ClinicalEvidence

Myocardial infarction (ST-elevation)

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ABSTRACT

INTRODUCTION: About one quarter of people having an acute myocardial infarction (MI) in the USA will die of it, half of them within 1 hour of the onset of symptoms. Cardiogenic shock develops in over 5% of people surviving the first hour after an acute MI, with a mortality of 50% to 80% in the first 48 hours. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: Which treatments improve outcomes in acute MI? Which treatments improve outcomes for cardiogenic shock after MI? We searched: Medline, Embase, The Cochrane Library, and other important databases up to October 2009 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 52 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: angiotensin-converting enzyme (ACE) inhibitors, aspirin, beta-blockers, calcium channel blockers, early cardiac surgery, early invasive cardiac revascularisation, glycoprotein IIb/IIIa inhibitors, intra-aortic balloon counterpulsation, nitrates (with or without thrombolysis), positive inotropes, primary percutaneous transluminal coronary angioplasty (PTCA), pulmonary artery catheterisation, thrombolysis (with or without low molecular weight heparin, with or without unfractionated heparin), vasodilators, and ventricular assistance devices and cardiac transplantation.

QUESTIONS

INTERVENTIONS

TREATMENTS IN MI (ST-ELEVATION)

CARDIOGENIC SHOCK AFTER ACUTE MI

Covered elsewhere in Clinical Evidence

Non ST-elevation acute coronary syndrome

Secondary prevention of ischaemic cardiac events

Prevention of cardiovascular events in diabetes

To be covered in future updates

Drug eluting stents

Intracoronary thrombolysis

Paramedic delivered thrombolysis

Routine use of statins post MI

Adding ACE inhibitors to aspirin

ACE inhibitors in people with a normal LV ejection fraction

Clopidogrel (alone or in combination with aspirin)

Key points

- About one quarter of people who have a myocardial infarction (MI) in the USA will die from it, half of them within 1 hour of the onset of symptoms.

  Cardiogenic shock develops in over 5% of people who survive the first hour after an MI, with a mortality of 50% to 80% in the first 48 hours.

- Aspirin reduces mortality, reinfarction, and stroke at 1 month compared with placebo in people with an acute MI.

  Thrombolysis within 6 hours reduces mortality but increases the risk of stroke or major bleeding in people with acute MI, with different agents seeming to have similar efficacy.

  Adding low molecular weight heparin to thrombolytics may reduce the risk of further cardiovascular events, but the combination has not been shown to improve survival.

- Beta-blockers reduce reinfarction in people with acute MI, but have no effect on mortality in the short term, and increase cardiogenic shock.

- ACE inhibitors reduce mortality in people with acute MI compared with placebo.

  Nitrates reduce mortality and improve symptoms in people not receiving thrombolysis, but may not be beneficial in people after thrombolysis.

  Calcium channel blockers have not been shown to reduce mortality after an acute MI, and early treatment with nifedipine may increase mortality.

- Primary PTCA within 12 hours of onset of chest pain reduces the risk of death, reinfarction, and stroke compared with thrombolysis.

- In people with cardiogenic shock, invasive cardiac revascularisation within 48 hours of acute MI reduces mortality at 12 months compared with medical treatment alone, but people aged over 75 years may not benefit.

  We don't know whether thrombolysis, vasodilators, intra-aortic balloon counterpulsation, ventricular assistance devices and cardiac transplantation, or early cardiac surgery improve survival in people with cardiogenic shock.

  There is a consensus that positive inotropes and pulmonary artery catheterisation are beneficial, but we found no trials that confirmed this.

DEFINITION

Acute MI: Acute MI is myocardial cell death caused by prolonged ischaemia due to sudden occlusion of a coronary artery. There are two types of acute MI: ST-segment elevation MI (STEMI; clinically appropriate symptoms with ST-segment elevation on ECG) and non-ST-segment elevation MI (NSTEMI; clinically appropriate symptoms with ST-segment depression or T-wave abnormalities on ECG). **Cardiogenic shock:** Defined clinically as a poor cardiac output plus evidence of tissue hypoxia that is not improved by correcting reduced intravascular volume. [1] When a pulmonary artery catheter is used, cardiogenic shock may be defined as a cardiac index below 2.2 L/minute/m^2 despite an elevated pulmonary capillary wedge pressure (at least 15 mm Hg). [1] [2] [3]

INCIDENCE/ PREVALENCE

Acute MI: Acute MI is one of the most common causes of mortality worldwide. In 1990, ischaemic heart disease was the world's leading cause of death, accounting for about 6.3 million deaths. The age-standardised incidence varies among and within countries. [4] Each year, about 900,000 people in the US experience acute MI, about 225,000 of whom die. About half of these people die within 1 hour of the onset of symptoms and before reaching a hospital. [5] Event rates increase with age for both sexes and are higher in men than in women and in poorer than richer people at all ages. The incidence of death from acute MI has fallen in many Western countries over the past 20 years. **Cardiogenic shock:** Cardiogenic shock occurs in about 7% of people admitted to hospital with acute MI. [6] Of these, about half have established cardiogenic shock at the time of admission to hospital, and most of the others develop it during the first 24 to 48 hours after admission. [7]

AETIOLOGY/ RISK FACTORS

Acute MI: Identified major risk factors for CVD include increasing age, male sex, raised low-density lipoprotein cholesterol, reduced high-density lipoprotein cholesterol, raised blood pressure, smoking, diabetes, family history of CVD, obesity, and sedentary lifestyle. For many of these risk factors, observational studies show a continuous gradient of increasing risk of CVD with increasing levels of the risk factor, with no obvious threshold level. The immediate mechanism of acute MI is rupture or erosion of an atheromatous plaque causing thrombosis and occlusion of coronary arteries and myocardial cell death. Factors that may convert a stable plaque into an unstable plaque (the "active plaque") have yet to be fully elucidated. Shear stresses, inflammation, and autoimmunity have been proposed. The changing rates of CHD in different populations are only partly explained by changes in the standard risk factors for ischaemic heart disease (particularly a fall in blood pressure and smoking). **Cardiogenic shock:** Cardiogenic shock after acute MI usually follows a reduction in functional ventricular myocardium, and is caused by left ventricular infarction (79% of people) more often than by right ventricular infarction (3% of people). [8] Cardiogenic shock after acute MI

may also be caused by cardiac structural defects, such as mitral valve regurgitation due to papillary muscle dysfunction (7% of people), ventricular septal rupture (4% of people), or cardiac tamponade after free cardiac wall rupture (1% of people). Major risk factors for cardiogenic shock after acute MI are previous MI, diabetes mellitus, advanced age, hypotension, tachycardia or bradycardia, congestive heart failure with Killip class II–III, and low left ventricular ejection fraction (ejection fraction under 35%). [7] [8]

PROGNOSIS

Acute MI: May lead to a host of mechanical and cardiac electrical complications, including death, ventricular dysfunction, congestive heart failure, fatal and non-fatal arrhythmias, valvular dysfunction, myocardial rupture, and cardiogenic shock. **Cardiogenic shock:** Mortality for people in hospital with cardiogenic shock after acute MI vary between 50% to 80%. [2] [3] [6] [7] Most deaths occur within 48 hours of the onset of shock (see figure 1, p 21). [9] People surviving until discharge from hospital have a reasonable long-term prognosis (88% survival at 1 year). [10]

AIMS OF INTERVENTION

To decrease mortality, to prevent recurrent infarction and ischaemia, to reduce complications (such as congestive heart failure, myocardial rupture, valvular dysfunction, and fatal and non-fatal arrhythmia), to restore blood supply to heart muscle, and to relieve pain.

OUTCOMES

Mortality: some studies also reported composite outcomes of mortality or cardiovascular events. **Cardiovascular events:** major cardiovascular events including recurrent acute MI, refractory ischaemia, and stroke at up to 6 months. **Bleeding:** rates of major bleeding, intracranial haemorrhage, stroke possibly associated with treatment, at up to 6 months. **Other adverse events:** including cardiogenic shock at up to 6 months.

METHODS

Clinical Evidence search and appraisal October 2009. The following databases were used to identify studies for this systematic review: Medline 1966 to October 2009, Embase 1980 to October 2009, and The Cochrane Database of Systematic Reviews 2009, Issue 4 (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language, at least single blinded, and containing more than 20 individuals of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We report outcomes of treatment from onset of symptoms up to 6 months in this review. We also include meta-analyses that combine outcomes from both before and after 6 months. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 26). The categorisation of the quality of the evidence (into high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *Clinical Evidence* population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com). Systematic reviews and RCTs that cover secondary prevention in mixed manifestations of atherosclerotic coronary artery disease are reported in the review on Secondary prevention of ischaemic cardiac events.

QUESTION Which treatments improve outcomes in people with myocardial infarction (ST-elevation)?

OPTION ASPIRIN

Mortality

Compared with placebo Aspirin is more effective at reducing all-cause and vascular mortality for up to 4 years in people with acute MI (high-quality evidence).

Cardiovascular events

Compared with placebo Aspirin is more effective at reducing recurrent infarction and non-fatal stroke at 1 month in people with acute MI (high-quality evidence).

For GRADE evaluation of interventions for acute MI, see table, p 26 .

Benefits: **Aspirin versus placebo:**
We found one systematic review (search date 1990, 9 RCTs, 18,773 people) comparing antiplatelet agents begun soon after the onset of acute MI and for at least 1 month afterwards versus placebo. [11] Almost all (over 95%) of the people in these studies were randomised to either aspirin or placebo. The review found that aspirin significantly reduced mortality, reinfarction, and stroke at 1 month compared with control. The absolute and relative benefits found in the systematic review are shown in figure 2, p 22 . In the systematic review, the most widely tested aspirin regimens were 75 to 325 mg daily. [11] Doses throughout this range seemed similarly effective, with no evidence that higher doses (aspirin 500–1500 mg: AR 1243/9223 [13%] with aspirin *v* 1514/9248 [16%] with placebo; OR 0.79, 95% CI presented graphically) were more effective than "medium" doses (aspirin 160–325 mg: AR 1303/11,906 [11%] with aspirin *v* 1740/11,862 [15%] with placebo; OR 0.72, 95% CI presented graphically) or "lower" doses (aspirin 75–160 mg: AR 129/1440 [9%] with aspirin *v* 168/1438 [12%] with placebo; OR 0.74, 95% CI presented graphically). The review found insufficient evidence for efficacy of doses below 75 mg daily. One RCT identified by the review found that a loading dose of 160 to 325 mg daily achieved a prompt antiplatelet effect. [12] The largest of the RCTs identified by the review (17,187 people with suspected acute MI) compared aspirin 162.6 mg versus placebo chewed and swallowed on the day of acute MI and continued daily for 1 month. [13] There was a 2.4% absolute reduction in vascular death at 35 days. The survival benefit was maintained for up to 4 years. [14]

Harms: The largest RCT identified by the review found no significant difference between aspirin and placebo in rates of cerebral haemorrhage or bleeds requiring transfusion (AR: 0.4% with aspirin and placebo). [13] It also found a small absolute excess of "minor" bleeding (ARI 0.6%, CI not reported; P <0.01).

Comment: None.

OPTION THROMBOLYSIS

Mortality
Compared with placebo Thrombolysis is more effective at reducing mortality at 35 days when given early in people with suspected acute MI, with benefit seen in people with ST elevation or bundle branch block, but increases mortality in people without ST elevation (moderate-quality evidence).

Streptokinase compared with tPA We don't know whether streptokinase is more effective at reducing mortality at 15 to 35 days in people with suspected acute MI (very low-quality evidence).

tPA compared with other thrombolytics We don't know whether tPA is more effective than other thrombolytics (reteplase, tenecteplase) at reducing mortality at 30 days in people with suspected acute MI (low-quality evidence).

Compared with primary PTCA Thrombolysis may be less effective at reducing mortality at 30 days after an acute MI (low-quality evidence).

Bleeding
Compared with placebo Thrombolysis increases the risk of stroke or other major bleed (high-quality evidence).

Streptokinase compared with tPA tPA may be associated with an increase risk of stroke compared with streptokinase at 15 days and also non-cerebral bleeds, but we don't know about total bleeds (low-quality evidence).

tPA compared with other thrombolytics Alteplase may be associated with an increase risk of major bleeding compared with tenecteplase. We don't know whether alteplase and reteplase or alteplase and lanoteplase differ with regard to major bleeds or stroke (low-quality evidence).

Compared with primary PTCA Thrombolysis may be associated with an increased risk of stroke (any stroke or haemorrhagic stroke) compared with primary PTCA at 4 to 6 weeks, but thrombolysis may be associated with a decreased risk of major bleeds compared with primary PTCA at 4 to 6 weeks (low-quality evidence).

For GRADE evaluation of interventions for acute MI, see table, p 26 .

Benefits: **Thrombolysis versus placebo:**
We found no systematic reviews. We found one non-systematic review of large RCTs (9 RCTs, 58,600 people with suspected acute MI) comparing thrombolysis versus placebo. [15] Baseline

electrocardiograms showed ST-segment elevation in 68% of people, and ST-segment depression, T-wave abnormalities, or no abnormality in the rest. The review found that thrombolysis significantly reduced mortality at day 35 compared with placebo (AR 2820/29,315 [9.6%] with thrombolysis *v* 3357/29,285 [11.5%] with placebo; RR 0.82, 95% CI 0.77 to 0.87). It found that mortality was lower at day 35 in people with ST elevation on ECG receiving thrombolysis (anterior ST elevation: AR 868/6587 [13%] with thrombolysis *v* 1120/6642 [17%] with control; inferior ST elevation: 493/6556 [7.5%] with thrombolysis *v* 542/6484 [8.4%] with control; other ST elevation 324/3053 [11%] with thrombolysis *v* 404/3024 [13%] with control; 95% CI presented graphically). It also found that mortality was lower at day 35 in those with bundle branch block changes on ECG receiving thrombolysis (AR 188/1007 [19%] with thrombolysis *v* 242/1025 [24%] with control; 95% CI presented graphically). However, it found that mortality at day 35 was higher in people with ST depression or normal ECGs who received thrombolysis (ST depression: AR 271/1779 [15%] with thrombolysis *v* 247/1784 [14%] with control; normal ECG: 30/995 [3%] with thrombolysis *v* 23/990 [2%] with control; 95% CI presented graphically). One of the RCTs included in the review found that thrombolysis significantly reduced mortality after 12 years compared with placebo (AR 36/107 [34%] with thrombolysis *v* 55/112 [49%] with placebo; ARR 15.0%, 95% CI 2.4% to 29.0%; RR 0.69, 95% CI 0.49 to 0.95; NNT 7, 95% CI 4 to 41). [16]

Prompt versus delayed thrombolysis:
The non-systematic review found that thrombolysis more effectively reduced mortality at day 35 when given soon after onset of symptoms (results presented graphically, see figure 3, p 23). [15] Too few people in the review received treatment more than 12 hours after the onset of symptoms to determine whether the benefits of thrombolytic treatment given after 12 hours would outweigh the risks (see comment below).

Streptokinase versus tPA:
We found no systematic review. We found one non-systematic review, [17] which identified 3 RCTs [18] [19] [20] (see table 1, p 24) comparing streptokinase versus tPA. The first RCT (12,381 people with ST-segment elevation and symptoms of acute MI for less than 6 hours) had blinded assessment of outcomes, but patients and treating doctors were not blinded. [18] People received either intravenous tPA 100 mg over 3 hours or streptokinase 1.5 MU over 1 hour. Half the people in each group were randomised to receive heparin. It found no significant difference in mortality, at a median of 15 days' follow-up, between tPA and streptokinase (AR 556/6182 [9.0%] with tPA *v* 536/6199 [8.6%] with streptokinase; P value not reported).

The second RCT (41,299 people with suspected acute MI within 24 hours of symptom onset) compared streptokinase 1.5 MU over 1 hour versus tPA 0.6 MU/kg every 4 hours, or anisoylated plasminogen streptokinase activator complex 30 U every 3 minutes. Half the people in each group were randomised to receive heparin. [19] It found no significant difference in mortality between groups at hospital discharge, or day 35 if sooner (AR 1455/13,780 [10.6%] with streptokinase *v* 1418/13,746 [10.3%] with tPA *v* 1448/13,773 [10.5%] with anisoylated plasminogen streptokinase activator complex; P value not reported).

The third RCT (41,021 people with ST elevation on ECG, within 6 hours of onset of symptoms) had blinded assessment of outcomes, but patients and treating doctors were not blinded. [20] Participants received either streptokinase alone, tPA alone, or combined streptokinase and tPA at reduced doses. All participants received heparin. People who received streptokinase were further randomised to receive either a subcutaneous or intravenous heparin regimen. It found that tPA significantly reduced mortality at 30 days compared with streptokinase (AR 6.3% with tPA plus intravenous heparin *v* 7.2% with streptokinase plus subcutaneous heparin *v* 7.4% with streptokinase plus intravenous heparin; P = 0.005; absolute numbers not reported). Meta-analysis of the 3 trials, weighted by sample size, found no significant difference between treatments in the combined outcome of any stroke or death (AR 9.4% for streptokinase-only regimens *v* 9.2% for tPA-based regimens, including the combined tPA and streptokinase arm in the third trial; ARR for tPA *v* streptokinase +0.2%, 95% CI –0.2% to +0.5%; absolute numbers not reported). [17]

tPA versus other thrombolytics:
We found 3 RCTs comparing tPA versus other thrombolytic agents in people with acute MI (participants also received aspirin and heparin). [21] [22] [23] The first RCT (15,059 people with acute MI within 6 hours of symptom onset, with either ST elevation or left bundle branch block on ECG) compared tPA (accelerated intravenous administration according to the study regimen) versus reteplase (recombinant plasminogen activator; two 10 MU intravenous boluses, 30 minutes apart). [21] It found no significant difference in mortality after 30 days (AR 7% with reteplase *v* 7% with alteplase; OR 1.03, 95% CI 0.91 to 1.18; P = 0.61; absolute numbers not reported).

The second RCT (16,949 people with acute MI within 6 hours of symptom onset, with either ST elevation or left bundle branch block on ECG) compared tPA (accelerated intravenous administration)

versus tenecteplase (a genetically engineered variant of tPA; 30–50 mg intravenous according to bodyweight as a single bolus). [22] It found no significant difference in mortality between treatments at 30 days (AR 6% with tenecteplase *v* 6% with tPA; RR 1.0, 95% CI 0.91 to 1.10; P = 0.02; absolute numbers not reported).

The third RCT (15,078 people within 6 hours of onset of ST-elevation acute MI) compared lanoteplase (a single-bolus thrombolytic drug derived from alteplase tPA) versus alteplase tPA (accelerated intravenous administration). [23] It found that mortality at 30 days was similar in the two groups (7% with lanoteplase *v* 7% with alteplase; RR 1.02, 95% CI upper limit 1.14, lower limit not reported; absolute numbers not reported). It found no significant difference in reinfarction (5% with lanoteplase *v* 6% with alteplase; P = 0.14; absolute numbers not reported).

Thrombolysis versus primary PTCA:
See benefits of primary PTCA versus thrombolysis, p 15 .

Harms:

Thrombolysis versus placebo:
Stroke/intracerebral haemorrhage
The non-systematic review found that thrombolytic treatment significantly increased the risk of stroke compared with control at days 0 to 35 (340/29,315 [1.2%] with thrombolysis *v* 224/29,285 [0.8%] with control; P <0.0001). [15]

Predictive factors for stroke/intracranial haemorrhage
Multivariate analysis of data from a large database of people who experienced intracerebral haemorrhage after thrombolytic treatment identified 4 independent predictors of increased risk of intracerebral haemorrhage: age 65 years or older (OR 2.2, 95% CI 1.4 to 3.5); weight less than 70 kg (OR 2.1, 95% CI 1.3 to 3.2); hypertension on admission (OR 2.0, 95% CI 1.2 to 3.2); and use of tPA rather than another thrombolytic agent (OR 1.6, 95% CI 1.0 to 2.5). [21] The absolute risk of intracranial haemorrhage was 0.26% in people on streptokinase in the absence of risk factors and 0.96%, 1.32%, and 2.17% in people with one, two, and 3 risk factors, respectively. [24] Analysis of 592 strokes in 41,021 people from the trials found 7 factors to be predictors of intracerebral haemorrhage: advanced age, lower weight, history of cerebrovascular disease, history of hypertension, higher systolic or diastolic pressure on presentation, and use of tPA rather than streptokinase. [25] [26]

Major bleeding
The non-systematic review found that thrombolytic treatment significantly increased the risk of major bleeding compared with placebo (ARI 0.7%, 95% CI 0.6% to 0.9%; NNH 143, 95% CI 111 to 166). [15] Bleeding was most common in people undergoing procedures (CABG or PTCA). Spontaneous bleeds were observed most often in the gastrointestinal tract. [20]

Prompt thrombolysis versus delayed:
The review did not give information on harms of prompt thrombolysis versus delayed. [15]

Streptokinase versus tPA:
The first RCT found an increased number of strokes and bleeding with tPA compared with streptokinase, but this was not significant (strokes: AR 54/6199 [0.9%] with streptokinase *v* 70/6182 [1.1%] with tPA; RR 1.30, 95% CI 0.91 to 1.85; total bleeds AR 490/6199 [8%] with streptokinase *v* 529/6182 [9%] with tPA; RR 1.09, 95% CI 0.96 to 1.24). [18] The second RCT found that tPA significantly increased strokes compared with streptokinase at 15 days (188/13,746 [1.4%] with tPA *v* 141/13,780 [1.0%] with streptokinase; P <0.01). It also found that tPA increased non-cerebral bleeds (AR 5.2% with tPA *v* 4.5% with streptokinase; P <0.01). [19] The third RCT found that the combination of tPA and intravenous heparin significantly increased the risk of haemorrhagic stroke compared with streptokinase plus subcutaneous or intravenous heparin (AR 0.52% with combined streptokinase groups *v* 0.72% with tPA; P = 0.03). [20]

tPA versus other thrombolytics:
The first RCT, which compared reteplase versus alteplase, found the incidence of stroke was similar in both groups (AR 0.9% with reteplase *v* 0.9% with alteplase; P value not reported). [21] The second RCT found that alteplase significantly increased major bleeding compared with tenecteplase (6% with alteplase *v* 5% with tenecteplase; P = 0.0002). [22] The third RCT found no significant difference in stroke between alteplase and lanoteplase, and found that major and moderate bleeding was similar in both groups (stroke: 1.9% with lanoteplase *v* 1.5% with alteplase; P = 0.135; major bleeding: 0.5% with lanoteplase *v* 0.6% with alteplase; P value not reported; moderate bleeding: 2.4% with lanoteplase *v* 2.4% with alteplase; P value not reported).

Thrombolysis versus primary PTCA:
See harms of primary PTCA versus thrombolysis, p 15 .

Comment:

Clinical guide:
Extrapolation of the data from the overview (see figure 3, p 23) suggests that, at least for people suspected of having an acute MI and with ST-segment elevation on their ECG, there may be some net benefit to treatment between 12 and 18 hours after symptom onset (ARR for death 1%). [15] The evidence from the RCT comparing reteplase versus tPA is consistent with a similar efficacy for both treatments, although formal equivalence cannot be established because the trial was designed as a superiority trial. [21] The evidence suggests that it is far more important to give prompt thrombolytic treatment than to debate which thrombolytic agent to use. A strategy of rapid thrombolysis in a broad population is likely to lead to the greatest impact on mortality. When the results of RCTs are taken together, tPA-based regimens do not seem to confer a significant advantage over streptokinase in the combined outcome of any stroke and death (unrelated to stroke). The legitimacy of combining the results of the 3 trials can be questioned, as the selection criteria and protocols differed in important aspects. [17]

OPTION ADDING LOW MOLECULAR WEIGHT HEPARIN TO THROMBOLYTICS

Mortality
Compared with thrombolytics alone Adding low molecular weight heparin to thrombolytics is no more effective at reducing mortality in people within 12 hours of an acute MI (high-quality evidence).

Compared with thrombolytics plus unfractionated heparin Adding low molecular weight heparin (mainly enoxaparin in analysis) to thrombolytics and adding unfractionated heparin to thrombolytics seem to be equally effective at reducing mortality at 7 and 30 days in people with ST-elevation MI (moderate-quality evidence).

Cardiovascular events
Compared with thrombolytics alone Adding low molecular weight heparin to thrombolytics is more effective at reducing reinfarction rates in people within 12 hours of an acute MI (high-quality evidence).

Compared with thrombolytics plus unfractionated heparin Adding low molecular weight heparin (mainly enoxaparin in analysis) to thrombolytics seems to be more effective than adding unfractionated heparin to thrombolytics at reducing reinfarction at 7 and 30 days in people with ST-elevation MI (moderate-quality evidence).

Bleeding
Compared with thrombolytics plus unfractionated heparin Adding low molecular weight heparin to thrombolytics (mainly enoxaparin in analysis) may be associated with an increased proportion of people with major bleeding events and minor bleeds compared with adding unfractionated heparin to thrombolytics in people with ST-elevation MI, but we don't know about intracranial haemorrhage (low-quality evidence).

For GRADE evaluation of interventions for acute MI, see table, p 26 .

Benefits:

Thrombolytics plus low molecular weight heparin versus thrombolytics alone:
We found one RCT (496 people, <12 hours of acute MI symptoms) comparing streptokinase (1.5 MU over 1 hour) plus enoxaparin (a low molecular weight heparin; 30 mg intravenous bolus then subcutaneously every 12 hours) versus streptokinase plus placebo. [27] It found that enoxaparin significantly reduced reinfarction compared with placebo at 30 days, although it found no significant difference in mortality between treatments (reinfarction: AR 6/253 [2%] with enoxaparin *v* 18/243 [7%] with placebo; OR 0.30, 95% CI 0.12 to 0.78; mortality: 17/253 [6.7%] with enoxaparin *v* 17/243 [7.0%] with placebo; OR 0.96, 95% CI 0.48 to 1.92).

Thrombolytics plus low molecular weight heparin versus thrombolytics plus unfractionated heparins:
We found two systematic reviews, which included similar RCTs and performed slightly different analyses. [28] [29] The first systematic review (search date 2007, 8 RCTs, 27,758 people) compared low molecular weight heparins versus unfractionated heparins in people with ST-elevation MI treated with thrombolysis. [28] The included RCTs evaluated enoxaparin (6 RCTs), parnaparin (1 RCT), and dalteparin (1 RCT). The thrombolytic used was tenecteplase (3 RCTs), tPA (2 RCTs), urokinase (1 RCT), streptokinase or APSAC or tPA (1 RCT), and streptokinase or tenecteplase or tPA (1 RCT). The review reported that the duration of treatment with low molecular weight heparin or unfractionated heparin was between 48 hours and 8 days, and that most people received unfractionated heparin for 2 to 4 days, whereas those receiving low molecular weight heparin were mostly treated for a longer time (between 4 and 8 days). The RCTs were performed between 1999 and 2005. One large RCT examining the effects of enoxaparin formed the majority of the results (20,479 people). The review found that low molecular weight heparins significantly reduced reinfarction compared with unfractionated heparin at 30 days (8 RCTs; 451/13,940 [3%] with low molecular weight heparins *v* 669/13,818 [5%] with unfractionated heparins; OR 0.65, 95% CI 0.58 to 0.64; P <0.0001). The review found lower 30-day mortality with low molecular weight heparins compared with unfractionated heparins, but differences between groups did not reach significance

(8 RCTs; 921/13,940 [6.6%] with low molecular weight heparins *v* 990/13,818 [7.2%] with unfractionated heparin; OR 0.92, 95% CI 0.84 to 1.01; P = 0.08). [28] The review reported that a limitation of the meta-analysis was that the conclusions could not be extended to people having primary percutaneous coronary intervention as no study had been undertaken in this group at the time of the analysis, and that further large RCTs with extensive use of clopidogrel and early planned angiography were needed.

The second systematic review (search date 2007, 7 RCTs, 27,604 people; see comments) compared low molecular weight heparins versus unfractionated heparins in people with ST-elevation MI treated with fibrinolytic therapy. [29] It included RCTs in people who had received aspirin and fibrinolytic therapy, compared subcutaneous low molecular weight heparin versus intravenous unfractionated heparin as an adjunctive thrombolytic therapy, and reported outcomes during in-hospital stay or at day 7 and at day 30. It included 7 RCTs identified by the first review and excluded 1 RCT identified by the first review, which examined the effects of parnaparin in people receiving urokinase. The included RCTs examined the effects of enoxaparin (6 RCTs) and dalteparin (1 RCT). The fibrinolysis used was tenecteplase (3 RCTs), tPA (2 RCTs), streptokinase or APSAC or tPA (1 RCT), and streptokinase or tenecteplase or tPA (1 RCT). The review reported that 3 RCTs mentioned that clopidogrel was also used (clopidogrel/ticlopidine, or clopidogrel alone, about 27–55% of people in each group) but the regimen was not clearly stated, whereas none of the other RCTs mentioned the administration of clopidogrel therapy. Of the 7 RCTs, 6 RCTs were open label and one large RCT (20,506 people) used a double dummy design. [29] The review found that, compared with unfractionated heparin, low molecular weight heparin significantly reduced reinfarction during hospital admission at 7 days and also at 30 days (7 days: 7 RCTs, 27,572 people; RR 0.55, 95% CI 0.47 to 0.63; P <0.001; 30 days: 6 RCTs, 25,933 people; RR 0.67, 95% CI 0.60 to 0.76; P <0.001; results presented graphically). It found no significant difference between groups in mortality during hospital admission at 7 days or at 30 days (7 days: 7 RCTs, 27,572 people; RR 0.92, 95% CI 0.84 to 1.02; P = 0.099; 30 days: 7 RCTs, 27,572 people; RR 0.927, 95% CI 0.849 to 1.011; P = 0.088; results presented graphically). A further report of the large RCT included in the reviews, which evaluated women alone, found that enoxaparin reduced the combined end point of death or non-fatal MI at 30 days compared with unfractionated heparin (AR 15% with enoxaparin *v* 18% with unfractionated heparin; P = 0.007; absolute numbers not reported). [30] When assessing each outcome separately, the RCT found that enoxaparin significantly reduced non-fatal MI, but not mortality at 30 days (non-fatal MI: AR 3% with enoxaparin *v* 4% with unfractionated heparin; P = 0.02; death: 12% with enoxaparin *v* 14% with unfractionated heparin; P = 0.09; absolute numbers not reported). [30]

Harms:

Thrombolytics plus low molecular weight heparin versus thrombolytics alone:
The RCT found more people who received enoxaparin had a major haemorrhage, but this did not reach statistical significance (AR 4.8% with enoxaparin *v* 2.5% with placebo; P = 0.2).

Thrombolytics plus low molecular weight heparin versus thrombolytics plus unfractionated heparins:
The first systematic review found that low molecular weight heparins significantly increased the proportion of people with major bleeding complications compared with unfractionated heparin (8 RCTs; 341/13,936 [2.4%] with low molecular weight heparin *v* 249/13,811 [1.8%] with unfractionated heparin; OR 1.37, 95% CI 1.16 to 1.61; P = 0.002). [28] It found no significant difference between groups in intracranial haemorrhage (8 RCTs; 126/13,859 [0.9%] with low molecular weight heparin *v* 102/13,740 [0.7%] with unfractionated heparin; OR 1.22, 95% CI 0.94 to 1.59; P = 0.13). [28] The second review found that low molecular weight heparin significantly increased the risk of major bleeding events and minor bleeding (major bleeding events [7 day]: RR 1.40, 95% CI 1.18 to 1.67; P <0.001; minor bleeding: RR 1.23, 95% CI 1.13 to 1.34; P <0.0001; absolute numbers not reported, results presented graphically). [29]

Comment:

Thrombolytics plus low molecular weight heparins versus thrombolytics plus unfractionated heparins:
The second review did a sensitivity analysis excluding one large RCT (20,506 people) to see if the overall analysis was overly affected by the dominant RCT in this field. [29] The sensitivity analysis found similar results to the overall analysis (30 day reinfarction: RR 0.67, 95% CI 0.59 to 0.76; 30 day mortality: RR 0.92, 95% CI 0.85 to 1.011; results presented graphically; absolute figures not reported). [29]

OPTION ADDING UNFRACTIONATED HEPARIN TO THROMBOLYTICS

Mortality
Compared with thrombolytics alone Adding unfractionated heparin to thrombolysis may be no more effective at reducing mortality at 15 to 35 days in people after an acute MI (low-quality evidence).

Compared with thrombolytics plus low molecular weight heparin Adding unfractionated heparin to thrombolytics and adding low molecular weight heparin (mainly enoxaparin in analysis) to thrombolytics seem to be equally effective at reducing mortality at 7 and 30 days in people with ST-elevation MI (moderate-quality evidence).

Cardiovascular events
Compared with thrombolytics alone Adding unfractionated heparin to thrombolysis may be no more effective at reducing reinfarction at 15 to 35 days in people after an acute MI (low-quality evidence).

Compared with thrombolytics plus low molecular weight heparin Adding unfractionated heparin to thrombolytics seems to be less effective than adding low molecular weight heparin (mainly enoxaparin in analysis) to thrombolytics at reducing reinfarction at 7 and 30 days in people with ST-elevation MI (moderate-quality evidence).

Bleeding
Compared with thrombolytics alone Adding unfractionated heparin to thrombolysis may increase total bleeds at 15 to 35 days after an acute MI, but may not increase the risk of stroke (low-quality evidence).

Compared with thrombolytics plus low molecular weight heparin Adding unfractionated heparin may be associated with a decreased proportion of people with major bleeding events and minor bleeds compared with adding low molecular weight heparin to thrombolytics (mainly enoxaparin in analysis) in people with ST-elevation MI, but we don't know about intracranial haemorrhage (low-quality evidence).

For GRADE evaluation of interventions for acute MI, see table, p 26 .

Benefits:

Unfractionated heparin plus thrombolytics versus thrombolytics alone:
We found two RCTs. [18] [19] The first RCT (12,490 people with ST elevation on ECG and symptoms of acute MI of <6 hours) compared streptokinase versus tPA with or without unfractionated heparin. Assessment of outcomes was by a blinded committee, although patients and treating doctors were not blinded. [18] It found no significant difference in mortality between thrombolytic plus heparin compared with thrombolytic alone at a median follow-up of 15 days (mortality: AR 518/6175 [8.3%] with thrombolytic plus heparin *v* 574/6206 [8.9%] with thrombolytic alone; P value not reported; reinfarction: 117/6182 [1.9%] with thrombolytic plus heparin *v* 146/6199 [2.3%] with thrombolytic alone; RR 0.80, 95% CI 0.63 to 1.02). The second RCT (41,299 people within 24 hours of onset of acute MI symptoms) compared 7 days of unfractionated heparin versus no heparin in people undergoing thrombolysis. The thrombolysis was either streptokinase, tPA, or anistreplase. [19] The RCT found no significant difference in mortality or reinfarction between thrombolytic plus heparin and thrombolytic alone at 35 days (mortality: AR 2132/20,656 [10.3%] with thrombolytic plus heparin *v* 2189/20,643 [10.6%] with thrombolytic alone; P reported as not significant; reinfarction: 3.2% with thrombolytic plus heparin *v* 3.5% with thrombolytic alone; P = 0.09; absolute numbers not reported).

Thrombolytics plus low molecular weight heparins versus thrombolytics plus unfractionated heparins:
See option on adding low molecular weight heparin to thrombolytics section, p 7 .

Harms:

Unfractionated heparin plus thrombolytics versus thrombolytics alone:
The first RCT found that heparin significantly increased total bleeds compared with no heparin (AR 655/6175 [11%] with heparin *v* 364/6206 [6%] with no heparin; RR 1.87, 95% CI 1.65 to 2.13). It found no significant difference in stroke between groups (AR 61/6175 [1.0%] with heparin *v* 63/6206 [1.0%] with no heparin). The second RCT found that heparin significantly increased non-cerebral bleeds, which were mainly minor (AR 6% with heparin *v* 4% with no heparin; P <0.0001). It found no significant difference in stroke between groups (261/20,656 [1.3%] with heparin *v* 240/20,643 [1.2%] with no heparin; reported as not significant; P value not reported).

Thrombolytics plus low molecular weight heparins versus thrombolytics plus unfractionated heparins:
See option on adding low molecular weight heparin to thrombolytics section, p 7 .

Comment:

None.

OPTION GLYCOPROTEIN IIB/IIIA INHIBITORS

Mortality
Glycoprotein IIb/IIIa inhibitors plus thrombolysis compared with thrombolysis alone Adding glycoprotein IIb/IIIa inhibitors to thrombolysis within 6 hours of an acute MI may be no more effective at reducing mortality at 30 days (low-quality evidence).

Glycoprotein IIb/IIIa inhibitors plus PTCA compared with PTCA plus placebo We don't know whether adding abciximab to PTCA (with or without stent) is more effective than adding placebo at reducing mortality. Adding abciximab to PTCA (with or without stent) may be more effective than adding placebo to PTCA (with or without stent) at reducing the composite outcome of death, reinfarction, or urgent target revascularisation at 30 days. Adding abciximab to PTCA with stent may be more effective than adding placebo to PTCA with stent at reducing the composite outcome of death or reinfarction, but we don't know whether it is more effective in people having PTCA with or without stent. Results varied by the specific analysis undertaken (low-quality evidence).

Cardiovascular events

Glycoprotein IIb/IIIa inhibitors plus thrombolysis compared with thrombolysis alone Adding glycoprotein IIb/IIIa inhibitors to thrombolysis within 6 hours of an acute MI may be no more effective at reducing stroke at 30 days (low-quality evidence).

Glycoprotein IIb/IIIa inhibitors plus PTCA compared with PTCA plus placebo Adding abciximab to PTCA with stent may be more effective than adding placebo at reducing reinfarction in people undergoing primary coronary stenting, but we don't know whether it is more effective in people having PTCA with or without stent. Results varied by the specific analysis undertaken (low-quality evidence).

Bleeding

Glycoprotein IIb/IIIa inhibitors plus thrombolysis compared with thrombolysis alone Adding abciximab to thrombolysis may increase the risk of severe or moderate extracranial bleeding at 30 days compared with thrombolysis alone in people within 6 hours of onset of an acute MI, but we don't know about intracranial haemorrhage (low-quality evidence).

Glycoprotein IIb/IIIa inhibitors plus PTCA compared with PTCA plus placebo Adding abciximab to PTCA may increase the risk of major bleeding compared with adding placebo. However, results varied by the specific analysis undertaken (low-quality evidence).

For GRADE evaluation of interventions for acute MI, see table, p 26 .

Benefits:

Glycoprotein IIb/IIIa inhibitors plus thrombolysis versus thrombolysis alone:
We found one RCT (16,588 people with acute MI and ST elevation on ECG, within 6 hours of onset of symptoms) comparing half-dose reteplase plus abciximab (0.25 mg/kg bolus plus 0.125 micrograms/kg/minute for 12 hours) with standard-dose reteplase alone (total dose 20 U). [31] Outcome assessment was blinded in this RCT, though participants and treating doctors were not blinded to treatment. It found no significant difference in either mortality or stroke at 30 days between combined treatment and standard-dose reteplase alone (mortality: AR 488/8260 [5.9%] for reteplase alone *v* 468/8328 [5.6%] for combined treatment; OR 0.95, 95% CI 0.83 to 1.08; stroke: AR 73/8260 [0.9%] for reteplase *v* 81/8328 [1.0%] for combined treatment; OR 1.10, 95% CI 0.80 to 1.51).

Glycoprotein IIb/IIIa inhibitors plus PTCA versus placebo plus PTCA:
We found two systematic reviews, which had slightly different inclusion criteria and performed different analyses. [32] [33] The first systematic review (search date not reported, 4 RCTs, 3266 people) compared abciximab with placebo/control in people undergoing PTCA for acute MI. [32] The review included RCTs that enrolled at least 200 people, reported clinical outcomes at 30 days and 6 months, and was in people who had undergone a primary percutaneous intervention (with or without stenting). Of the 4 included RCTs, one RCT did not include stenting, two RCTs included stenting, and one RCT had a factoral design including both stenting and PTCA from which a two-way pooled comparison of abciximab versus control was extracted by the review. The review found that abciximab significantly reduced the combined end point of death, reinfarction, or urgent target revascularisation at 30 days compared with control (AR 5.0% with abciximab *v* 8.6% with placebo; OR 0.54, 95% CI 0.40 to 0.72; absolute numbers not reported). [32] It found no significant difference between groups in either death or reinfarction (death: AR 2.1% with abciximab *v* 2.9% with placebo; OR 0.73, 95% CI 0.46 to 1.16; reinfarction: AR 1.2% with abciximab *v* 1.6% with placebo; OR 0.72, 95% CI 0.39 to 1.34; absolute numbers not reported). [32] At 6 months, the combined outcome of death, reinfarction, or urgent target revascularisation was significantly reduced with abciximab compared with control (AR 17% with abciximab *v* 20% with placebo; OR 0.80, 95% CI 0.67 to 0.97; absolute numbers not reported); the combined outcome of death or reinfarction was not significantly reduced (AR 6% with abciximab *v* 7% with placebo OR 0.85, 95% CI 0.65 to 1.15; absolute numbers not reported). [32]

The second systematic review (search date not reported, 3 RCTs, 1101 people) compared abciximab versus placebo in people undergoing primary coronary stenting of ST-elevation MI and analysed patient level data. [33] It included RCTs with ST-elevation MI defined clinically without angiographic selection criteria, which included reperfusion therapy without fibrinolytic agent and with systematic primary stenting, had at least 1 year follow-up, and was able to share all case-specific data. All people received aspirin and unfractionated heparin as well as a thienopyridine after stenting. The review included two RCTs included by the first review, excluded two RCTs included by the first

review, and included one RCT published subsequent to the first review. The review found that abciximab significantly reduced the primary composite end point of death or reinfarction compared with placebo (Kaplan–Meier estimated cumulative hazard rate, over 3 years of follow-up: 12.9% with abciximab *v* 19.0% with placebo; RR 0.63, 95% CI 0.45 to 0.89; P = 0.008; results presented graphically). It found that abciximab reduced mortality but differences between groups did not reach significance (Kaplan–Meier estimated cumulative hazard rate for death, over 3 years of follow-up: 10.8% with abciximab *v* 14.3% with placebo; RR 0.695, 95% CI 0.482 to 1.003; P = 0.052; results presented graphically). The review found that abciximab significantly reduced reinfarction rate compared with placebo (Kaplan–Meier estimated cumulative hazard rate, over 3 years of follow-up: 2.3% with abciximab *v* 5.5% with placebo; RR 0.41, 95% CI 0.20 to 0.83; P = 0.013; results presented graphically). [33]

Timing of administration of glycoprotein IIb/IIIa inhibitors in people undergoing PTCA:
We found one systematic review (search date not reported, 6 RCTs, 951 people) comparing early administration (before transfer to the catheterisation laboratory) versus late administration (at the time of PTCA) of intravenous glycoprotein IIb/IIIa inhibitors in people with acute ST-segment elevation MI undergoing PTCA. [34] The trials evaluated abciximab (3 RCTs, 665 people) or tirofiban (3 RCTs, 286 people). The review found no significant difference between early and late administration in mortality at 30 days to 1 year (AR 16/467 [3%] with early administration *v* 22/466 [5%] with late administration; OR 0.72, 95% CI 0.37 to 1.40; P = 0.42).

Harms:

Glycoprotein IIb/IIIa inhibitors plus thrombolysis versus thrombolysis alone:
The RCT found that abciximab plus half-dose thrombolysis significantly increased severe or moderate extracranial bleeding at 30 days compared with full-dose thrombolysis (AR 5% with combined treatment *v* 2% with full-dose thrombolysis; OR 2.03, 95% CI 1.70 to 2.42). [31] However, it found no significant difference in rates of intracranial haemorrhage (AR 1.0% with combined treatment *v* 0.9% with thrombolysis alone; OR 1.10, 95% CI 0.80 to 1.81).

Glycoprotein IIb/IIIa inhibitors plus PTCA versus placebo plus PTCA:
The first systematic review in people undergoing PTCA found a significantly increased risk of major bleeding associated with the use of abciximab compared with control (AR 3% with abciximab *v* 2% with control; OR 1.74, 95% CI 1.11 to 2.72; absolute numbers not reported). [32] The second systematic review in people undergoing primary coronary stenting of ST-elevation MI found no significant difference in major bleeding (14/551 (2.5%) people with abciximab *v* 11/550 (2.0%) people with placebo; P >0.05). [33]

Timing of administration of glycoprotein IIb/IIIa inhibitors in people undergoing PTCA:
The systematic review gave no information on adverse effects. [34] Of the 6 RCTs identified by the systematic review, the first RCT comparing early versus late tirofiban administration before primary coronary angioplasty found similar rates of minor or major bleeding complications, although the trial may have been too small to detect clinically important differences (AR for minor bleeding 10% with early *v* 6% with late; P >0.05; AR for major bleeding 2% with early *v* 2% with late; P >0.05). [35] The second RCT found no significant difference between groups in the rates of non-CABG-related major bleeding at 30 days (5% with early *v* 3% with late; P = 0.47). [36] The third RCT reported no significant difference in rates of bleeding requiring transfusion between early and late administration (AR 2/28 [7.1%] with early *v* 2/30 [6.7%] with late; P >0.20). [37] The fourth RCT did find increased bleeding with early administration compared with late administration, but this was not significant (AR 16/56 [29%] with early *v* 11/56 [20%] with late; P = 0.10). [38] The fifth and sixth RCTs were reported from abstracts, and gave no information on adverse effects. [34]

Comment: None.

OPTION BETA-BLOCKERS

Mortality
Compared with placebo or no beta-blocker Beta-blockers may be no more effective at reducing mortality at 28 days in people with an acute MI, although they may have other long-term benefits (low-quality evidence).

Cardiovascular events
Compared with placebo Beta-blockers are more effective at reducing reinfarction at 28 days in people with an acute MI, but increase the risk of cardiogenic shock when given soon after an infarction (high-quality evidence).

For GRADE evaluation of interventions for acute MI, see table, p 26 .

Benefits:

Beta-blockers versus no beta-blockers:
We found two systematic reviews (search date not reported, 16 RCTs with short-term oral beta-blockers, 3611 people; 31 RCTs with intravenous beta-blockers, 11,309 people; [39] and search

date 1997, 51 RCTs, 29,260 people [40]) and one subsequent RCT [41] that evaluated beta-blockers in people with acute MI. The first, earlier review found no significant difference in mortality between oral beta-blockers and no oral beta-blockers at 7 to 28 days (AR 165/1900 [9%] with oral beta-blockers *v* 165/1711 [10%] with no beta-blockers; P value not reported). It also found no significant difference in mortality between intravenous beta-blockers and no intravenous beta-blockers at 1 week (AR 194/5676 [3%] with intravenous beta-blocker *v* 205/5633 [4%] with no intravenous beta-blocker; P value not reported). [39] It found that beta-blockers significantly reduced late mortality compared with no beta-blockers at 6 weeks to 2 years (AR 827/10,452 [8%] with beta-blocker *v* 986/9860 [10%] with no beta-blocker; OR 0.77, 95% CI 0.7 to 0.85; P <0.0001). [39]

The more recent review analysed 51 short-term RCTs (people within 6 weeks of onset of symptoms of acute MI). [40] In most of the RCTs, the participants did not receive thrombolysis. Seven of the RCTs identified reported no deaths, and many reported only a few. The RCTs reporting at least one death found no significant difference in mortality between beta-blockers and no beta-blockers at 3 days to 36 months (ARR 0.4%; OR 0.96, 95% CI 0.85 to 1.08; absolute numbers not reported). No significant difference in reducing mortality was found between different classes of beta-blocker (grouped by cardioselectivity or intrinsic sympathomimetic activity). Most of the identified RCTs evaluated propranolol, timolol, or metoprolol.

The subsequent RCT (45,852 people within 24 hours of onset of symptoms of acute MI) compared metoprolol (up to 15 mg intravenously then 200 mg orally daily) versus placebo. [41] The RCT assessed outcomes at 28 days, or on hospital discharge if sooner. It found that metoprolol significantly reduced reinfarction at 28 days (464/22,929 [2%] with metoprolol *v* 568/22,923 [3%] with placebo; OR 0.82, 95% CI 0.72 to 0.92; P = 0.001). However, it found no significant difference in the combined end point of death, reinfarction, or cardiac arrest at 28 days (2166/22,929 [9%] with metoprolol *v* 2261/22,923 [10%] with placebo; OR 0.96, 95% CI 0.90 to 1.01; P = 0.10). It also found no significant difference in mortality at 28 days when this was assessed separately (1774/22,929 [7.7%] with metoprolol *v* 1797/22,923 [7.8%] with placebo; OR 0.99, 95% CI 0.92 to 1.05; P = 0.69). See beta-blockers under secondary prevention of ischaemic cardiac events.

Early versus delayed treatment:
We found one RCT (1434 people with acute MI who had received tPA thrombolysis) comparing early versus delayed metoprolol treatment. [42] Early treatment began on day 1 (intravenous then oral) and delayed treatment on day 6 (oral). It found that early treatment significantly reduced rates of reinfarction and recurrent chest pain after 6 days (reinfarction: AR 3% with early treatment *v* 5% with delayed treatment; P = 0.02; chest pain: 19% with early treatment *v* 24% with delayed treatment; P <0.02). There were no significant differences in mortality or left ventricular ejection fraction between the two groups at 6 days (mortality: AR 17/720 [2%] with early treatment *v* 17/714 [2%] delayed treatment; P = 0.98; left ventricular ejection fraction: reported as not significant; AR and P value not reported).

Harms:

Beta-blockers versus no beta-blockers:
People with asthma or severe congestive cardiac failure were excluded from most trials. The RCT found that metoprolol significantly increased cardiogenic shock compared with placebo (AR 1141/22,929 [5%] with metoprolol *v* 885/22,923 [4%] with placebo; OR 1.30, 95% CI 1.19 to 1.41; P <0.0001). [41] The first systematic review found no significant difference in cardiogenic shock between beta-blockers and control, but noted that this result may be unreliable because of sparse data (AR 148/4681 [3.2%] with beta-blockers *v* 144/4697 [3.0%] with control; P value not reported). The second systematic review gave no information on harms.

Early versus delayed treatment:
The RCT found that people given immediate rather than delayed beta-blockers after tPA experienced increased frequency of heart failure during hospital admission, although the result was not statistically significant (15% with immediate *v* 12% with delayed; P = 0.10). [42] The presence of first-degree heart block and bundle branch block was associated with more adverse events.

Comment:

Most trials involving the use of beta-blockers in acute MI have been conducted predominantly in people considered to be at low risk of heart failure (because of the supposed deleterious effect of beta-blockers on left ventricular function), and many of these trials took place in the pre-thrombolytic era. Beta-blockers may reduce rates of cardiac rupture and ventricular fibrillation. This may explain why people older than 65 years and those with large infarcts benefited most, as they have higher rates of these complications. The trial comparing early versus delayed beta-blockade after thrombolysis was too small to detect an effect on mortality. [42]

Clinical guide:
Early use of beta-blockers reduces the risk of reinfarction, but increases the risk of cardiogenic shock. [41] It is therefore prudent after an acute MI to start beta-blockers in hospital only when the patient has become haemodynamically stable.

OPTION ACE INHIBITORS

Mortality
Compared with placebo Angiotensin-converting enzyme (ACE) inhibitors are more effective at reducing overall mortality and sudden cardiac death after 2 to 42 months when started within 14 days of an acute MI (high-quality evidence).

For GRADE evaluation of interventions for acute MI, see table, p 26 .

Benefits:

Angiotensin-converting enzyme (ACE) inhibitors versus placebo:
We found one systematic review (search date 1997, 15 RCTs with at least 6 weeks' follow-up, 15,104 people) comparing ACE inhibitors started within 14 days of acute MI versus placebo. [43] It found that ACE inhibitors decreased overall mortality and sudden cardiac death compared with placebo after 2 to 42 months (overall mortality: 14% with ACE inhibitors *v* 17% with placebo; OR 0.83, 95% CI 0.71 to 0.97; sudden cardiac death: 5% with ACE inhibitors *v* 7% with placebo; OR 0.80, 95% CI 0.70 to 0.92; absolute numbers not reported). [43]

Harms:

Angiotensin-converting enzyme (ACE) inhibitors versus placebo:
The systematic review gave no information on harms. [43] We found one additional non-systematic review of RCTs (search date not reported, 4 RCTs, 98,496 people within 36 hours of acute MI), which found that ACE inhibitors significantly increased persistent hypotension and renal dysfunction at 6 weeks compared with placebo (hypotension: AR 18% with ACE inhibitor *v* 9% with control; CI for difference not reported; P <0.01; renal dysfunction: AR 1.3% with ACE inhibitor *v* 0.6% with control; P <0.01). [44] The relative and absolute risks of these adverse effects were uniformly distributed across both the high and lower cardiovascular risk groups.

Comment:

ACE inhibitors in people with acute MI work best when treatment is started within 24 hours. The evidence does not show which people with an acute MI should be offered ACE inhibitors, nor how long after an acute MI it remains beneficial to start treatment. We found one systematic review (search date not reported; based on individual data from about 100,000 people in RCTs of ACE inhibitors), which found that people receiving both aspirin and ACE inhibitors had the same relative risk reduction as those receiving ACE inhibitors alone. [45] Of the 12 RCTs in the systematic review that reported on left ventricular function among participants, all reported a mean left ventricular ejection fraction of 54% or less. Six of these RCTs reported a mean left ventricular ejection fraction of 40% or less. However, there is debate over whether ACE inhibitors also benefit people with normal left ventricular function after acute MI.

OPTION NITRATES PLUS THROMBOLYSIS

Mortality
Compared with thrombolysis plus placebo Adding nitrates to thrombolysis seems no more effective at decreasing mortality at 5 to 6 weeks (moderate-quality evidence).

Cardiovascular events
Compared with thrombolysis plus placebo Adding nitrates to thrombolysis seems to be no more effective at decreasing reinfarction at 5 to 6 weeks (moderate-quality evidence).

For GRADE evaluation of interventions for acute MI, see table, p 26 .

Benefits:

Nitrates versus placebo in people receiving thrombolysis:
We found two RCTs comparing nitrates versus placebo in people with acute MI who also received thrombolysis. [46] [47] The first RCT (58,050 people with acute MI) compared isosorbide mononitrate (a daily, controlled-release preparation) versus placebo. Seventy per cent of the participants also received thrombolysis, and 14% from both groups also took nitrates outside the study protocol. [46] It found no significant difference in mortality between isosorbide mononitrate and placebo at day 35 (AR 2129/29,018 [7%] with nitrates *v* 2190/29,032 [8%] with placebo; OR 0.97, 95% CI 0.91 to 1.03; P = 0.3). The second RCT (17,817 people with acute MI) compared intravenous glyceryl trinitrate for 24 hours, followed by transdermal glyceryl trinitrate, versus no nitrates. Only 72% of the participants also received thrombolysis, and 57% of the control group received additional nitrates outside of the study protocol. It found no significant difference in mortality or reinfarction between nitrates and placebo at 6 weeks (mortality: AR 617/9453 [6.5%] with nitrates *v* 653/9442 [6.9%]

with no nitrates; OR 0.94, 95% CI 0.84 to 1.05; P = 0.28; reinfarction: 292/9453 [3.1%] with nitrates *v* 303/9442 [3.2%] with no nitrates; OR 0.96, 95% CI 0.82 to 1.13).

Harms: **Nitrates versus placebo in people receiving thrombolysis:**
The large RCTs found no significant harms associated with routine use of nitrates. [46] [47]

Comment: Results for the two large RCTs were limited because a large proportion of people took nitrates outside the studies' protocols, there was a high rate of concurrent use of other hypotensive agents, people were relatively low risk, and nitrates were not titrated to blood pressure and heart rate. [46] [47] The RCTs found that nitrates were a useful adjunctive treatment to help control symptoms in people with acute MI.

OPTION NITRATES WITHOUT THROMBOLYSIS

Mortality
Compared with placebo Nitrates are more effective at reducing mortality at 1 to 12 months in people not receiving thrombolysis after an acute MI (high-quality evidence).

For GRADE evaluation of interventions for acute MI, see table, p 26 .

Benefits: **Nitrates versus placebo:**
We found one systematic review (search date not reported, 10 RCTs, 2000 people with acute MI who did not receive thrombolysis) comparing intravenous glyceryl trinitrate or sodium nitroprusside versus placebo. [48] The review found that nitrates significantly reduced mortality compared with placebo at 1 to 12 months (AR 131/1021 [13%] with nitrates *v* 193/1020 [19%] with placebo; OR 0.65, 95% CI 0.51 to 0.82).

Harms: **Nitrates versus placebo:**
The systematic review gave no information on adverse effects. [48]

Comment: None.

OPTION CALCIUM CHANNEL BLOCKERS

Mortality
Compared with placebo Calcium channel blockers are no more effective at reducing mortality after an acute MI, and may increase mortality in people with congestive heart failure (high-quality evidence).

For GRADE evaluation of interventions for acute MI, see table, p 26 .

Benefits: **Calcium channel blockers versus placebo:**
Dihydropyridine calcium channel blockers:
We found two RCTs comparing short-acting nifedipine versus placebo within the first few days of an acute MI. [49] [50] The first RCT (4491 people) was terminated prematurely because of concerns about safety. [49] It found that nifedipine increased mortality by 33% compared with placebo, although the increase did not reach significance. The second RCT (1006 people) found no significant difference in mortality between nifedipine and placebo (19% with nifedipine *v* 16% with placebo; OR 1.60, 95% CI 0.86 to 3.00). [50] We found no RCTs of sustained-release nifedipine, amlodipine, or felodipine in this setting.

Verapamil:
We found one systematic review (search date 1997, 7 RCTs, 6527 people with acute MI). [51] It found no significant difference in mortality between verapamil and placebo (RR 0.86, 95% CI 0.71 to 1.04).

Harms: Two systematic reviews (search dates not reported; including both randomised and observational trials) investigating the use of calcium channel blockers in people with acute MI found non-significant increases in mortality of about 4% and 6%. [52] [53] One RCT (2466 people with acute MI) compared diltiazem (60 mg orally 4 times daily starting 3–15 days after acute MI) versus placebo. [54] It found no significant difference in total mortality or reinfarction between diltiazem and placebo. Subgroup analysis in people with congestive heart failure found that diltiazem significantly increased death and reinfarction (RRI 1.41, 95% CI 1.01 to 1.96).

Comment: None.

OPTION PRIMARY PTCA VERSUS THROMBOLYSIS

Mortality
Compared with thrombolysis Primary PTCA may be more effective at reducing mortality at 30 days after an acute MI (low-quality evidence).

Bleeding
Compared with thrombolysis Primary PTCA may be associated with a decreased risk of stroke (any stroke or haemorrhagic stroke) compared with thrombolysis at 4 to 6 weeks, but primary PTCA may be associated with an increased risk of major bleeds compared with thrombolysis at 4 to 6 weeks (low-quality evidence).

For GRADE evaluation of interventions for acute MI, see table, p 26 .

Benefits:

We found two systematic reviews. [55] [56] The first systematic review (search date not reported, 23 RCTs, 7739 people with or without cardiogenic shock) compared primary PTCA versus thrombolysis (streptokinase and fibrin-specific agents) in people with acute ST-segment MI. [55] It found that PTCA significantly reduced the combined end point of death, non-fatal reinfarction, and stroke at 4 to 6 weeks compared with thrombolysis (AR 253/3089 [8%] with PTCA *v* 442/3085 [14%] with thrombolysis; OR 0.53, 95% CI 0.45 to 0.63; P = 0.35). Results were similar for PTCA compared with streptokinase and for PTCA compared with fibrin-specific agents (streptokinase trials: 8 RCTs, 1837 people: 50/921 [5%] with PTCA *v* 90/916 [10%] with streptokinase; OR 0.40, 95% CI 0.28 to 0.58; fibrin-specific agent trials: 15 RCTs, 5902 people: 220/2951 [8%] with PTCA *v* 270/2951 [9%] with fibrin-specific agents; OR 0.57, 95% CI 0.48 to 0.63). The second systematic review (search date 2002, [56] 22 RCTs including 19 trials from the first review, 6763 people) compared PTCA versus in-hospital thrombolysis. It found that PTCA significantly reduced mortality at 30 days compared with fibrinolysis (5.3% with PTCA *v* 7.9% with fibrinolysis; P <0.001; absolute numbers not reported).

Harms:

Stroke:
The first review found that PTCA significantly reduced the risk of stroke compared with thrombolysis at 4 to 6 weeks (any stroke: AR 30/3135 [1%] with PTCA *v* 64/3136 [2%] with thrombolysis; P = 0.0004; haemorrhagic stroke: 1/1830 [0.1%] with PTCA *v* 21/1846 [1.1%] with thrombolysis; P <0.0001). [55] The second review gave no information on harms. [56]

Major bleeding:
The first review also found that PTCA increased major bleeding at 4 to 6 weeks compared with thrombolysis (AR 7% with PTCA *v* 5% with thrombolysis; OR 1.30, 95% CI 1.02 to 1.56). [55] The second review gave no information on harms. [56]

Comment:

Although collectively the trials found an overall short-term and long-term reduction in deaths with PTCA compared with thrombolysis, there were several pitfalls common to individual RCTs, which may have inflated the benefit of PTCA. [57] RCTs comparing PTCA versus thrombolysis could not be easily blinded, and the ascertainment of end points that required some judgement, such as reinfarction or stroke, may have been influenced by the investigators' knowledge of the treatment allocation (the vast majority of the earlier trials did not have blinded adjudication events committees). In addition, the RCTs conducted before the GUSTO RCT (published 1997) [58] should be viewed as hypothesis generating, in that the combined outcome (death, reinfarction, and stroke) was not prospectively defined, and attention was only placed on these end points after there seemed to be some benefit on post hoc analysis. The lower mortality and reinfarction rates reported with primary PTCA are promising but not conclusive, and the real benefits may well be smaller. Only in a minority of centres (such as those that participated in the randomised trials) that perform a high volume of PTCA, and in the hands of experienced interventionists, may primary PTCA be clearly superior to thrombolytic treatment. Elsewhere, primary PTCA may be of greatest benefit in people with contraindications to thrombolysis, in people in cardiogenic shock, or in people in whom the mortality reduction with thrombolysis is modest and the risk of intracranial haemorrhage is increased, for example, elderly people. [59] The value of PTCA over thrombolysis in people presenting to hospital more than 12 hours after onset of chest pain remains to be tested. The second review reported a trend that PTCA had greatest reduction in 30-day mortality compared with thrombolysis when there were longer delays in presentation to hospital; however, these comparisons did not reach significance. In one large RCT, the collective rate of haemorrhagic stroke in people given thrombolysis was 1.1%, substantially higher than that observed in trials comparing thrombolysis versus placebo. [58] This may have been because the trials summarised above were in older people and used tPA. However, the lower rates of haemorrhagic stroke with primary PTCA were consistent across almost all trials, and this may be the major advantage of PTCA over thrombolysis.

QUESTION **Which treatments improve outcomes in people with cardiogenic shock after acute MI?**

OPTION EARLY INVASIVE CARDIAC REVASCULARISATION

Mortality

Compared with medical treatment alone Early invasive cardiac revascularisation may be more effective at reducing mortality at 1 to 6 months in people with cardiogenic shock within 48 hours of an acute MI (low-quality evidence).

Note

We found no clinically important results from RCTs about the effects of early PTCA compared with CABG in people with cardiogenic shock after an acute MI.

For GRADE evaluation of interventions for acute MI, see table, p 26 .

Benefits:

Early invasive cardiac revascularisation versus initial medical treatment alone:
We found no systematic review. We found two RCTs in people with cardiogenic shock within 48 hours of an acute MI comparing early invasive cardiac revascularisation versus initial medical treatment alone (see comment below). [2] [3] [60] The first RCT (302 people) found that early invasive cardiac revascularisation significantly reduced mortality at 6 months (see table 2, p 25). [2] [60] The second RCT (55 people) found that early invasive cardiac revascularisation reduced mortality at 30 days, although the difference was not significant (see table 2, p 25). [3]

PTCA versus CABG:
We found no RCTs in people with cardiogenic shock after acute MI that compared PTCA versus CABG.

Harms:

Early invasive cardiac revascularisation versus initial medical treatment alone:
Prespecified subgroup analysis in the first RCT found that there was a non-significant increase in 30-day mortality in people aged 75 years or more with early invasive cardiac revascularisation compared with initial medical treatment alone (56 people in subgroup; 18/24 [75%] with early invasive cardiac revascularisation *v* 17/32 [53%] with medical treatment alone; RR 1.41, 95% CI 0.95 to 2.11). [2] [60] The first RCT also found that acute renal failure (defined as a serum creatinine level greater than 265 micromol/L) was significantly more common in the medical treatment alone group than in the early cardiac revascularisation group (36/150 [24%] with medical treatment *v* 20/152 [13%] with early cardiac revascularisation; RR 1.82, 95% CI 1.1 to 3.0; NNH 9, 95% CI 5 to 48). Other harms reported by the RCT included major haemorrhage, sepsis, and peripheral vascular occlusion, although comparative data between groups for these harms were not reported. The second RCT did not report harms. [3]

Comment:

In the first RCT, medical treatment included intra-aortic balloon counterpulsation and thrombolytic treatment. [2] [60] In the second RCT, medical treatment was not defined. [3] The second RCT was stopped prematurely because of difficulties with recruitment. Both RCTs were conducted in centres with expertise in early invasive cardiac revascularisation. Their results may not necessarily be reproducible in other settings. [2] [3] [60]

OPTION THROMBOLYSIS

Mortality

Compared with no thrombolysis Thrombolysis may be no more effective at reducing inpatient mortality after 21 days in people with cardiogenic shock after an acute MI (low-quality evidence).

For GRADE evaluation of interventions for acute MI, see table, p 26 .

Benefits:

We found no systematic review. We found one RCT (11,806 people with acute MI) comparing streptokinase versus no thrombolysis and performed a subgroup analysis on people with cardiogenic shock (see comment below). [61] Outcomes were assessed by a blinded committee, though the participants and treating doctors were not blinded. The subgroup analysis found no significant difference in inpatient mortality after 21 days (280 people; 102/146 [70%] with thrombolysis *v* 94/134 [70%] with no thrombolysis; RR 1.0, 95% CI 0.85 to 1.16; see comment).

Harms:

The RCT gave no information on adverse effects in the subgroup of people with cardiogenic shock. [61] Overall, adverse reactions attributed to streptokinase were found in 705/5860 (12%) people either during or after streptokinase infusion. These adverse reactions included minor and major bleeding (3.7%), allergic reactions (2.4%), hypotension (3.0%), anaphylactic shock (0.1%), shivering/fever (1.0%), ventricular arrhythmias (1.2%), and stroke (0.2%). See harms of thrombolysis in acute MI, p 4 .

Comment: Data presented are from a retrospective subgroup analysis. [61] Randomisation was not stratified by the presence of cardiogenic shock. One RCT in people with cardiogenic shock complicating acute MI compared an emergency revascularisation strategy with initial medical stabilisation (see benefits of early invasive revascularisation, p 16). [2] [60] A subsequent report of this RCT analysed the effects of thrombolytic therapy, with or without intra-aortic balloon counterpulsation, on 12-month survival. [62] The trial reported that among the 150 people randomised to initial medical stabilisation, 63% received thrombolytic therapy as recommended per protocol (not randomly assigned). The trial found that in those people with initial medical stabilisation, thrombolysis was associated with an improved 1 year survival rate compared with no thrombolytic therapy (mortality HR adjusted for age and previous MI 0.62, 95% CI 0.41 to 0.93). [62] In those people in the emergency revascularisation group, it found no significant difference in survival between thrombolytic therapy and no thrombolytic therapy (mortality HR adjusted for age and previous MI 1.06, 95% CI 0.67 to 1.66). [62] Overall, it found a similar rate of severe bleeding between those receiving and those not receiving thrombolytic therapy (31% with thrombolytic therapy *v* 26% with no thrombolytic therapy; P = 0.37). [62] However, the administration of thrombolytic therapy (with or without intra-aortic balloon pump deployment) was not randomised, but was arranged by protocol, and the analysis was post hoc.

OPTION POSITIVE INOTROPES (DOBUTAMINE, DOPAMINE, ADRENALINE [EPINEPHRINE], NORADRENALINE [NOREPINEPHRINE], AMRINONE)

We found no direct information from RCTs about whether inotropes are better than no active treatment.

For GRADE evaluation of interventions for acute MI, see table, p 26 .

Benefits: We found no systematic reviews and no RCTs.

Harms: See comment section and harms of positive entropic drugs under heart failure.

Comment: Three non-systematic reviews of observational studies, which did not meet our inclusion criteria, evaluated positive inotropes in people with cardiogenic shock after acute MI. [1] [63] [64] They found that positive inotropes may worsen cardiac ischaemia and induce ventricular arrhythmias. [1] [63] [64]

OPTION VASODILATORS (ACE INHIBITORS, NITRATES)

We found no direct information from RCTs about whether vasodilators are better than no active treatment.

For GRADE evaluation of interventions for acute MI, see table, p 26 .

Benefits: We found no systematic review or RCTs.

Harms: We found no RCTs.

Comment: The risk of worsening hypotension has led to concern about treating acute cardiogenic shock with any vasodilator. [64]

OPTION PULMONARY ARTERY CATHETERISATION

We found no clinically important results from RCTs about pulmonary artery catheterisation compared with no catheterisation in people with an acute MI. There is consensus that pulmonary artery catheterisation benefits people with cardiogenic shock after an acute MI.

For GRADE evaluation of interventions for acute MI, see table, p 26 .

Benefits: We found no systematic review and no RCTs.

Harms: Observational studies have found an association between pulmonary artery catheterisation and increased morbidity and mortality, but it is unclear whether this arises from an adverse effect of the catheterisation or because people with a poor prognosis were selected for catheterisation. [65] Harms such as major arrhythmias, injury to the lungs, thromboembolism (see thromboembolism), and sepsis occur in 0.1% to 0.5% of people undergoing pulmonary artery catheterisation. [65]

Comment: Pulmonary artery catheterisation helps to diagnose cardiogenic shock, guide correction of hypovolaemia, optimise filling pressures for both the left and right sides of the heart, and adjust doses of inotropic drugs. [1] There is consensus that pulmonary artery catheterisation benefits people

with cardiogenic shock after acute MI, [66] [67] although we found no evidence to confirm or reject this view.

OPTION INTRA-AORTIC BALLOON COUNTERPULSATION

We found no clinically important results from RCTs about intra-aortic balloon counterpulsation compared with no intra-aortic balloon counterpulsation in people after an acute MI.

For GRADE evaluation of interventions for acute MI, see table, p 26 .

Benefits: We found no systematic reviews or RCTs.

Harms: We found no RCTs.

Comment: We found two additional small RCTs (30 people [68] and 20 people [69]) comparing intra-aortic balloon counterpulsation versus standard treatment in people after acute MI. Neither RCT specifically recruited people with cardiogenic shock after acute MI. Neither RCT found a reduction in mortality with intra-aortic balloon counterpulsation.

Clinical guide:
There is consensus that intra-aortic balloon counterpulsation is beneficial in people with cardiogenic shock after acute MI. We found no evidence to confirm or reject this view.

OPTION VENTRICULAR ASSISTANCE DEVICES AND CARDIAC TRANSPLANTATION

We found no direct information from RCTs about ventricular assistance devices or cardiac transplantation in people with cardiogenic shock after an acute MI.

For GRADE evaluation of interventions for acute MI, see table, p 26 .

Benefits: We found no systematic review and no RCTs.

Harms: We found no evidence of harms specifically associated with ventricular assistance devices or cardiac transplantation in people with cardiogenic shock after acute MI.

Comment: **Clinical guide:**
Reviews of observational studies [1] [64] [70] and retrospective reports [71] [72] have suggested that ventricular assistance devices may improve outcomes in selected people when used alone or as a bridge to cardiac transplantation. The availability of ventricular assistance devices and cardiac transplantation is limited to a few specialised centres. Results may not be applicable to other settings.

OPTION EARLY CARDIAC SURGERY

We found no direct information from RCTs about early surgical interventions in people with cardiogenic shock after an acute MI.

For GRADE evaluation of interventions for acute MI, see table, p 26 .

Benefits: We found no systematic review and no RCTs.

Harms: We found no evidence about the adverse effects of surgery in people with cardiogenic shock after acute MI.

Comment: **Clinical guide:**
Non-systematic reviews of observational studies have suggested that death is inevitable after free wall rupture without early surgical intervention and that surgery for both mitral valve regurgitation and ventricular septal rupture is more effective when carried out within 24 to 48 hours. [1] [64]

GLOSSARY

Intra-aortic balloon counterpulsation A technique in which a balloon is placed in the aorta and inflated during diastole and deflated just before systole.

Invasive cardiac revascularisation A term used to describe either percutaneous transluminal coronary angioplasty or coronary artery bypass grafting.

Cardiac index A measure of cardiac output derived from the formula: cardiac output/unit time divided by body surface area (L/minute/m^2).

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

Killip class A categorisation of the severity of heart failure based on easily obtained clinical signs. The main clinical features are Class I: no heart failure; Class II: crackles audible halfway up the chest; Class III: crackles heard in all the lung fields; Class IV: cardiogenic shock.

Low-quality evidence 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.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Ventricular assistance device A mechanical device placed in parallel to a failing cardiac ventricle that pumps blood in an attempt to maintain cardiac output. Because of the risk of mechanical failure, thrombosis, and haemolysis, ventricular assistance devices are normally used for short-term support while preparing for a heart transplant.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Adding low molecular weight heparin to thrombolytics New evidence added. [28] [29] Categorisation unchanged (Likely to be beneficial).

Adding unfractionated heparin to thrombolytics New evidence added. [28] [29] Categorisation unchanged (Unlikely to be beneficial).

Glycoprotein IIb/IIIa inhibitors New evidence added. [33] Categorisation unchanged (Trade-off between benefits and harms).

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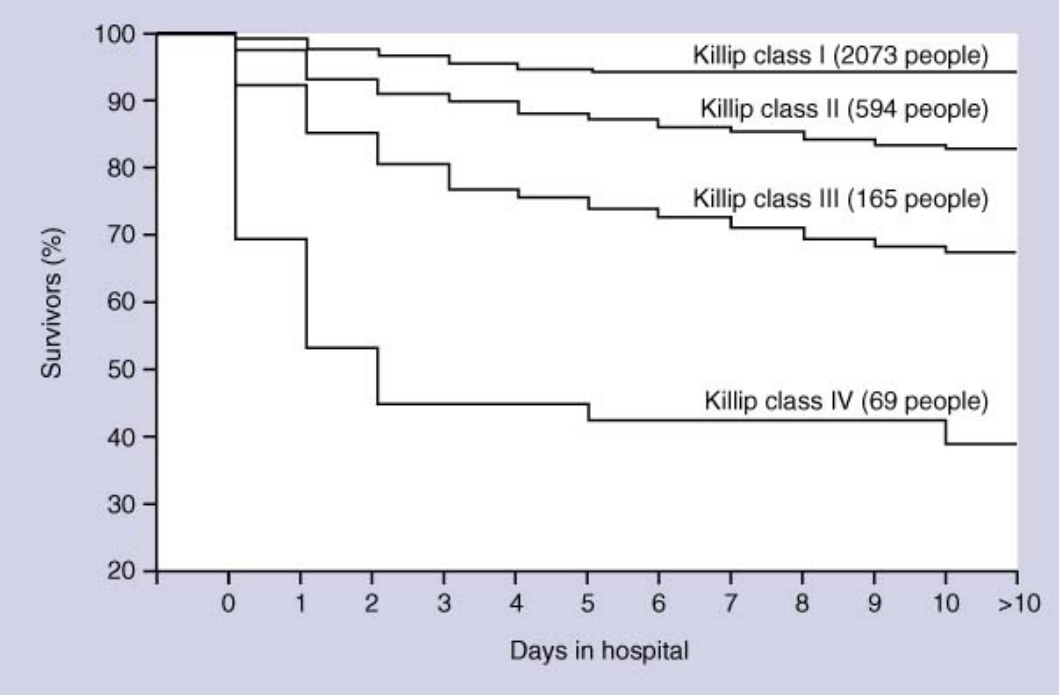

FIGURE 1 **The AMIS registry Kaplan–Meier survival curves as a function of Killip class at hospital admission for 3138 people (2901 evaluable) admitted in 50 Swiss hospitals between 1977 and 1998. Published with permission: Urban P, Bernstein MS, Costanza MC, et al, for the AMIS investigators. An internet-based registry of acute MI in Switzerland. *Kardiovasc Med* 2000;3:430–441 (see text).**

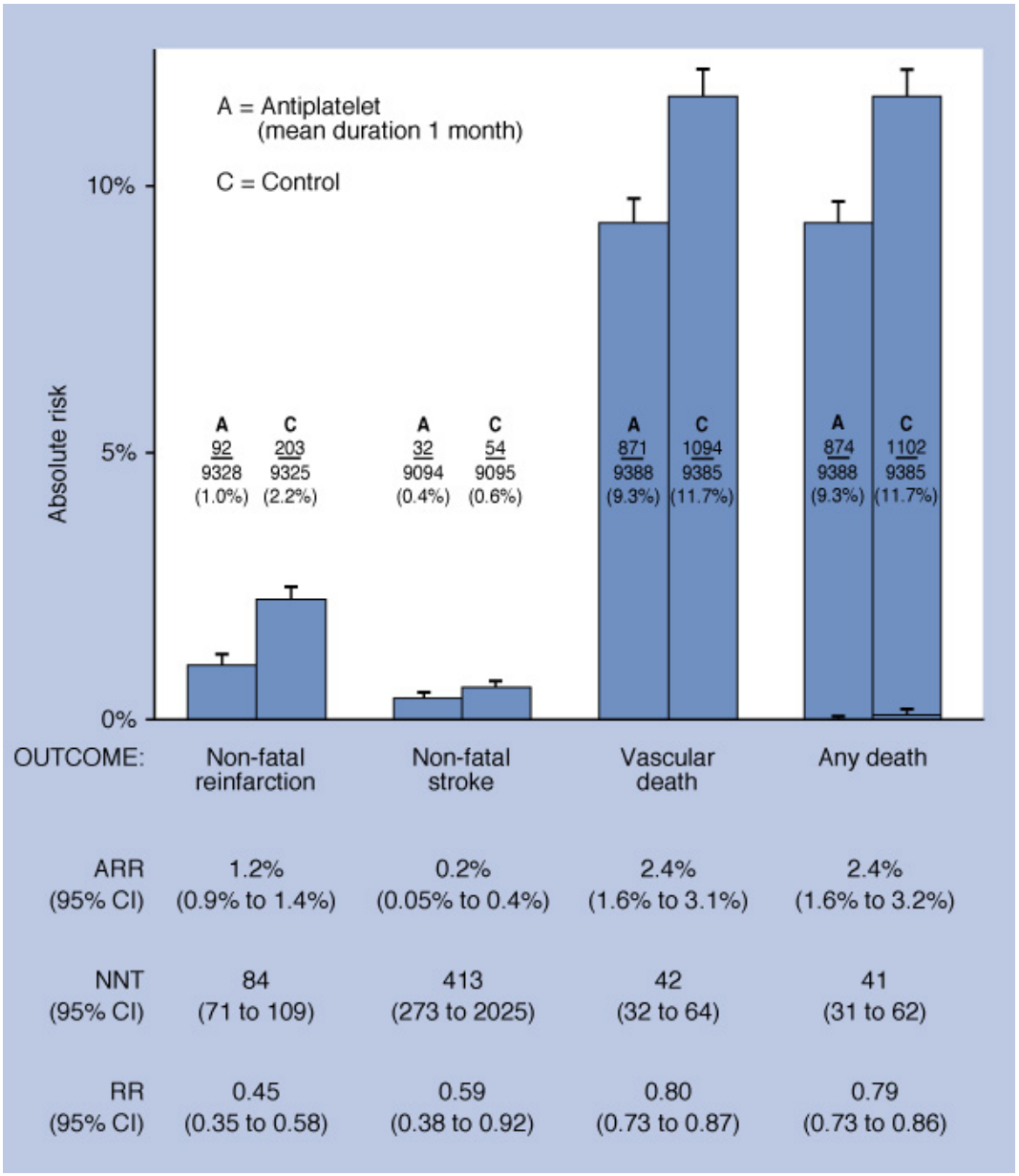

FIGURE 2 **Absolute effects of antiplatelet treatment on outcomes in people with a prior suspected or definite acute MI. The columns show the absolute risks over 1 month for each category; the error bars are the upper 95% CI. In the "any death" column, non-vascular deaths are represented by lower horizontal lines. The table displays for each outcome the absolute risk reduction (ARR), the number of people needing treatment for 1 month to avoid one additional event (NNT), and the risk reduction (RR), with their 95% CI values (see text, p 3). Published with permission.**

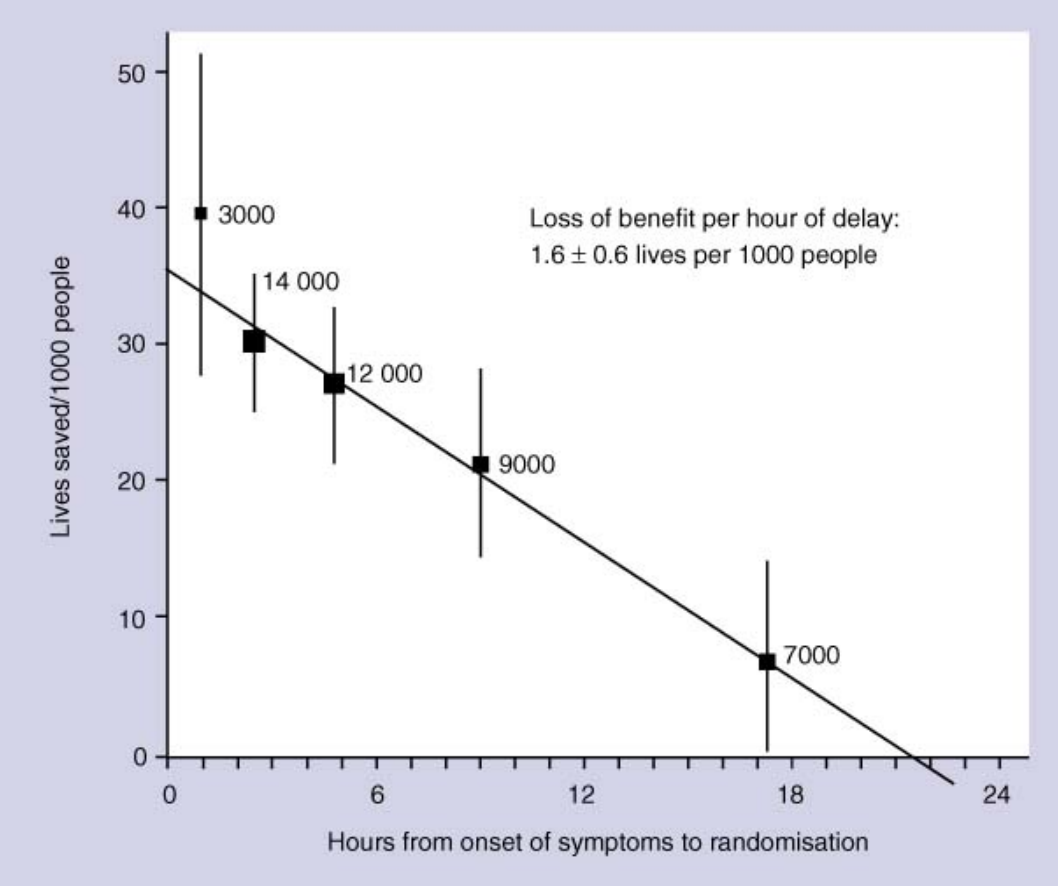

FIGURE 3 **Absolute number of lives saved at 1 month/1000 people receiving thrombolytic treatment plotted against the time from the onset of symptoms to randomisation among 45,000 people with ST-segment elevation or bundle branch block. Numbers along the curve are the number of people treated at different times (see text, p 4). Published with permission: Collins R, Peto R, Baigent BM, et al. Aspirin, heparin and fibrinolytic therapy in suspected AMI. *N Engl J Med* 1997;336:847–860. Copyright © 1997 Massachusetts Medical Society. All rights reserved.**

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TABLE 1 **Direct randomised comparisons of the standard streptokinase regimen with various tPA-based fibrinolytic regimens in people with suspected acute MI in the GISSI-2, ISIS-3, and GUSTO-1 trials (see text, p 4).** [18] [19] [20]

Trial and treatment	Number of people randomised	Any stroke: absolute number (%)	Any death: absolute number (%)	Death not related to stroke:* absolute number (%)	Stroke or death: absolute number (%)
GISSI-2† [18]					
Streptokinase	10,396	98 (0.9)	958 (9.2)	916 (8.8)	1014 (9.8)
tPA	10,372	136 (1.3)	993 (9.6)	931 (9.0)	1067 (10.3)
Effect/1000 people treated with tPA instead of streptokinase		3.7 ± 1.5 more	3.6 ± 4.0 more	1.7 ± 4.0 more	5.3 ± 4.2 more
ISIS-3‡ [19]					
Streptokinase	13,780	141 (1.0)	1455 (10.6)	1389 (10.1)	1530 (11.1)
tPA	13,746	188 (1.4)	1418 (10.3)	1325 (9.6)	1513 (11.0)
Effect/1000 people treated with tPA instead of streptokinase		3.5 ± 1.3 more	2.4 ± 3.7 fewer	4.4 ± 3.6 fewer	1.0 ± 3.8 fewer
GUSTO-1§ [20]					
Streptokinase (sc heparin)	9841	117 (1.2)	712 (7.3)	666 (6.8)	783 (8.0)
Streptokinase (iv heparin)	10,410	144 (1.4)	763 (7.4)	709 (6.8)	853 (8.2)
tPA alone	10,396	161 (1.6)	653 (6.3)	585 (5.6)	746 (7.2)
tPA plus streptokinase	10,374	170 (1.6)	723 (7.0)	647 (6.2)	817 (7.9)
Effect/1000 people treated with tPA-based regimens instead of streptokinase		3.0 (± 1.2) more	6.6 (± 2.5) fewer	8.6 (± 2.4) fewer	5.5 (± 2.6) fewer
chi^2/2 heterogeneity of effects between 3 trials		0.7	5.6	7.0	5.4
P value		0.3	0.06	0.03	0.07
Weighted average of all 3 trials¶					
Effect/1000 people treated with tPA-based regimens instead of streptokinase		3.3 (± 0.8) more	2.9 (± 1.9) fewer	4.9 (± 1.8) fewer	1.6 (± 1.9) fewer
P value		<0.001	>0.1	0.01	0.4

Trial and treatment	Number of people randomised	Any stroke: absolute number (%)	Any death: absolute number (%)	Death not related to stroke:* absolute number (%)	Stroke or death: absolute number (%)

Values are numbers (%). This table should not be used to make direct non-randomised comparisons between the absolute event rates in different trials, because the patient populations may have differed substantially in age and other characteristics. Deaths recorded throughout the first 35 days are included for GISSI-2 and ISIS-3 and throughout the first 30 days for GUSTO-1. Numbers randomised and numbers with follow-up are from the ISIS-3 report [19] and GUSTO-1 [20] (supplemented with revised GUSTO-1 data from the National Auxiliary Publications Service), and numbers with events and the percentages (based on participants with follow-up) are from the ISIS-3 report [19] and Van de Werf, et al. [61] Plus-minus values are ± standard deviation. In all 3 trials, streptokinase was given in intravenous infusions of 1.5 MU over a period of 1 hour.
*Death not related to stroke was defined as death without recorded stroke.
†In the GISSI-2 trial, the tPA regimen involved an initial bolus of 10 mg, followed by 50 mg in the first hour and 20 mg in each of the second and third hours.
‡In the ISIS-3 trial, the tPA regimen involved 40,000 clot-lysis U/kg of body weight as an initial bolus, followed by 360,000 U/kg in the first hour and 67,000 U/kg in each of the next 3 hours.
§In the GUSTO-1 trial, the tPA-alone regimen involved an initial bolus of 15 mg, followed by 0.75 mg/kg (up to 50 mg) in the first 30 minutes and 0.5 mg/kg (up to 35 mg) in the next hour; in the GUSTO-1 trial the other tPA-based regimen involved 0.1 mg/kg of tPA (up to 9 mg) as an initial bolus and 0.9 mg/kg (up to 81 mg) in the remainder of the first hour, plus 1 MU of streptokinase in the first hour.
¶The weights are proportional to the sample sizes of the trials, so this average gives most weight to the GUSTO-1 trial and least to the GISSI-2 trials. [17]
iv, intravenous; tPA, tissue plasminogen activator; sc, subcutaneous.

TABLE 2 **Comparison of early invasive cardiac revascularisation versus initial medical treatment on mortality at 30 days, 6 months, and 12 months (see text, p 16).** [2] [3] [60]

Time after acute MI	Mortality in early invasive cardiac revascularisation group: number dead/total number (%)	Mortality in medical treatment alone group: number dead/total number (%)	ARR (95% CI)	RR (95% CI)	NNT (95% CI)
SHOCK study [2] [60]					
30 days	71/152 (47)	84/150 (56)	+9.3% (–2 to +20.2)	0.83 (0.67 to 1.04)	NA
6 months	76/152 (50)	94/150 (63)	12.7% (1.5 to 23.4)	0.80 (0.65 to 0.98)	8 (5 to 68)
12 months	81/152 (53)	99/150 (66)	12.7% (1.6 to 23.3)	0.80 (0.67 to 0.97)	8 (5 to 61)
SMASH study [3]					
30 days	22/32 (69)	18/23 (78)	+9.5% (–14.6 to +30.6)	0.88 (0.64 to 1.2)	NA
12 months	23/32 (74)	19/23 (83)	+10.7% (–12.7 to +30.9)	0.87 (0.65 to 1.16)	NA

NA, not applicable.

TABLE **GRADE evaluation of interventions for acute MI**

Important outcomes	Cardiovascular events, bleeding, mortality, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
Which treatments improve outcomes in people with acute MI?									
9 (18,773) [11]	Mortality	Aspirin *v* placebo	4	0	0	0	0	High	
9 (18,773) [11]	Cardiovascular events	Aspirin *v* placebo	4	0	0	0	0	High	
9 (58,600) [15]	Mortality	Thrombolysis *v* placebo	4	0	−1	0	0	Moderate	Consistency point deducted for different results for different subgroups
3 (94,701) [18] [19] [20]	Mortality	tPA *v* streptokinase	4	−2	−1	0	0	Very low	Quality points deducted for no blinding and incomplete reporting of results. Consistency point deducted for conflicting results across studies
3 (47,086) [21] [22] [23]	Mortality	tPA *v* other thrombolytics	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for different selection criteria and protocols for different studies
9 (58,600) [15]	Bleeding	Thrombolysis *v* placebo	4	0	0	0	0	High	
3 (at least 39,907) [18] [19] [20]	Bleeding	Streptokinase *v* tPA	4	−2	0	0	0	Low	Quality points deducted for no blinding and incomplete reporting of results
3 (47,086) [21] [22] [23]	Bleeding	tPA *v* other thrombolytics	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for different selection criteria and protocols for different studies
1 (496) [27]	Mortality	Thrombolytic plus low molecular weight heparin *v* thrombolytic plus placebo	4	0	0	0	0	High	
1 (496) [27]	Cardiovascular events	Thrombolytic plus low molecular weight heparin *v* thrombolytic plus placebo	4	0	0	0	0	High	
8 (27,758) [28] [29] [30]	Mortality	Thrombolytic plus low molecular weight heparin *v* thrombolytic plus unfractionated heparin	4	−1	0	0	0	Moderate	Quality point deducted for weak methods (lack of blinding in some RCTs, incomplete reporting of results in 1 large RCT)
8 (27,758) [28] [29] [30]	Cardiovascular events	Thrombolytic plus low molecular weight heparin *v* thrombolytic plus unfractionated heparin	4	−1	0	0	0	Moderate	Quality point deducted for weak methods (lack of blinding in some RCTs, incomplete reporting of results in 1 large RCT)
8 (27,758) [28] [29] [30]	Bleeding	Thrombolytic plus low molecular weight heparin *v* thrombolytic plus unfractionated heparin or placebo	4	−2	0	0	0	Low	Quality points deducted for weak methods (lack of blinding in some RCTs, incomplete reporting of background interventions which might affect bleeding) and incomplete reporting of results in 1 review
2 (53,789) [18] [19]	Mortality	Thrombolytics plus unfractionated heparin *v* thrombolytics alone	4	−2	0	0	0	Low	Quality points deducted for no blinding and incomplete reporting of results
2 (53,789) [18] [19]	Cardiovascular events	Thrombolytics plus unfractionated heparin *v* thrombolytics alone	4	−2	0	0	0	Low	Quality points deducted for no blinding and incomplete reporting of results

Important outcomes	Cardiovascular events, bleeding, mortality, adverse effects								
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
2 (53,789) [18] [19]	Bleeding	Thrombolytics plus unfractionated heparin *v* thrombolytics alone	4	−2	0	0	0	Low	Quality points deducted for no blinding and incomplete reporting of results
1 (16,588) [31]	Mortality	Glycoprotein IIb/IIIa inhibitors plus thrombolysis *v* thrombolysis alone	4	−1	0	−1	0	Low	Quality point deducted for no blinding. Directness point deducted for different doses of thrombolytics in 2 groups
1 (16,588) [31]	Cardiovascular events	Glycoprotein IIb/IIIa inhibitors plus thrombolysis *v* thrombolysis alone	4	−1	0	−1	0	Low	Quality point deducted for no blinding. Directness point deducted for different doses of thrombolytics in 2 groups
7 (at least 1101) [32] [33]	Mortality	Glycoprotein IIb/IIIa inhibitors plus PTCA *v* PTCA plus placebo	4	−2	0	0	0	Low	Quality points deducted for incomplete reporting of results and use of composite outcomes
7 (at least 1101) [32] [33]	Cardiovascular events	Glycoprotein IIb/IIIa inhibitors plus PTCA *v* PTCA plus placebo	4	−2	0	0	0	Low	Quality points deducted for incomplete reporting of results and use of composite outcomes
1 (unclear) [31]	Bleeding	Glycoprotein IIb/IIIa inhibitors plus thrombolysis *v* thrombolysis alone	4	−2	0	0	0	Low	Quality points deducted for no blinding and incomplete reporting of results
7 (at least 1101) [32] [33]	Bleeding	Glycoprotein IIb/IIIa inhibitors plus PTCA *v* PTCA plus placebo	4	−1	−1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for inconsistent results depending on analysis
At least 52 (at least 60,772) [40] [41] [42]	Mortality	Beta-blockers *v* placebo or no beta-blocker	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for narrow range of inclusion criteria and lack of use of thrombolysis in many studies
1 (45,852) [40]	Cardiovascular events	Beta-blockers *v* placebo or no beta-blocker	4	0	0	0	0	High	
15 (15,104) [43]	Mortality	ACE inhibitors *v* placebo	4	0	0	0	0	High	
2 (75,867) [46] [47]	Mortality	Nitrates plus thrombolysis *v* thrombolysis plus placebo	4	0	0	−1	0	Moderate	Directness point deducted because of high numbers of people not receiving thrombolysis or receiving nitrates outside the study protocol
1 (17,817) [47]	Cardiovascular events	Nitrates plus thrombolysis *v* thrombolysis plus placebo	4	0	0	−1	0	Moderate	Directness point deducted because of high numbers of people not receiving thrombolysis or receiving nitrates outside the study protocol
10 (2041) [48]	Mortality	Nitrates without thrombolysis *v* placebo	4	0	0	0	0	High	
9 (12,024) [49] [50] [51]	Mortality	Calcium channel blockers *v* placebo	4	0	0	0	0	High	
At least 22 (at least 6763) [56] [55]	Mortality	Primary PTCA *v* thrombolysis	4	−2	0	0	0	Low	Quality points deducted for lack of blinding and use of non-defined composite outcome in early studies
23 (7739) [55]	Bleeding	Primary PTCA *v* thrombolysis	4	−2	0	0	0	Low	Quality points deducted for lack of blinding and use of non-defined composite outcome in early studies
What treatments improve outcomes for cardiogenic shock after acute MI?									
2 (357) [2] [60] [3]	Mortality	Early invasive cardiac revascularisation *v* medical treatment alone	4	0	0	−2	0	Low	Directness points deducted for uncertainty about comparators and uncertain generalisability of results

Important outcomes	**Cardiovascular events, bleeding, mortality, adverse effects**								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
1 (280) [61]	Mortality	Thrombolysis *v* no thrombolysis	4	−2	0	0	0	Low	Quality points deducted for retrospective subgroup analysis and blinding flaws

Type of evidence: 4 = RCT.
Consistency: similarity of results across studies.
Directness: generalisability of population or outcomes.
Effect size: based on relative risk or odds ratio.