicated in selective angiography group	Percentage of people in selective angiography group who had urgent angiography and PCI where indicated
[168]			minutes after initiation of FT or deteriorating haemodynamic status	39.3% recurrent ischaemia 9.5% failed FT
GRACIA-1 (2004) [102]	16.7 hours (mean)	80%	Spontaneous recurrent ischaemia with ECG changes; positive stress test under β-blockade with a heart rate of < 100 bpm or < 5 METS; hypotension or ventricular tachycardia on effort	21% before discharge
WEST (2006) [12]	4.9 hour (median)	97%	No definition given	14% rescue PCI, median 197 min after randomisation

Table 65: Adjuvant pharmacotherapies

Study	GPIs	Oral antiplatelets	Anticoagulants
NORDISTEMI (2010)[34] Bøhmer 2011[35]	At operators discretion Early angiography: 14% Deferred angiography: 6%	Aspirin 300 mg Clopidogrel loading dose 300 mg (all participants), followed by 75 mg for 9 months in case of stents, otherwise at discretion of treating physician	Enoxaparin, until revascularisation or discharge for a maximum of 7 days
TRANSFER-AMI (2009)[50]	At operators discretion Overall 83% of participants undergoing PCI	Aspirin (dose not reported) Clopidogrel loading dose 300 mg* (75 mg for participants aged > 75 years); Deferred angiography approach: 69% (within the first 6 hours); Early angiography: 89%	Unfractionated heparin or enoxaparin, no data on treatment duration. Participants aged > 75 years did not receive enoxaparin
Agati et al. (2007) [1]	In case of PCI, abciximab by protocol	Aspirin (no data on loading dose) 100 mg/day Clopidogrel loading dose 300 mg in case of PCI, followed by 75 mg/day for 6 months	Enoxaparin at randomisation (no further treatment in participants receiving PCI), otherwise for 7 days
WEST (2006) [12]	Abciximab in case of PCI (unless within 3 hours of fibrinolysis) Early angiography: 48% Selective approach: Not reported	Aspirin 160–325 mg Clopidogrel loading dose 300 mg in case of PCI	Enoxaparin for a minimum of 72 hours

Study	GPIs	Oral antiplatelets	Anticoagulants
CAPITAL- AMI (2005)[168]	Prescribed in 14% of participants; used only when angiographic result was sub-optimal	Aspirin 160 mg followed by 325 mg/day Clopidogrel loading dose 300 mg in case of PCI, followed by 75 mg/day for at least 1 month; Early angiography: 91%; selective approach: 57%	Unfractionated heparin (stopped after PCI), otherwise for 48 hours
GRACIA-1 (2004) [102]	Strongly recommended in interventional participants with clear angiographic evidence of thrombus Early angiography: 32% Selective approach: Not reported	Aspirin 200–500 mg Clopidogrel loading dose 300 mg (or ticlopidine 500 mg) in case of PCI	Unfractionated heparin (stopped after PCI), otherwise for 48 hours
SIAM III (2003) [268]	At operators discretion Early angiography: 10% Deferred angiography 16%	Aspirin 250 mg Clopidogrel (no data on dose) for 1 month after PCI†	Unfractionated heparin, no data on treatment duration

**Protocol was amended during enrolment to strongly recommend concomitant treatment with clopidogrel*

†Most participants randomised to the deferred angiography arm received clopidogrel 2 weeks later than those randomised to the early angiography arm

Table 66: Outcome definitions

Study	Definition
Reinfarction	
NORDISTEMI (2010)[34] Bøhmer 2011[35]	(i) In the first 18 hours: recurrent symptoms of ischaemia at rest accompanied by new ST-segment elevation of ≥ 0.1 mV in at least 2 contiguous leads, lasting ≥ 30 minutes. (ii) After 18 hours: new Q waves in 2 or more leads, or new increase in concentrations of creatine kinase-MB or troponins above the upper limit of normal (> 3× upper limit of normal after PCI and > 5× upper limit of normal after coronary artery bypass graft), and > 50% higher than the previous value.
TRANSFER-AMI (2009) [50]	(i) During the first 18 hours after enrolment: reinfarction was diagnosed on the basis of recurrent ST-segment elevation and recurrent chest pain lasting at least 30 minutes. (ii) After 18 hours: the diagnosis of reinfarction required that there be an elevation in the MB fraction of creatine kinase to higher than the upper limit of the normal range (more than 3 times the upper limit of normal after PCI and more than 5 times the upper limit of normal after coronary-artery bypass surgery) or new Q waves.
WEST (2006) [12]	(i) In the first 18 hours after randomisation: Recurrent signs and symptoms of ischaemia at rest accompanied by new or recurrent ST-segment elevations of ≥ 0.1 mV in at least 2 contiguous leads lasting ≥ 30 minutes.

Study	Definition
	(ii) After 18 hours: (a) New Q-waves (by Minnesota Code Criteria) in 2 or more leads and/or enzyme evidence of reinfarction: re-evaluation of CK-MB or troponin to above the upper limit of normal and increased by > 50% over the previous value. (b) The total CK must either be re-elevated to 2× or more the upper limit of normal and increased by > 25% or be re-elevated to > 200 U/mL over the previous value. If re-evaluated to less than 2× the upper limit of normal, the total CK must exceed the upper limit of normal by > 50% and exceed the previous value by 2-fold or be re-elevated to > 200 U/ml. (iii) Reinfarction after PCI (± stenting): CK greater than 3× the upper limit of normal and 50% greater than the previous value and/or new Q-waves (Minnesota Code) in 2 or more contiguous leads. (iv) Reinfarction after CABG surgery: CK greater than 5× the upper limit of normal and ≥ 50% greater than the previous value and/or new Q-waves (Minnesota Code) in 2 or more contiguous leads.
CAPITAL- AMI (2005)[168]	Recurrent ischaemic symptoms at rest lasting ≥ 30 minutes and accompanied by: 1) new or recurrent ST-segment elevation of ≥ 1 mm in any contiguous leads; 2) new left bundle branch block; or 3) re-elevation in serum creatine kinase level to greater than twice the upper limit of normal and ≥50% above the lowest level measured after infarction. If reinfarction occurred within 18 hours, enzyme criteria were not used.
GRACIA-1 (2004) [102]	Typical chest pain lasting > 30 minutes with a new increment of creatine kinase MB isoenzyme with or without new ECG abnormalities. The movement of this isoenzyme had to meet the following criteria: (a) if new chest pain arose within 48 hours of initial infarction, creatine kinase MB isoenzyme re-elevation was judged positive when it appeared during the descendent phase of this isoenzyme curve of the initial infarction and reached at least 150% of the last measurement; (b) if it occurred more than 48 hours after the initial infarction, this re-elevation was judged positive when it clearly corresponded to a creatine kinase MB isoenzyme curve before that of the initial infarction and reached a peak at least 3 times the normal value; and (c) if it occurred within 48 hours of angioplasty or surgery, this re-elevation was judged positive when it clearly corresponded to a creatine kinase MB isoenzyme curve before that of the initial infarction and reached a peak at least 5× the normal value.
SIAM III (2003) [268]	2 or more of the following criteria: (1) chest pain lasting for more than 30 minutes; (2) a new significant ST-elevation; (3) rise in the serum creatine kinase level to > 3× upper normal limit.
Stroke	
NORDISTEMI (2010)[34] Bøhmer 2011[35]	A new focal, neurological deficit of vascular origin lasting more than 24 hours.
TRANSFER-AMI (2009) [50]	Not defined; recorded in this review as cases of intracranial bleeding.
WEST (2006) [12]	Not defined; recorded in this review as cases of intracranial haemorrhage or non-haemorrhagic stroke.
CAPITAL- AMI (2005) [168]	Focal neurological deficit, compatible with damage in the territory of a major cerebral artery with signs or symptoms persisting for > 24 hours and was classified as haemorrhagic or non-haemorrhagic according to computerised tomography.

Study	Definition
GRACIA-1 (2004) [102]	Not defined; recorded in this review as cases of intracranial bleeding.
SIAM III (2003) [268]	Not defined; but appears to include both haemorrhagic and ischaemic cerebrovascular events.
Unplanned revascularisation	
CAPITAL- AMI (2005)[168]	Not defined; recorded in this review as unscheduled PCI or CABG.
GRACIA-1 (2004) [102]	Induced by spontaneous ischaemia or non-invasive stress tests (PCI or CABG). Revascularisation of participants assigned to the conservative group after spontaneous ischaemia in hospital, or after detecting high-risk ischaemia in a pre-discharge non-invasive test, was regarded as part of this strategy. However, in this review, pre-discharge revascularisation in the conservative group was included in the short-term analysis of 'unplanned revascularisation' and also contributed to the 'long-term analysis of 'unplanned revascularisation'.
SIAM III (2003) [268]	Any reintervention or CABG involving the infarct-related artery.
Heart failure	
TRANSFER-AMI (2009) [50]	Heart failure that required treatment 6 hours or more after enrolment and either pulmonary oedema on a chest radiograph, rales, or a pulmonary-capillary wedge pressure greater than 18 mm Hg.
WEST (2006) [12]	Physician's decision to treat congestive heart failure with a diuretic, intravenous inotropic agent or intravenous vasodilator and either: (i) the presence of pulmonary oedema or pulmonary vascular congestion on chest X-ray believed to be of cardiac cause or (ii) at least 2 of the following: (a) rales greater than one-third up the lung fields believed to be due to congestive heart failure; (b) PCWP >18 mmHg; (c) Dyspnoea, with documented pO_2 less than 80 mmHg on room air or O_2 saturation < 90% on room air, without significant lung disease.
CAPITAL- AMI (2005) [168]	When any 2 of the following were present: 1) dyspnoea; 2) pulmonary venous congestion with interstitial or alveolar oedema on chest radiograph; 3) crackles greater than or equal to one-third of the way up the lung fields; and 4) third heart sound associated with tachycardia. Includes people with cardiogenic shock.
Recurrent ischaemia	
NORDISTEMI (2010)[34] Bøhmer 2011[35]	Unstable angina (chest pain at rest suspicious for coronary disease with or without ECG changes), recurrent angina grade II to IV (Canadian Cardiovascular Society classification) or serious arrhythmias (ventricular tachycardia/ventricular fibrillation) that appeared more than 12 hours after randomisation.
TRANSFER-AMI (2009) [50]	Chest pain lasting 5 minutes or longer associated with ST-segment or T-wave changes.

Study	Definition
WEST (2006) [12]	Symptoms of ischaemia with ST-deviation or definite T-wave inversion persisting for at least 10 minutes despite medical management while in hospital.
CAPITAL- AMI (2005) [168]	Recurrent symptoms of ischaemia at rest associated with new ST-segment or T-wave changes, hypotension, or pulmonary oedema.
GRACIA-1 (2004) [102]	Spontaneous (at rest) recurrence of typical angina pectoris (or anginal equivalent) that had to coincide with new ECG abnormalities.
SIAM III (2003) [268]	Unplanned hospitalisation or unplanned angiography due to post-infarction angina, recurrent angina pectoris lasting > 15 minutes despite the administration of nitrates or being accompanied by ECG changes, pulmonary oedema, or hypotension.
Major bleeding	
NORDISTEMI (2010)[34] Bøhmer 2011[35]	'Severe bleeding' according to GUSTO scale, including intracranial haemorrhage.
TRANSFER-AMI (2009) [50]	TIMI criteria (includes CABG related).
Agati et al. (2007) [1]	Not defined.
WEST (2006) [12]	Bleeding that causes haemodynamic compromise requiring blood or fluid replacement, inotropic support, ventricular assist devices, surgical intervention, or cardiopulmonary resuscitation to maintain a sufficient cardiac output.
CAPITAL- AMI (2005) [168]	TIMI criteria.
GRACIA-1 (2004) [102]	Any complication causing death, need for surgery or transfusion, or extended time in hospital.
SIAM III (2003)[268]	Need for transfusion, bleeding requiring surgical intervention with a timely connection with the coronary intervention, bleeding documented by computed tomography or ultrasound, intra-cerebral as well as ocular, retroperitoneal, abdominal, intestinal, or urogenital, or a decrease in haemoglobin > 4% within 72 hours with a timely connection with the coronary intervention.
Minor bleeding	
NORDISTEMI (2010)[34] Bøhmer	According to GUSTO scale (for this review we grouped together cases of moderate plus minor bleeding).

Study	Definition
2011[35]	
TRANSFER-AMI (2009) [50]	TIMI criteria.
Agati et al. (2007)[1]	Not defined.
CAPITAL- AMI (2005)[168]	TIMI criteria.
Health-related quality of life	
NORDISTEMI (2010)[34] Bøhmer 2011[35]	Assessed using the 15D instrument. This is a generic, multidimensional, standardised, self-administered evaluative tool with 15 dimensions and 5 levels for each dimension (no problems to severe problems). The 15D scores were translated into a single index score with values from zero (dead) to 1.0 (perfect health) using a simple algorithm.

Table 67: Clinical evidence profile: routine early angiography versus routine deferred angiography and routine early angiography versus selective angiography

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Routine early angiography	Comparator	Relative (95% CI)	Absolute	Quality	Importance
All-cause mortality (short-term) – Selective [12,103,168]												
3 (a)	Randomised trials	Serious (b)	No serious inconsistency	No serious indirectness	Very serious (c)	None	9/438 (2.1%)	13/435 (3%)	RR 0.69 (0.3 to 1.59)	9 fewer per 1000 (from 21 fewer to 18 more)	VERY LOW	CRITICAL
All-cause mortality (short-term) – Routine deferred [34,50,128]												
3 (a)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious (c)	None	31/752 (4.1%)	29/735 (3.9%)	RR 1.05 (0.64 to 1.72)	2 more per 1000 (from 14 fewer to 28 more)	LOW	CRITICAL
All-cause mortality (longer-term) – Selective [103,168]												
2 (d)	Randomised trials	No serious	No serious inconsistency	No serious indirectness	Very serious (c)	None	12/334 (3.6%)	19/335 (5.7%)	RR 0.63 (0.31 to	21 fewer per 1000	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Routine early angiography	Comparator	Relative (95% CI)	Absolute		
		risk of bias							1.29)	(from 39 fewer to 16 more)		
All-cause mortality (longer-term) – Routine deferred [34,50,128]												
3 (e)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious (c)	None	37/744 (5%)	36/724 (5%)	RR 1 (0.64 to 1.56)	0 fewer per 1000 (from 18 fewer to 28 more)	LOW	CRITICAL
Health-related quality of life (assessed by 15D instrument) (short-term) – Routine deferred (better indicated by higher values) [34]												
1 (a)	Randomised trials	Very serious (f)	no serious inconsistency	No serious indirectness	Serious (g)	None	130 (h)	129 (h)	-	MD 0.02 higher (0.02 lower to 0.06 higher)	VERY LOW	CRITICAL
Health-related quality of life (assessed by 15D instrument) (longer-term) – Routine deferred (better indicated by higher values) [34]												
1 (i)	Randomised trials	Very serious (f)	No serious inconsistency	No serious indirectness	Serious (g)	None	130 (h)	129 (h)	-	MD 0.02 higher (0.02 lower to 0.06 higher)	VERY LOW	CRITICAL
Stroke (short-term) – Selective [12,103,168]												
3 (j)	Randomised trials	Serious (b)	No serious inconsistency	No serious indirectness	Very serious (c)	None	2/438 (0.46%)	2/435 (0.46%)	RR 0.98 (0.2 to 4.88)	0 fewer per 1000 (from 4 fewer to 18 more)	VERY LOW	CRITICAL
Stroke (short-term) – Routine deferred [34,50,128]												
3 (k)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious (c)	None	8/752 (1.1%)	13/735 (1.8%)	RR 0.6 (0.25 to 1.44)	7 fewer per 1000 (from 13 fewer to 8 more)	LOW	CRITICAL
Stroke (longer-term) – Selective [168]												
1 (l)	Randomised trials	Serious (m)	No serious inconsistency	No serious indirectness	Very serious (c)	None	1/86 (1.2%)	1/84 (1.2%)	RR 0.98 (0.06 to	0 fewer per 1000 (from	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Routine early angiography	Comparator	Relative (95% CI)	Absolute	Quality	Importance
									15.36)	11 fewer to 171 more)		
Stroke (longer-term) – Routine deferred[34]												
1 (n)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious (c)	None	3/134 (2.2%)	7/132 (5.3%)	RR 0.42 (0.11 to 1.6)	31 fewer per 1000 (from 47 fewer to 32 more)	LOW	CRITICAL
Intracranial bleeding (short-term) – Selective [12,103,168]												
3(j)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious (c)	None	1/438 (0.23%)	2/435 (0.46%)	RR 0.6 (0.08 to 4.5)	2 fewer per 1000 (from 4 fewer to 16 more)	LOW	CRITICAL
Intracranial bleeding (short-term) – Routine deferred[34,50,128]												
3 (k)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious (c)	None	6/752 (0.8%)	11/735 (1.5%)	RR 0.53 (0.2 to 1.44)	7 fewer per 1000 (from 12 fewer to 7 more)	LOW	CRITICAL
Intracranial bleeding (longer-term) – Selective[168]												
1 (l)	Randomised trials	Serious (m)	No serious inconsistency	No serious indirectness	Very serious (c)	None	1/86 (1.2%)	1/84 (1.2%)	RR 0.98 (0.06 to 15.36)	0 fewer per 1000 (from 11 fewer to 171 more)	VERY LOW	CRITICAL
Reinfarction (short-term) – Selective[12,103,168]												
3 (a)	Randomised trials	Serious (b)	No serious inconsistency	No serious indirectness	Serious (o)	None	13/438 (3%)	24/435 (5.5%)	RR 0.53 (0.28 to 1.02)	26 fewer per 1000 (from 40 fewer to 1 more)	LOW	IMPORTANT
Reinfarction (short-term) – Routine deferred[34,50,128]												
3 (a)	Randomised	No	No serious	No serious	No serious	None	22/752	39/735	RR 0.55	24 fewer	HIGH	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Routine early angiography	Comparator	Relative (95% CI)	Absolute	Quality	Importance
	trials	serious risk of bias	inconsistency	indirectness	imprecision		(2.9%)	(5.3%)	(0.33 to 0.92)	per 1000 (from 4 fewer to 36 fewer)		
Reinfarction (longer-term) – Selective [103,168]												
2 (d)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	14/334 (4.2%)	27/335 (8.1%)	RR 0.52 (0.28 to 0.97)	39 fewer per 1000 (from 2 fewer to 58 fewer)	HIGH	IMPORTANT
Reinfarction (longer-term) – Routine deferred [34,50,128]												
3 (e)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	27/744 (3.6%)	47/724 (6.5%)	RR 0.56 (0.35 to 0.89)	29 fewer per 1000 (from 7 fewer to 42 fewer)	HIGH	IMPORTANT
Heart failure (short-term) – Selective [12,168]												
2 (a)	Randomised trials	Serious (p)	No serious inconsistency	No serious indirectness	Very serious (c)	None	26/190 (13.7%)	25/184 (13.6%)	RR 1.01 (0.6 to 1.68)	1 more per 1000 (from 54 fewer to 92 more)	VERY LOW	IMPORTANT
Heart failure (short-term) – Routine deferred [50]												
1 (a)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	16/536 (3%)	29/522 (5.6%)	RR 0.54 (0.3 to 0.98)	26 fewer per 1000 (from 1 fewer to 39 fewer)	HIGH	IMPORTANT
Heart failure (longer-term) – Selective [168]												
1 (l)	Randomised trials	Serious (m)	No serious inconsistency	No serious indirectness	Very serious (c)	None	12/86 (14%)	12/84 (14.3%)	RR 0.98 (0.47 to 2.05)	3 fewer per 1000 (from 76 fewer to 150 more)	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Routine early angiography	Comparator	Relative (95% CI)	Absolute	Quality	Importance
Recurrent ischaemia (short-term) – Selective [12,103,168]												
3 (q)	Randomised trials	No serious risk of bias	Serious (r)	No serious indirectness	No serious imprecision	None	15/438 (3.4%)	45/435 (10.3%)	RR 0.34 (0.19 to 0.59)	68 fewer per 1000 (from 42 fewer to 84 fewer)	MODERATE	IMPORTANT
Recurrent ischaemia (short-term) – Routine deferred [34,50,128]												
3 (a)	Randomised trials	No serious risk of bias	Serious (r)	No serious indirectness	No serious imprecision	None	12/752 (1.6%)	47/735 (6.4%)	RR 0.25 (0.14 to 0.46)	48 fewer per 1000 (from 35 fewer to 55 fewer)	MODERATE	IMPORTANT
Recurrent ischaemia (longer-term) – Selective [103,168]												
2 (d)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	50/334 (15%)	109/335 (32.5%)	RR 0.46 (0.34 to 0.62)	176 fewer per 1000 (from 124 fewer to 215 fewer)	HIGH	IMPORTANT
Recurrent ischaemia (longer-term) – Routine deferred [34,128]												
2 (e)	Randomised trials	No serious risk of bias	Very serious (s)	No serious indirectness	No serious imprecision	None	24/216 (11.1%)	43/213 (20.2%)	RR 0.55 (0.34 to 0.88)	91 fewer per 1000 (from 24 fewer to 133 fewer)	LOW	IMPORTANT
Unplanned revascularisation (short-term) – Selective [103,168]												
2 (q)	Randomised trials	No serious risk of bias	Serious (r)	No serious indirectness	No serious imprecision	None	18/334 (5.4%)	95/335 (28.4%)	RR 0.19 (0.12 to 0.3)	230 fewer per 1000 (from 199 fewer to 250 fewer)	MODERATE	IMPORTANT
Unplanned revascularisation (short-term) – Routine deferred [128]												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Routine early angiography	Comparator	Relative (95% CI)	Absolute		
1 (a)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious (c)	None	2/82 (2.4%)	2/81 (2.5%)	RR 0.99 (0.14 to 6.84)	0 fewer per 1000 (from 21 fewer to 144 more)	LOW	IMPORTANT
Unplanned revascularisation (longer-term) – Selective [103,168]												
2 (d)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	29/334 (8.7%)	127/335 (37.9%)	RR 0.23 (0.16 to 0.33)	292 fewer per 1000 (from 254 fewer to 318 fewer)	HIGH	IMPORTANT
Unplanned revascularisation (longer-term) – Routine deferred [128]												
1 (l)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious (c)	None	22/82 (26.8%)	25/81 (30.9%)	RR 0.87 (0.54 to 1.41)	40 fewer per 1000 (from 142 fewer to 127 more)	LOW	IMPORTANT
Major bleeding (short-term) – Selective [1,12,103,168]												
4 (t)	Randomised trials	Serious (u)	No serious inconsistency	No serious indirectness	Very serious (c)	None	13/468 (2.8%)	11/465 (2.4%)	RR 1.17 (0.53 to 2.55)	4 more per 1000 (from 11 fewer to 37 more)	VERY LOW	IMPORTANT
Major bleeding (short-term) – Routine deferred [34,50,128]												
3 (k)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious (c)	None	50/752 (6.6%)	56/735 (7.6%)	RR 0.87 (0.6 to 1.26)	10 fewer per 1000 (from 30 fewer to 20 more)	LOW	IMPORTANT
Minor bleeding (short-term) – Selective [1,168]												
2 (t)	Randomised trials	Serious (p)	No serious inconsistency	No serious indirectness	No serious imprecision	None	24/116 (20.7%)	11/114 (9.6%)	RR 2.09 (1.09 to 3.98)	105 more per 1000 (from 9 more to 288	MODERATE	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Routine early angiography	Comparator	Relative (95% CI)	Absolute	Quality	Importance
										more)		
Minor bleeding (short-term) – Routine deferred [34,50]												
2 (k)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious (v)	None	40/670 (6%)	33/654 (5%)	RR 1.19 (0.76 to 1.85)	10 more per 1000 (from 12 fewer to 43 more)	MODERATE	IMPORTANT
Length of hospital stay (index admission) - Selective (better indicated by lower values)[103]												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	248	251	-	MD 3.4 lower (4.39 to 2.41 lower)	HIGH	IMPORTANT
Length of hospital stay (index admission) - Selective (better indicated by lower values) [168]												
1	Randomised trials	Serious (m)	No serious inconsistency	No serious indirectness	Very serious (w)	None	86	84	-	Routine early angio:5 (4 to 7); selective: 6 (5.5 to 8)	VERY LOW	IMPORTANT
Length of hospital stay (index admission) – Routine deferred (better indicated by lower values) [34]												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious (w)	None	134	132	-	Routine early angio:5 (4 to 6); routine deferred: 5 (4 to 7)	LOW	IMPORTANT

(a) 30 days follow-up
(b) 2/3 studies (>50% of pooled population) unclear randomisation process and allocation concealment (CAPITAL-AMI, WEST)
(c) Confidence interval crosses both default MIDs (0.75, 1.25) and line of no effect
(d) CAPITAL-AMI: 6 months follow-up; GRACIA-1: 12 months follow-up
(e) NORDISTEMI: 12 months follow-up; rest 6 months follow-up
(f) Study arms were unbalanced in terms of 15D score at baseline. See also table 6

(g) Confidence interval crosses 1 MID (0.03) and line of no effect
(h) Seven participants were unwilling to register the 15D questionnaire and were excluded from the analysis. This study did not report which group these participants were originally allocated to. Values of 130 and 129 participants were used for the early invasive and routine deferred groups respectively and a sensitivity analysis demonstrated the robustness of this approach
(i) At 7 months follow-up
(j) CAPITAL-AMI: 30 days follow-up; rest: in-hospital follow-up
(k) NORDISTEMI at 30 days follow-up; rest in-hospital follow-up
(l) 6 months follow-up
(m) Unclear randomisation process and allocation concealment
(n) 12 months follow-up
(o) Confidence interval crosses 1 default MID (0.75) and line of no effect
(p) 2/2 studies unclear randomisation process and allocation concealment
(q) GRACIA-1: In-hospital follow-up; rest 30 days follow-up
(r) Unexplained heterogeneity I^2>50%
(s) Unexplained heterogeneity I^2>75%
(t) In-hospital follow-up
(u) 3/4 studies (>50% pooled population) unclear randomisation process and allocation concealment (CAPITAL-AMI, WEST, Agati et al.)
(v) Confidence interval crosses 1 default MID (1.25) and line of no effect
(w) Results reported as median (range), which unlike results reported as mean (SD) cannot be pooled and analysed together

Table 68: Clinical evidence profile: routine early angiography versus combined comparator arms of routine deferred angiography and selective angiography

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Routine early angiography**	**Comparator**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
All-cause mortality (short-term) [12,34,50,103,128,168]												
6 (a)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious (b)	None	40/1190 (3.4%)	42/1170 (3.6%)	RR 0.93 (0.61 to 1.43)	3 fewer per 1000 (from 14 fewer to 15 more)	LOW	CRITICAL
All-cause mortality (longer-term) [34,50,103,128,168]												
5 (c)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious (b)	None	49/1078 (4.5%)	55/1059 (5.2%)	RR 0.88 (0.6 to 1.27)	6 fewer per 1000 (from 21 fewer to 14 more)	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Routine early angiography	Comparator	Relative (95% CI)	Absolute	Quality	Importance
Health-related quality of life (assessed by 15D instrument) (short-term) (better indicated by higher values) [34]												
1 (a)	Randomised trials	Very serious (d)	No serious inconsistency	No serious indirectness	Serious (e)	None	130 (f)	129 (f)	-	MD 0.02 higher (0.02 lower to 0.06 higher)	VERY LOW	CRITICAL
Health-related quality of life (assessed by 15D instrument) (longer-term) (better indicated by higher values) [34]												
1 (g)	Randomised trials	Very serious (d)	No serious inconsistency	No serious indirectness	Serious (e)	None	130 (f)	129 (f)	-	MD 0.02 higher (0.02 lower to 0.06 higher)	VERY LOW	CRITICAL
Stroke (short-term) [12,34,50,103,128,168]												
6 (h)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious (b)	None	10/1190 (0.84%)	15/1170 (1.3%)	RR 0.67 (0.31 to 1.45)	4 fewer per 1000 (from 9 fewer to 6 more)	LOW	CRITICAL
Stroke (longer-term) [34,168]												
2 (i)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious (b)	None	4/220 (1.8%)	8/216 (3.7%)	RR 0.49 (0.15 to 1.61)	19 fewer per 1000 (from 31 fewer to 23 more)	LOW	CRITICAL
Intracranial bleeding (short-term) [12,34,50,103,128,168]												
6 (h)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious (b)	None	7/1190 (0.59%)	13/1170 (1.1%)	RR 0.55 (0.22 to 1.33)	5 fewer per 1000 (from 9 fewer to 4 more)	LOW	CRITICAL
Intracranial bleeding (longer-term) [168]												
1 (j)	Randomised trials	Serious (k)	No serious inconsistency	No serious indirectness	Very serious (b)	None	1/86 (1.2%)	1/84 (1.2%)	RR 0.98 (0.06 to 15.36)	0 fewer per 1000 (from 11 fewer to 171 more)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Routine early angiography	Comparator	Relative (95% CI)	Absolute	Quality	Importance
Reinfarction (short-term) [12,34,50,103,128,168]												
6 (a)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	35/1190 (2.9%)	63/1170 (5.4%)	RR 0.54 (0.36 to 0.81)	25 fewer per 1000 (from 10 fewer to 34 fewer)	HIGH	IMPORTANT
Reinfarction (longer-term) [34,50,103,128,168]												
5 (c)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	41/1078 (3.8%)	74/1059 (7%)	RR 0.54 (0.37 to 0.79)	32 fewer per 1000 (from 15 fewer to 44 fewer)	HIGH	IMPORTANT
Heart failure (short-term) [12,50,168]												
3 (a)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious (l)	None	42/726 (5.8%)	54/706 (7.6%)	RR 0.75 (0.51 to 1.11)	19 fewer per 1000 (from 37 fewer to 8 more)	MODERATE	IMPORTANT
Heart failure (longer-term) [168]												
1 (j)	Randomised trials	Serious (k)	No serious inconsistency	No serious indirectness	Very serious (b)	None	12/86 (14%)	12/84 (14.3%)	RR 0.98 (0.47 to 2.05)	3 fewer per 1000 (from 76 fewer to 150 more)	VERY LOW	IMPORTANT
Recurrent ischaemia (short-term) [12,34,50,103,128,168]												
6 (m)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	27/1190 (2.3%)	92/1170 (7.9%)	RR 0.29 (0.19 to 0.44)	56 fewer per 1000 (from 44 fewer to 64 fewer)	HIGH	IMPORTANT
Recurrent ischaemia (longer-term) [34,103,128,168]												
4 (c)	Randomised trials	No serious risk of bias	Serious (n)	No serious indirectness	No serious imprecision	None	74/550 (13.5%)	152/548 (27.7%)	RR 0.49 (0.38 to 0.63)	141 fewer per 1000 (from 103 fewer to 172 fewer)	MODERATE	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Routine early angiography	Comparator	Relative (95% CI)	Absolute	Quality	Importance
Unplanned revascularisation (short-term) [103,128,168]												
3 (m)	Randomised trials	No serious risk of bias	Serious(n)	No serious indirectness	No serious imprecision	None	20/416 (4.8%)	97/416 (23.3%)	RR 0.2 (0.13 to 0.32)	187 fewer per 1000 (from 159 fewer to 203 fewer)	MODERATE	IMPORTANT
Unplanned revascularisation (longer-term) [103,128,168]												
3 (o)	Randomised trials	No serious risk of bias	Very serious (p)	No serious indirectness	No serious imprecision	None	51/416 (12.3%)	152/416 (36.5%)	RR 0.33 (0.25 to 0.44)	245 fewer per 1000 (from 205 fewer to 274 fewer)	LOW	IMPORTANT
Major bleeding (short-term) [1,12,34,50,103,128,168]												
7 (q)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious (b)	None	63/1220 (5.2%)	67/1200 (5.6%)	RR 0.92 (0.66 to 1.28)	4 fewer per 1000 (from 19 fewer to 16 more)	LOW	IMPORTANT
Minor bleeding (short-term) [1,34,50,168]												
4 (q)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious (r)	None	64/786 (8.1%)	44/768 (5.7%)	RR 1.42 (0.99 to 2.04)	24 more per 1000 (from 1 fewer to 60 more)	MODERATE	IMPORTANT
Length of hospital stay (index admission) (better indicated by lower values) [103]												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	248	251	-	MD 3.4 lower (4.39 to 2.41 lower)	HIGH	IMPORTANT
Length of hospital stay (index admission) (better indicated by lower values) [168]												
1	Randomised trials	Serious (k)	No serious inconsistency	No serious indirectness	Very serious (s)	None	86	84	-	Routine early angio:5 (4 to 7); comparator: 6	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Routine early angiography	Comparator	Relative (95% CI)	Absolute		
										(5.5 to 8)		
Hospital stay (index admission) (better indicated by lower values) [34]												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious (s)	None	134	132	-	Routine early angio:5 (4 to 6); comparator: 5 (4 to 7)	LOW	IMPORTANT

(a) 30 days follow-up.
(b) Confidence interval crosses both default MIDs (0.75, 1.25) and line of no effect.
(c) GRACIA-1 and NORDISTEMI: 12 months follow-up; rest 6 months follow-up.
(d) Study arms were unbalanced in terms of 15D score at baseline.
(e) Confidence interval crosses 1 MID (0.03) and line of no effect.
(f) Seven participants were unwilling to register the 15D questionnaire and were excluded from the analysis. This study did not report which group these participants were originally allocated to. Values of 130 and 129 participants were used for the routine early and routine deferred arms respectively and a sensitivity analysis demonstrated the robustness of this approach.
(g) 7 months follow-up.
(h) CAPITAL-AMI, NORDISTEMI: 30 days follow-up; rest in-hospital follow-up.
(i) NORDISTEMI: 12 months follow-up; rest 6 months follow-up.
(j) 6 months follow-up.
(k) Unclear randomisation process and allocation concealment.
(l) Confidence interval crosses 1 default MID (0.75) and line of no effect.
(m) GRACIA-1: In-hospital follow-up; rest 30 days follow-up.
(n) Unexplained heterogeneity I^2>50%.
(o) GRACIA-1: 12 months follow-up; rest 6 months follow-up.
(p) Unexplained heterogeneity I^2>75%.
(q) NORDISTEMI: 30 days follow-up; rest in-hospital follow-up.
(r) Confidence interval crosses 1 default MID (1.25) and line of no effect.
(s) Results reported as median (range), which unlike results reported as mean (SD) cannot be pooled and analysed together.

Change in health-related quality of life could not be analysed without access to patient-level data.[35] The values listed below give an indication of how baseline differences between the groups may influence interpretation of results recorded at 1-month and 7-month follow-up**.**

Table 69: Health-related quality of life (assessed by 15D instrument)

Time (months)	Routine early angiography	Routine deferred angiography	Mean difference
0 (baseline)*	0.913 ± 0.092	0.902 ± 0.089	0.011
1	0.873 ± 0.156	0.856 ± 0.167	0.017
7	0.889 ± 0.160	0.872 ± 0.182	0.017

*Values are mean ± SD. *4 days before STEMI*

No data was reported on cardiovascular mortality.

16.4 Economic evidence

One economic evaluation was included that compared routine early angiography with routine deferred angiography following STEMI successfully treated by fibrinolysis.[35] This is summarised in the economic evidence profile below (Table 70) and the economic evidence table in Appendix H.

No relevant economic evaluations were identified that compared routine early angiography with selective angiography following STEMI successfully treated by fibrinolysis. See also the economic article selection flow diagram in Appendix E.

Table 70: Economic evidence profile: routine early angiography versus deferred angiography

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	ICER	Uncertainty
Bøhmer 2011[35] (Norway)	Partially applicable (a)	Potentially serious limitations (b)	• Cost–utility analysis (QALYs) • Within-trial analysis (NORDISTEMI – 12 months)[34] • Routine early angiography (< 24 hours) versus routine deferred angiography (within 2 weeks if not clinically indicated earlier)	£501 (c)	0.008 QALYs	£62,648 per QALY gained (c)	Early angiography had a 49% probability of being cost effective at a £41,061 threshold. (d) ICER increased to £108,463 when all costs were included and reduced to £20,077 when intra-cardiac defibrillator costs were excluded.

(a) Some uncertainty about the applicability of Norway resource use and unit costs. Utility instrument used in QALY estimation does not meet NICE reference case (15D instrument with Finnish VAS-based valuation set).

(b) One-year time horizon may not fully capture differences in costs and health outcomes. Within-trial analysis therefore by definition does not reflect all evidence available (see clinical review for comparison with other studies) – judged to be one of the more relevant clinical trials, although people were considered to be fairly low risk. Limited sensitivity analysis.

(c) Recalculated from reported numbers to exclude sick leave costs in line with NICE reference case. Base-case analysis used here excluded in-hospital costs deemed 'unrelated' by authors; those costs were included in a sensitivity analysis. Converted from 2008 Norwegian Kroner using purchasing power parities.[249]

(d) It was not possible to recalculate the probability of being cost effective, and so this result includes sick leave costs. Since sick leave costs were higher for early strategy than for the deferred strategy, if this had been excluded it is likely that the probability of the early strategy being cost effective at this threshold would have been higher.

16.5 Evidence statements

Clinical

Routine early versus selective or routine deferred angiography (analysed as separate subgroups – see Table 67).

All-cause mortality

- Very low and low quality evidence suggested that routine early angiography is potentially more clinically effective when compared to selective angiography at decreasing all-cause mortality at ≤30 days and in the longer term, but the direction of the estimate of effect could favour either intervention [3 studies, n = 873 and n = 669 respectively].
- Low quality evidence suggested that there may be no clinical difference between routine early angiography when compared to routine deferred angiography at decreasing all-cause mortality at ≤30 days and in the longer term, but the direction of the estimate of effect could favour either intervention [3 studies, n = 1487 and n = 1468 respectively].

Health-related quality of life (assessed by 15D instrument)

- Very low quality evidence suggested that there may be no clinical difference between routine early angiography when compared to routine deferred angiography at improving health-related quality of life at ≤30 days and longer term, but the direction of effect favoured routine early angiography [1 study, n = 259].

Stroke

- Very low quality evidence suggested that there may be no clinical difference between routine early angiography and selective angiography at reducing the incidence of stroke at ≤30 days and in the longer term, but the direction of the estimate of effect could favour either intervention [3 studies, n = 873 and n = 170 respectively].
- Low quality evidence suggest that routine early angiography is potentially more clinically effective when compared to routine deferred angiography at reducing in the incidence of stroke at ≤30 days and in the longer term, but the direction of the estimate of effect could favour either intervention [3 studies, n = 1487; 1 study n = 266 respectively]

Intracranial bleeding

- Very low and low quality evidence suggested that routine early angiography is potentially more clinically effective when compared to selective angiography at reducing the incidence of intracranial bleeding at ≤30 days and longer term, but the direction of the estimate of effect could favour either intervention [3 studies, n = 170 and n = 873 respectively].
- Low quality evidence suggested that routine early angiography is potentially more clinically effective when compared to routine deferred angiography at reducing the incidence of intracranial bleeding at ≤30 days, but the direction of the estimate of effect could favour either intervention [3 studies, n = 1487].

Recurrent ischaemia

- Moderate and high quality evidence showed that routine early angiography is more clinically effective when compared to selective angiography at reducing the incidence of recurrent ischaemia at ≤30 days and longer term [3 studies, n = 873 and 2 studies n = 669 respectively]
- Moderate and low quality evidence showed that routine early angiography is more clinically effective when compared to routine deferred angiography at reducing the incidence of recurrent ischaemia at ≤30 days [3 studies, n = 1487 and 2 studies, n = 429 respectively].

Reinfarction

When comparing routine early angiography to selective angiography for reducing the incidence of re infarction:

- Low quality evidence suggested that routine early angiography is potentially more clinically effective at ≤30 days [3 studies, n = 873]
- High quality evidence showed that routine early angiography is more clinically effective in the longer term [2 studies, n = 669].
- High quality evidence showed that routine early angiography is more clinically effective when compared to routine deferred angiography at reducing the incidence of reinfarction at ≤30 days and in the longer term [3 studies, n = 1487 and n = 1468 respectively].

Heart failure

- Very low quality evidence suggested that there may be no clinical difference between routine early angiography and selective angiography at reducing the incidence of heart failure at ≤30 days and in the longer term. In the longer term the estimate of effect could favour either intervention [2 studies, n = 374 and n = 170 respectively].
- High quality evidence showed that routine early angiography is more clinically effective when compared to routine deferred angiography at reducing the incidence of heart failure at ≤30 days [1 study, n = 1058].

Unplanned revascularisation

- Moderate and high quality evidence showed that routine early angiography is more clinically effective when compared to selective angiography at reducing the rate of unplanned revascularisation failure at ≤30 days and in the longer term [2 studies, n = 669].
- Low quality evidence suggested that there may be no clinical difference between routine early angiography and routine deferred angiography at reducing the rate of unplanned revascularisation failure at ≤30 days and in the longer term, but the direction of the estimate could favour either intervention [1 study, n = 163].

Major bleeding

- Very low and low quality evidence suggested that there may be no clinical difference between routine early angiography and selective or routine deferred angiography at reducing the incidence of major bleeding at ≤30 days, but the direction of the estimate could favour either intervention [4 studies, n = 933 and 3 studies, n = 1487 respectively].

Minor bleeding

- Moderate quality evidence showed that selective angiography is more clinically effective when compared to routine early angiography at reducing the incidence of minor bleeding at ≤30 days [2 studies, n = 230].
- Moderate quality evidence suggested that there may be no clinical difference between routine early angiography and routine deferred angiography at reducing the incidence of minor bleeding at ≤30 days, but the direction of estimate of effect favoured routine deferred angiography [2 studies, n = 1324].

Length of hospital stay

- High quality evidence showed that routine early angiography is more clinically effective than selective angiography at reducing length of hospital stay [1 study, n = 499].

All-cause mortality

- Low quality evidence suggested that there may be no clinical difference between routine early angiography and routine deferred or selective angiography at improving all-cause mortality at ≤30

days and in the longer term, but the direction of the estimate of effect could favour either intervention [6 studies, n = 2360 and 5 studies, n = 2137 respectively].

Health-related quality of life (assessed by 15D instrument)

- Very low quality evidence suggested that there may be no clinical difference between routine early angiography when compared to routine deferred or selective angiography at improving health-related quality of life at ≤30 days or in the longer term, but the direction of effect favoured routine early angiography [1 study, n = 259].

Stroke

- Low quality evidence suggested that routine early angiography is potentially associated with a reduced incidence of stroke at ≤30 days and in the longer term when compared to routine deferred or selective angiography, but the direction of the estimate of effect could favour either intervention [6 studies, n = 2360 and 2 studies, n = 436 respectively].

Intracranial bleeding

When comparing early angiography to deferred or selective angiography for reducing the incidence of intracranial bleeding:

- Low quality evidence suggested that early angiography is potentially more clinically effective ≤30 days, but the direction of the estimate of effect could favour either intervention [6 studies, n = 2360].
- Very low quality evidence suggested that there may be no clinical difference in the longer term, but the direction of the estimate of effect could favour either intervention [1 study, n = 170].

Reinfarction

- High quality evidence showed that routine early angiography is more clinically effective when compared to routine deferred or selective angiography at reducing the incidence of reinfarction at ≤30 days and in the longer term [6 studies, n = 2360 and 5 studies, n = 2137 respectively].

Heart failure

- Moderate and very low quality evidence suggested that there may be no clinical difference between routine early angiography and routine deferred or selective angiography at reducing the incidence of heart failure at ≤30 days and in the longer term (but in the longer term the direction of the estimate of effect could favour either intervention. [3 studies, n = 1432 and 1 study, n = 170 respectively].

Recurrent ischaemia

- High and moderate quality evidence showed that routine early angiography is more clinically effective when compared to routine deferred or selective angiography at reducing the incidence of recurrent ischaemia at ≤30 days and in the longer term [6 studies, n = 2360 and 4 studies, n = 1098 respectively].

Unplanned revascularisation

- Moderate and low quality evidence showed that routine early angiography is more clinically effective when compared to routine deferred or selective angiography at reducing the rate of unplanned revascularisation failure at ≤30 days and in the longer term [3 studies, n = 832].

Major bleeding

- Low quality evidence suggested that there may be no clinical difference between routine early angiography and routine deferred or selective angiography at reducing the incidence of major bleeding at ≤30 days, but the direction of the estimate could favour either intervention [7 studies, n = 2420].

Minor bleeding

- Moderate quality evidence suggested that routine deferred or selective angiography are potentially more clinically effective than routine early angiography at reducing the incidence of minor bleeding at ≤ 30 days [4 studies, n = 1554].

Length of hospital stay

- High quality evidence showed that routine early angiography is more clinically effective than routine deferred or selective angiography at reducing length of hospital stay [1 study, n = 499].

Economic

- One cost–utility analysis found that a routine early angiography strategy was not cost effective compared to a routine deferred angiography strategy following STEMI successfully treated by fibrinolysis (ICER: £62,648 per QALY gained). This analysis was assessed as partially applicable with potentially serious limitations.
- No relevant economic evaluations were identified that compared routine early angiography with selective angiography following STEMI successfully treated by fibrinolysis.

16.6 Recommendations and link to evidence

Recommendations	**The current recommendations can be found at: www.nice.org.uk/guidance/ng185**
Relative values of different outcomes	For this review question the GDG considered the outcomes of all-cause mortality, all-cause stroke, intracranial bleeding and quality of life as critical to decision-making. Myocardial reinfarction, heart failure and major bleeding were considered important, and recurrent ischaemia, unplanned revascularisation, minor bleeding and length of hospital stay as less important to decision-making. No data were found for cardiovascular mortality.
Trade-off between clinical benefits and harms	This review provides evidence that a strategy of routine early coronary angiography within 24 hours of fibrinolysis in people with acute STEMI has no beneficial effect on mortality, stroke, or intracranial haemorrhage, relative to strategies of routine deferred angiography or selective angiography. Early routine angiography was associated with a reduction in risk of reinfarction, recurrent ischaemia, and unplanned revascularisation relative to deferred routine or selective angiography, but interpretation of this evidence is complicated by a number of issues. The GDG debated the relative importance of the differences in rates of reinfarction, recurrent ischaemia and unplanned revascularisation between the 2 strategies. Myocardial reinfarction in people treated by fibrinolysis is associated with an increased risk of mortality[115,140] but the GDG noted that definitions of reinfarction varied between the trials in the review and adjudication of reinfarction in people with STEMI undergoing PCI within a few hours of fibrinolysis is problematic. Moreover, rates of reinfarction related to interventional procedures were not reported and in coronary intervention trials the prognostic significance of procedure-related myocardial infarction is controversial.[254]The definition of recurrent ischaemia also varied across trials and the prognostic significance of this end point is unclear. People with recurrent ischaemia would have generally been referred for urgent coronary arteriography and these people probably accounted for the higher rate of unplanned revascularisation in the routine delayed and selective angiography groups.

	The GDG noted that the pooled mortality rates in the evidence review were relatively low (3.4% in the routine early angiography group), probably because several trials recruited people who had survived the very early high risk phase of STEMI and excluded people with other high risk features (for example, cardiogenic shock). The time between fibrinolysis and angiography in the routine early angiography arms of the trials ranged from 1.4 hours (CAPITAL-AMI[168]) to 20 hours (Agati et al.[1]). Hence in some trials angiography may have been carried out in people with salvageable myocardium, but in other trials angiography was probably carried out in people with completed infarcts. The GDG concluded that there is some uncertainty about the benefits of a strategy of routine early coronary angiography in people with STEMI treated by fibrinolysis, relative to strategies of routine deferred or selective angiography. For those who remain clinically stable following successful fibrinolysis the GDG agreed that angiography should be considered but the optimal timing of the intervention is unclear. People likely to benefit most from early angiography and subsequent myocardial revascularisation will be those who are clinically unstable, as they are at highest absolute risk of adverse cardiovascular events. The GDG therefore made a consensus recommendation that people with recurrent myocardial ischaemia after fibrinolysis should be offered coronary arteriography as soon as possible.
Economic considerations	One published cost-effectiveness analysis was identified.[35] This was based on the NORDISTEMI study[34,35] included in the clinical review. NORDISTEMI[34,35] found that a strategy of routine early angiography (arrival in the cardiac catheter laboratory median 130 minutes after administration of tenecteplase) was not cost effective compared to a strategy of deferred angiography (defined as angiography where clinically indicated or otherwise within 2 weeks of hospital discharge). The incremental cost-effectiveness ratio was around £60,000 per QALY gained. This analysis was judged partially applicable with potentially serious limitations. The GDG was concerned that the study may underestimate cost effectiveness. In particular Norway is more rural than England and Wales and this may mean the difference in transportation costs (which drove the difference in costs between the strategies) may be higher than in England and Wales. Half of the difference in transportation costs in the study was attributable to helicopter ambulance costs in the routine early angiography group. If the cost difference between the strategies is overestimated, cost effectiveness would be underestimated. Another issue was that while NORDISTEMI[34,35] was one of the more contemporary studies, and therefore potentially more relevant, the mortality rate observed was half that of a UK STEMI population. This suggests that the population was at low risk and so the potential absolute benefits to people with STEMI could have been underestimated, which would have reduced cost effectiveness. The initial resource use and cost to the NHS of providing routine early angiography is considered likely to be higher than both routine deferred angiography and selective angiography. While the number of initial procedures will be the same with strategies of routine early angiography and routine deferred angiography, provision of early angiography (within 24 hours of fibrinolysis) may incur higher transportation costs (for emergency ambulance transfer to a PCI-capable hospital) and require an increase in catheter laboratory capacity. A strategy of selective angiography is considered likely to have the lowest

	initial costs as a lower number of people will undergo an invasive cardiac procedure. However, in the clinical review downstream revascularisation rates were higher with a selective strategy, which would at least partially offset this lower initial cost. Reductions in clinical events such as reinfarction and ischaemia observed with a routine early strategy may also lead to reductions in later resource use and so offset higher initial costs. The GDG concluded that there was uncertainty about whether or not routine early angiography was cost effective for all people but that cost effectiveness was likely to be greatest in the subgroup of people who are unstable following successful fibrinolysis as they were likely to gain the greatest clinical benefit.
Quality of evidence	The GDG noted that the trials in this review enrolled people over a 10 year period (1998–2008). Interpretation of the results is confounded by differences between trials in design, participant risk profile, pharmacological and interventional treatment, and outcome definitions. Several of the trials were not powered to detect differences in clinically important end points, although this was improved by pooling data where possible. The time between administration of fibrinolysis and randomisation varied between trials. For example, in NORDISTEMI[34,35] people were randomised at the time fibrinolysis was given, and people in the selective angiography arm were considered for rescue PCI if there was < 50% resolution of ST-segment elevation at 60 minutes. By contrast, in GRACIA-1[102] people were enrolled 6 hours after fibrinolysis and people undergoing rescue PCI were therefore probably excluded. This may partly explain the variation in rates of invasive management in the deferred routine and selective angiography groups between studies. The use of antiplatelet therapy varied across trials. In most trials an ADP receptor antagonist was used only after PCI, but in NORDISTEMI[34] all people were prescribed clopidogrel. Use of GPI also varied between trials. The definitions of end points were either not reported or varied across trials. Definition of reinfarction in people with STEMI is difficult and varied widely across the trials. The definition of recurrent ischaemia required new electrocardiographic abnormality, but in some trials also included new arrhythmia or anginal symptoms. The trials also used different definitions for bleeding and stroke. The GDG noted that length of hospital stay has reduced over time and so older studies may not be representative of current practice.
Other considerations	In the Open Artery Trial (OAT)[132,133] routine PCI in 2201 stable people with a totally occluded infarct-related artery and without severe inducible ischaemia 3–28 days after myocardial infarction did not reduce longer-term adverse clinical events rates. This trial suggests that reopening occluded infarct-related coronary arteries more than 3 days after myocardial infarction does not confer benefit, although this evidence was considered only partially relevant because only 19% of the participants were treated with fibrinolysis within 24 hours of symptom onset of STEMI.

17 Adjunctive pharmacotherapy and associated NICE guidance

This section was updated and replaced in 2020.

See www.nice.org.uk/guidance/ng185 for the 2020 evidence review.

18 Acronyms and abbreviations

Acronym	Definition
IABP	Intra-aortic balloon pump
ACS	Acute coronary syndrome
CABG	Coronary artery bypass graft
CVD	Cardiovascular disease
ECG	Electrocardiographic / electrocardiogram
fPPCI	Facilitated primary percutaneous coronary intervention
FT	Fibrinolytic therapy
GCS	Glasgow Coma Scale
GPI	Glycoprotein IIb/IIIa receptor antagonist
HR	Hazard ratio
HRQoL	Health-related quality of life
ITT	Intention to treat
IQR	Interquartile range
LBBB	Left bundle branch block
LMWH	Low molecular weight heparin
MD	Mean difference
MI	Myocardial infarction
MID	Minimal important difference
MILQ	Multidimensional index of life quality
n	Number
NA	Not applicable
NSTEMI	non-ST-segment-elevation myocardial infarction
NYHA	New York Heart Association
RCT	Randomised control trial
PCI	Percutaneous coronary intervention
PPCI	Primary percutaneous coronary intervention
RF	Repeated fibrinolysis
RR	Risk ratio (or relative risk)
SBP	Systolic blood pressure
SD	Standard deviation
STEMI	ST-segment-elevation myocardial infarction
UFH	Unfractionated heparin

19 Glossary

Term	Definition
Abstract	Summary of a study, which may be published alone or as an introduction to a full scientific paper.
Algorithm (in guidelines)	A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows.
Allocation concealment	The process used to prevent advance knowledge of group assignment in a RCT. The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants.
Applicability	The degree to which the results of an observation, study or review are likely to hold true in a particular clinical practice setting.
Arm (of a clinical study)	Subsection of individuals within a study who receive one particular intervention, for example placebo arm
Association	Statistical relationship between 2 or more events, characteristics or other variables. The relationship may or may not be causal.
Baseline	The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.
Before-and-after study	A study that investigates the effects of an intervention by measuring particular characteristics of a population both before and after taking the intervention, and assessing any change that occurs.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results that is caused by the way the study is designed or conducted.
Blinding	Keeping the study participants, caregivers, researchers and outcome assessors unaware about the interventions to which the participants have been allocated in a study.
Carer (caregiver)	Someone other than a health professional who is involved in caring for a person with a medical condition.
Case–control study	Comparative observational study in which the investigator selects individuals who have experienced an event (for example, developed a disease) and others who have not (controls), and then collects data to determine previous exposure to a possible cause.
Case-series	Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.
Clinical efficacy	The extent to which an intervention is active when studied under controlled research conditions.
Clinical effectiveness	The extent to which an intervention produces an overall health benefit in routine clinical practice.
Clinician	A healthcare professional providing direct patient care, for example doctor, nurse or physiotherapist.
Cochrane Review	The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration).
Cohort study	A retrospective or prospective follow-up study. Groups of individuals to be followed up are defined on the basis of presence or absence of exposure to a suspected risk factor or intervention. A cohort study can be comparative, in which case 2 or more groups are selected on the basis of differences in their exposure to the agent of interest.

Comorbidity	Co-existence of more than 1 disease or an additional disease (other than that being studied or treated) in an individual.
Comparability	Similarity of the groups in characteristics likely to affect the study results (such as health status or age).
Concordance	This is a recent term whose meaning has changed. It was initially applied to the consultation process in which doctor and patient agree therapeutic decisions that incorporate their respective views, but now includes patient support in medicine taking as well as prescribing communication. Concordance reflects social values but does not address medicine-taking and may not lead to improved adherence.
Confidence interval (CI)	A range of values for an unknown population parameter with a stated 'confidence' (conventionally 95%) that it contains the true value. The interval is calculated from sample data, and generally straddles the sample estimate. The 'confidence' value means that if the method used to calculate the interval is repeated many times, then that proportion of intervals will actually contain the true value.
Confounding	In a study, confounding occurs when the effect of an intervention on an outcome is distorted as a result of an association between the population or intervention or outcome and another factor (the 'confounding variable') that can influence the outcome independently of the intervention under study.
Control group	A group of patients recruited into a study that receives no treatment, a treatment of known effect, or a placebo (dummy treatment) - in order to provide a comparison for a group receiving an experimental treatment, such as a new drug.
Cost–benefit analysis	A type of economic evaluation where both costs and benefits of healthcare treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment.
Cost–consequences analysis (CCA)	A type of economic evaluation where various health outcomes are reported in addition to cost for each intervention, but there is no overall measure of health gain.
Cost-effectiveness analysis (CEA)	An economic study design in which consequences of different interventions are measured using a single outcome, usually in 'natural' units (For example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness.
Cost–utility analysis (CUA)	A form of cost-effectiveness analysis in which the units of effectiveness are quality-adjusted life-years (QALYs).
Credible Interval	The Bayesian equivalent of a confidence interval.
Decision analysis	An explicit quantitative approach to decision-making under uncertainty, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes.
Discounting	Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
Dominance	An intervention is said to be dominated if there is an alternative intervention that is both less costly and more effective.
Drop-out	A participant who withdraws from a trial before the end.
Economic evaluation	Comparative analysis of alternative health strategies (interventions or programmes) in terms of both their costs and consequences.
Effect (as in effect	The observed association between interventions and outcomes or a statistic

measure, treatment effect, estimate of effect, effect size)	to summarise the strength of the observed association.
Effectiveness	See 'Clinical effectiveness'.
Efficacy	See 'Clinical efficacy'.
Epidemiological study	The study of a disease within a population, defining its incidence and prevalence and examining the roles of external influences (For example, infection, diet) and interventions.
EQ-5D (EuroQol-5D)	A standardise instrument used to measure a health outcome. It provides a single index value for health status.
Evidence	Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals and/or patients).
Exclusion criteria (literature review)	Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.
Exclusion criteria (clinical study)	Criteria that define who is not eligible to participate in a clinical study.
Extended dominance	If Option A is both more clinically effective than Option B and has a lower cost per unit of effect, when both are compared with a do-nothing alternative then Option A is said to have extended dominance over Option B. Option A is therefore more efficient and should be preferred, other things remaining equal.
Extrapolation	In data analysis, predicting the value of a parameter outside the range of observed values.
Follow-up	Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables.
Generalisability	The extent to which the results of a study based on measurement in a particular patient population and/or a specific context hold true for another population and/or in a different context. In this instance, this is the degree to which the guideline recommendation is applicable across both geographical and contextual settings. For instance, guidelines that suggest substituting one form of labour for another should acknowledge that these costs might vary across the country.
Gold standard	See 'Reference standard'.
GRADE / GRADE profile	A system developed by the GRADE Working Group to address the shortcomings of present grading systems in healthcare. The GRADE system uses a common, sensible and transparent approach to grading the quality of evidence. The results of applying the GRADE system to clinical trial data are displayed in a table known as a GRADE profile.
Harms	Adverse effects of an intervention.
Health economics	The study of the allocation of scarce resources among alternative healthcare treatments. Health economists are concerned with both increasing the average level of health in the population and improving the distribution of health.
Health-related quality of life (HRQoL)	A combination of an individual's physical, mental and social well-being; not merely the absence of disease.
Heterogeneity or Lack of homogeneity	The term is used in meta-analyses and systematic reviews when the results or estimates of effects of treatment from separate studies seem to be very different – in terms of the size of treatment effects or even to the extent that some indicate beneficial and others suggest adverse treatment effects. Such results may occur as a result of differences between studies in terms of the patient populations, outcome measures, definition of variables or duration of

	follow-up.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of effect.
Inclusion criteria (literature review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Incremental analysis	The analysis of additional costs and additional clinical outcomes with different interventions.
Incremental cost	The mean cost per patient associated with an intervention minus the mean cost per patient associated with a comparator intervention.
Incremental cost-effectiveness ratio (ICER)	The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another.
Incremental net benefit (INB)	The value (usually in monetary terms) of an intervention net of its cost compared with a comparator intervention. The INB can be calculated for a given cost effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the INB is calculated as: (£20,000 x QALYs gained) – Incremental cost.
Indirectness	The available evidence is different to the review question being addressed, in terms of PICO (population, intervention, comparison and outcome).
Intention-to-treat analysis (ITT)	A strategy for analysing data from a randomised controlled trial. All participants are included in the arm to which they were allocated, whether or not they received (or completed) the intervention given to that arm. Intention-to-treat analysis prevents bias caused by the loss of participants, which may disrupt the baseline equivalence established by randomisation and which may reflect non-adherence to the protocol.
Intervention	Healthcare action intended to benefit the patient, for example, drug treatment, surgical procedure, psychological therapy.
Intraoperative	The period of time during a surgical procedure.
Kappa statistic	A statistical measure of inter-rater agreement that takes into account the agreement occurring by chance.
Length of stay	The total number of days a participant stays in hospital.
Licence	See ‘Product licence’.
Life-years gained	Mean average years of life gained per person as a result of the intervention compared with an alternative intervention.
Likelihood ratio	The likelihood ratio combines information about the sensitivity and specificity. It tells you how much a positive or negative result changes the likelihood that a patient would have the disease. The likelihood ratio of a positive test result (LR+) is sensitivity divided by 1- specificity.
Long-term care	Residential care in a home that may include skilled nursing care and help with everyday activities. This includes nursing homes and residential homes.
Markov model	A method for estimating long-term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle).
Meta-analysis	A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result. The aim is to derive more precise and clear information from a large data pool. It is generally more reliably likely to confirm or refute a hypothesis than the individual trials.
Multivariate model	A statistical model for analysis of the relationship between 2 or more predictor (independent) variables and the outcome (dependent) variable.

Number needed to treat (NNT)	The number of patients that who on average must be treated to prevent a single occurrence of the outcome of interest.
Observational study	Retrospective or prospective study in which the investigator observes the natural course of events with or without control groups; for example, cohort studies and case–control studies.
Odds ratio	A measure of treatment effectiveness. The odds of an event happening in the treatment group, expressed as a proportion of the odds of it happening in the control group. The 'odds' is the ratio of events to non-events.
Opportunity cost	The loss of other healthcare programmes displaced by investment in or introduction of another intervention. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.
Outcome	Measure of the possible results that may stem from exposure to a preventive or therapeutic intervention. Outcome measures may be intermediate end points or they can be final end points. See 'Intermediate outcome'.
P value	The probability that an observed difference could have occurred by chance, assuming that there is in fact no underlying difference between the means of the observations. If the probability is less than 1 in 20, the p value is less than 0.05; a result with a p value of less than 0.05 is conventionally considered to be 'statistically significant'.
Perioperative	The period from admission through surgery until discharge, encompassing the pre-operative and post-operative periods.
Placebo	An inactive and physically identical medication or procedure used as a comparator in controlled clinical trials.
Polypharmacy	The use or prescription of multiple medications.
Postoperative	Pertaining to the period after patients leave the operating theatre, following surgery.
Power (statistical)	The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed.
Preoperative	The period before surgery commences.
Primary care	Healthcare delivered to patients outside hospitals. Primary care covers a range of services provided by general practitioners, nurses, dentists, pharmacists, opticians and other healthcare professionals.
Primary outcome	The outcome of greatest importance, usually the one in a study that the power calculation is based on.
Product licence	An authorisation from the MHRA to market a medicinal product.
Prognosis	A probable course or outcome of a disease. Prognostic factors are patient or disease characteristics that influence the course. Good prognosis is associated with low rate of undesirable outcomes; poor prognosis is associated with a high rate of undesirable outcomes.
Prospective study	A study in which people are entered into the research and then followed up over a period of time with future events recorded as they happen. This contrasts with studies that are retrospective.
Publication bias	Also known as reporting bias. A bias caused by only a subset of all the relevant data being available. The publication of research can depend on the nature and direction of the study results. Studies in which an intervention is not found to be effective are sometimes not published. Because of this, systematic reviews that fail to include unpublished studies may overestimate the true effect of an intervention. In addition, a published report might present a biased set of results (for example, only outcomes or subgroups where a statistically significant difference was found).

Quality of life	See 'Health-related quality of life'.
Quality-adjusted life year (QALY)	An index of survival that is adjusted to account for the patient's quality of life during this time. QALYs have the advantage of incorporating changes in both quantity (longevity/mortality) and quality (morbidity, psychological, functional, social and other factors) of life. Used to measure benefits in cost–utility analysis. The QALYs gained are the mean QALYs associated with one treatment minus the mean QALYs associated with an alternative treatment.
Randomisation	Allocation of participants in a research study to 2 or more alternative groups using a chance procedure, such as computer-generated random numbers. This approach is used in an attempt to ensure there is an even distribution of participants with different characteristics between groups and thus reduce sources of bias.
Randomised controlled trial (RCT)	A comparative study in which participants are randomly allocated to intervention and control groups and followed up to examine differences in outcomes between the groups.
RCT	See 'Randomised controlled trial'.
Receiver operated characteristic (ROC) curve	A graphical method of assessing the accuracy of a diagnostic test. Sensitivity Is plotted against 1-specificity. A perfect test will have a positive, vertical linear slope starting at the origin. A good test will be somewhere close to this ideal.
Reference standard	The test that is considered to be the best available method to establish the presence or absence of the outcome – this may not be the one that is routinely used in practice.
Relative risk (RR)	The number of times more likely or less likely an event is to happen in one group compared with another (calculated as the risk of the event in group A/the risk of the event in group B).
Reporting bias	See publication bias.
Resource implication	The likely impact in terms of finance, workforce or other NHS resources.
Retrospective study	A retrospective study deals with the present/ past and does not involve studying future events. This contrasts with studies that are prospective.
Review question	In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.
Secondary outcome	An outcome used to evaluate additional effects of the intervention deemed a priori as being less important than the primary outcomes.
Selection bias	A systematic bias in selecting participants for study groups, so that the groups have differences in prognosis and/or therapeutic sensitivities at baseline. Randomisation (with concealed allocation) of patients protects against this bias.
Sensitivity	Sensitivity or recall rate is the proportion of true positives which are correctly identified as such. For example in diagnostic testing it is the proportion of true cases that the test detects. See the related term 'Specificity'
Sensitivity analysis	A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results. One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study. Multi-way simple sensitivity analysis (scenario analysis): 2 or more parameters are varied at the same time and the overall effect on the results is evaluated.

	Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified. Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (For example, Monte Carlo simulation).
Significance (statistical)	A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ($p < 0.05$).
Specificity	The proportion of true negatives that a correctly identified as such. For example in diagnostic testing the specificity is the proportion of non-cases incorrectly diagnosed as cases. See related term 'Sensitivity'. In terms of literature searching a highly specific search is generally narrow and aimed at picking up the key papers in a field and avoiding a wide range of papers.
Stakeholder	Those with an interest in the use of the guideline. Stakeholders include manufacturers, sponsors, healthcare professionals, and patient and carer groups.
Systematic review	Research that summarises the evidence on a clearly formulated question according to a pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis.
Time horizon	The time span over which costs and health outcomes are considered in a decision analysis or economic evaluation.
Treatment allocation	Assigning a participant to a particular arm of the trial.
Univariate	Analysis which separately explores each variable in a data set.
Utility	A measure of the strength of an individual's preference for a specific health state in relation to alternative health states. The utility scale assigns numerical values on a scale from 0 (death) to 1 (optimal or 'perfect' health). Health states can be considered worse than death and thus have a negative value.

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