Non ST-elevation acute coronary syndrome.

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ABSTRACT

INTRODUCTION: Non ST-elevation acute coronary syndrome (NSTE-ACS, here defined as unstable angina and non ST-elevation MI) is characterised by episodes of chest pain at rest or with minimal exertion, which increase in frequency or severity, often with dynamic ECG changes. Between 9% and 19% of people with NSTE-ACS die in the first 6 months after diagnosis, with about half of these deaths occurring within 4 weeks of diagnosis. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of: antiplatelet; antithrombin; anti-ischaemic; lipid-lowering; and invasive treatments? We searched: Medline, Embase, The Cochrane Library, and other important databases up to December 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 32 systematic reviews, RCTs, or observational studies that met our inclusion criteria. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: aspirin, beta-blockers, calcium channel blockers, clopidogrel, direct thrombin inhibitors, glycoprotein IIb/IIIa inhibitors (oral or intravenous), heparin (low molecular weight, unfractionated), fondaparinux, nitrates, routine early cardiac catheterisation and revascularisation, statins, and warfarin.

QUESTIONS

INTERVENTIONS

ANTIPLATELETS

Beneficial

Trade off between benefits and harms

ANTITHROMBIN TREATMENTS

Likely to be beneficial

Unlikely to be beneficial

ANTI-ISCHAEMIC TREATMENTS

Unknown effectiveness

LIPID-LOWERING TREATMENTS

Likely to be beneficial

INVASIVE TREATMENTS

Likely to be beneficial

Covered elsewhere in Clinical Evidence

Acute myocardial infarction

Secondary prevention of ischaemic cardiac events

Angina (chronic stable)

Key points

- Non ST-elevation acute coronary syndrome (NSTE-ACS, here defined as unstable angina and non ST-elevation MI) is characterised by episodes of chest pain at rest or with minimal exertion, which increase in frequency or severity, often with dynamic ECG changes.
- Aspirin reduces the risk of death, MI, and stroke compared with placebo in people with NSTE-ACS at doses up to 325 mg daily; higher doses of aspirin are no more effective, and increase the risk of bleeding complications.

Adding clopidogrel to aspirin may reduce the combined outcome of mortality, stroke, or MI, but may increase the risk of bleeding.

- Intravenous glycoprotein IIb/IIIa platelet receptor inhibitors may reduce the combined end point of death and MI in NSTE-ACS, but increase the risk of bleeding.
- Unfractionated or low molecular weight heparin plus aspirin may reduce death or MI at 1 week, but longer-term benefits are unclear.

  Low molecular weight heparin may reduce MI compared with unfractionated heparin.
- Fondaparinux (a factor Xa inhibitor) seems to be as effective as low molecular weight heparin at reducing death or MI, and cause less major bleeding.
- Compared with unfractionated heparin, direct thrombin inhibitors (hirudin and bivalirudin) may result in similar frequency of mortality or MI and may reduce the risk of bleeding.
- Warfarin has not been shown to be beneficial and increases the risk of major bleeding.
- We don't know whether intravenous nitrates, beta-blockers, or calcium channel blockers reduce the risk of MI or death, although they may reduce the frequency and severity of chest pain.
- We found insufficient RCT evidence to assess statins in people with NSTE-ACS but observational data suggest that intensive lipid therapy is beneficial if initiated within 12 days of NSTE-ACS presentation and that statins improve clinical outcomes in the long term.
- CAUTION: Short-acting dihydropyridine calcium channel blockers may increase mortality in people with CHD.
- Early routine cardiac catheterisation and revascularisation may reduce death and non-fatal MI compared with conservative strategies (medical treatment with or without later cardiac catheterisation and revascularisation).

DEFINITION

Acute coronary syndrome (ACS) is a term that encompasses unstable angina, non ST-elevation MI (alternatively described as non Q-wave MI, often referred to as non-STEMI), and ST-elevation MI (alternatively described as Q-wave MI, often referred to as STEMI). Unstable angina and non-STEMI are overlapping entities and will be discussed together in this review as non ST-elevation ACS (NSTE-ACS). STEMI is discussed elsewhere (see review on acute myocardial infarction). Unstable angina and non-STEMI is a spectrum of disease that involves an imbalance of supply and demand of oxygen available to the myocardium. [1] This balance is sometimes disrupted, causing symptoms such as new-onset exertional angina, pre-existing angina that is refractory to nitroglycerin, or angina at rest. The pathophysiology governing anginal symptoms is usually due to atherosclerotic plaque that nearly obstructs coronary vessels. The distinguishing feature between unstable angina and non-STEMI is the presence of elevated cardiac markers such as troponin, which imply myocardial damage. Patient history alone is insufficient to make a diagnosis of ACS. The clinical dilemma of distinguishing between cardiac and non-cardiac pain requires a combination of patient history, ECG, and biomarkers. Overlapping clinical entities in the ACS spectrum of disease allows for similar treatment strategies, and many trials include people with either unstable angina or non-STEMI. We have included systematic reviews and RCTs in a mixed population of people with unstable angina, non-STEMI, or both, which we refer to here as NSTE-ACS.

INCIDENCE/ PREVALENCE

In the USA, NSTE-ACS accounts for more than 1.4 million hospital admissions a year. [2] In industrialised countries, the annual incidence of unstable angina is about 6/10,000 people in the general population.

AETIOLOGY/ RISK FACTORS

Risk factors are the same as for other manifestations of ischaemic heart disease — older age, previous atheromatous CVD, diabetes mellitus, smoking, hypertension, hypercholesterolaemia, male sex, and a family history of premature ischaemic heart disease. NSTE-ACS can also occur in association with other disorders of the circulation, including valvular disease, arrhythmias, and cardiomyopathies. [1]

PROGNOSIS

Between 9% and 19% of people with NSTE-ACS die in the first 6 months after diagnosis, with about half of these deaths occurring within 30 days of diagnosis. [3] Several risk factors may indicate poor prognosis and include severity of presentation (e.g., duration of pain, speed of progression, evidence of heart failure), medical history (e.g., previous ACS, acute MI, left ventricular dysfunction), other clinical parameters (e.g., age, diabetes), ECG changes (e.g., severity of ST-segment depression and deep T-wave inversion), biomarkers (e.g., presence of troponin concentration elevation), and change in clinical status (e.g., recurrent chest pain, silent ischaemia, haemodynamic instability). [1] However, several key prognostic indicators associated with adverse outcomes may be used to aid clinical decision making. Variables including age 65 years or over, at least three risk factors for coronary artery disease, known significant coronary stenosis, degree of ST-segment deviation, recurrent anginal symptoms in 24 hours, use of aspirin in last 7 days, and elevated cardiac biomarkers can be used to generate a scoring system to predict high-risk patients who may expe-

rience true ischaemic cardiac events and death (TIMI [thrombolysis in MI] risk score). [4] The more of these factors that are present, the greater the likelihood of adverse ischaemic events. This helps in stratifying patients according to risk, and in identifying high-risk patients.

AIMS OF INTERVENTION To relieve pain and ischaemia; to prevent death and MI; to identify people at high risk who require revascularisation; to facilitate early hospital discharge in people at low and medium risk; to modify risk factors; to prevent death, MI, and recurrent ischaemia after discharge from hospital, with minimum adverse effects.

OUTCOMES **Mortality**, **MI**, **cardiovascular events** (including composite outcomes of mortality, MI, vascular death, or stroke), refractory ischaemia; readmission to hospital for cardiovascular events, **adverse effects** of treatment.

METHODS *Clinical Evidence* search and appraisal December 2009. The following databases were used to identify studies for this systematic review: Medline 1966 to December 2009, Embase 1980 to December 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 not possible. 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. We report RCTs assessing outcomes of treatment from onset of symptoms up to 6 months in this review. We also included systematic reviews that combined outcomes from both before and after 6 months. 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. 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 have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 18). 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).

QUESTION What are the effects of antiplatelet treatments in people with non ST-elevation acute coronary syndrome?

OPTION ASPIRIN

Cardiovascular events
Compared with placebo Aspirin is more effective at reducing the combined outcome of vascular death, MI, or stroke at 14 days to 18 months in people with unstable angina (moderate-quality evidence).

Adverse effects
Compared with placebo Aspirin increases the risk of major extracranial bleeding (moderate-quality evidence).

For GRADE evaluation of interventions for non ST-elevation acute coronary syndrome, see table, p 18 .

Benefits: **Aspirin versus placebo:**
One systematic review (search date 1997, 287 RCTs, 135,000 people) compared antiplatelet treatment versus placebo in people at high risk of vascular events. [5] Twelve of the RCTs (5031 people) evaluated people with unstable angina. The review found that antiplatelet treatment in these people (8 RCTs aspirin, 1 RCT aspirin plus dipyridamole, 2 RCTs ticlopidine, 1 RCT triflusal)

reduced the combined outcome of vascular death, MI, or stroke compared with placebo at 14 days to 18 months (AR: 199/2497 [8%] with antiplatelet treatment *v* 336/2534 [13%] with placebo; OR 0.54, 95% CI reported graphically; P <0.0001). The individual trials from the review that evaluated aspirin alone also found consistent benefit in reduced deaths and MI. The review concluded that, overall, there is no added cardiovascular benefit for aspirin doses >325 mg daily.

Harms:

Aspirin versus placebo:
The systematic review did not give any information on harms separately from people with unstable angina. Overall, it found that antiplatelet treatment significantly increased major extracranial bleeding compared with placebo, but the absolute risk was low (AR: 535/47,158 [1.1%] with antiplatelet treatment *v* 333/47,168 [0.7%] with placebo; OR 1.6, 95% CI 1.4 to 1.8). It found no significant difference in non-vascular mortality between antiplatelet treatment and placebo (AR: 785/71,656 [1.1%] with antiplatelet treatment *v* 872/71,876 [1.2%] with placebo; OR 0.92, 95% CI 0.82 to 1.03). [5] Adverse effects are more common with aspirin doses greater than 325 mg. Some people have a marked allergy to aspirin.

Comment:

Patients with acute coronary syndrome who are allergic to or do not respond to aspirin are likely to benefit from alternative antiplatelet treatment.

OPTION CLOPIDOGREL

Cardiovascular events

Clopidogrel plus aspirin compared with aspirin alone Adding clopidogrel to aspirin is more effective at reducing the combined outcome of cardiovascular death, MI, or stroke at 30 days in people with NSTE-ACS (moderate-quality evidence).

Adverse effects

Clopidogrel plus aspirin compared with aspirin alone Adding clopidogrel to aspirin increases the risk of major bleeding at 3 to 9 months (high-quality evidence).

For GRADE evaluation of interventions for non ST-elevation acute coronary syndrome, see table, p 18 .

Benefits:

Clopidogrel plus aspirin versus aspirin alone:
We found one RCT (12,562 people with NSTE-ACS) comparing clopidogrel (300 mg orally within 24 hours of onset of symptoms followed by 75 mg/day) versus placebo. [6] All participants received aspirin (75–325 mg/day). It found that clopidogrel significantly reduced the combined outcome of death from cardiovascular causes, MI, and stroke at 30 days compared with placebo (AR presented graphically; RR 0.82, 95% CI 0.70 to 0.95). [6]

Harms:

Clopidogrel plus aspirin versus aspirin alone:
The RCT found that clopidogrel plus aspirin significantly increased major bleeding compared with aspirin alone at 3 to 9 months, but haemorrhagic stroke was similar in both groups (major bleeding: AR: 231/6259 [4%] with clopidogrel *v* 169/6303 [3%] with placebo; RR 1.4, 95% CI 1.1 to 1.7; haemorrhagic stroke 0.1% with clopidogrel *v* 0.1% with placebo; RR and CI values not reported). [6] Post-hoc subgroup analysis showed that increasing aspirin dose increased the risk of major bleeding, with little corresponding reduction in cardiovascular risk. [7] The study concluded that the optimum daily dose of aspirin for use in combination with clopidogrel was 75 to 100 mg. One systematic review (search date 2002) of RCTs of antiplatelet agents for different indications, including acute coronary syndrome, found that the weighted mean rate of major bleeding with ticlopidine or clopidogrel was 2% (95% CI 1.9% to 2.3%; 8 RCTs, 18,574 people) and the rate of minor bleeding was 5% (95% CI 4.6% to 5.7%; 1 RCT, 6259 people). [8] Clopidogrel is associated with other adverse effects, including diarrhoea and rash.

Comment:

Post-hoc subgroup analysis found the reduction in cardiovascular death, MI, and stroke with clopidogrel across all risk groups (low, medium, and high, as classified by Thrombolysis In MI [TIMI] risk score) of NSTE-ACS. [9] A second post-hoc subgroup analysis found that giving clopidogrel on admission to the hospital did not increase the rate of bleeding requiring transfusion in patients undergoing coronary artery bypass graft (CABG) compared with when clopidogrel was withheld for >5 days. It is therefore recommended that clopidogrel is not withheld in high-risk patients upon admission, unless there is a clear contraindication.

OPTION INTRAVENOUS GLYCOPROTEIN IIB/IIIA PLATELET RECEPTOR INHIBITORS

Cardiovascular events

Compared with placebo in people not receiving a thienopyridine Intravenous glycoprotein IIb/IIIa inhibitors may be more effective at reducing the combined outcome of death or MI at 30 days in people with high-risk NSTE-ACS (moderate-quality evidence).

Compared with placebo in people receiving a thienopyridine In people at high risk who require urgent percutaneous coronary intervention (PCI), combining abciximab with clopidogrel further reduces the composite end point of mortality, MI, or target vessel revascularisation at 30 days (moderate-quality evidence).

Adverse effects
Compared with placebo in people not receiving a thienopyridine Intravenous glycoprotein IIb/IIIa inhibitors increase the risk of major bleeding at 30 days (moderate-quality evidence).

Compared with placebo in people receiving a thienopyridine In people at high risk who require urgent PCI, adding abciximab to clopidogrel does not increase the risk of bleeding at 30 days (high-quality evidence).

For GRADE evaluation of interventions for non ST-elevation acute coronary syndrome, see table, p 18 .

Note:
The clinical benefit of glycoprotein IIb/IIIa inhibitors should be weighed against the increased risk of bleeding.

Benefits:

Intravenous glycoprotein IIb/IIIa inhibitors versus placebo in people not receiving a thienopyridine:
We found one systematic review (6 RCTs, 31,402 people with NSTE-ACS) comparing intravenous glycoprotein IIb/IIIa inhibitors versus placebo. [10] The participants in all the identified RCTs had ischaemic ECG changes or elevated cardiac enzymes. Routine invasive treatment was not planned for the participants of any of the RCTs. However, 38% of people in the glycoprotein IIb/IIIa inhibitor group and 39% of people in the control group had undergone either percutaneous coronary intervention (PCI) or CABG by day 30.

The review found that intravenous glycoprotein IIb/IIIa inhibitors (abciximab, eptifibatide, lamifiban, and tirofiban) significantly reduced the combined outcome of death and MI at 30 days (AR: 1980/18,297 [11%] with glycoprotein IIb/IIIa inhibitors *v* 1550/13,105 [12%] with control; OR 0.9, 95% CI 0.84 to 0.98; P = 0.015).

The RCTs identified by the systematic review pre-dated the routine use of thienopyridines.

Intravenous glycoprotein IIb/IIIa inhibitors versus placebo in people receiving a thienopyridine:
We found one RCT (2022 people with high-risk NSTE-ACS undergoing urgent PCI) comparing intravenous abciximab versus placebo in people receiving pre- and post-procedure clopidogrel. [11] All participants received intravenous heparin during the PCI procedure and received pre-treatment (at least 2 hours before the procedure) with oral clopidogrel 600 mg plus oral aspirin 500 mg. During hospital stay after PCI, all participants also received a bolus plus infusion of clopidogrel 75 mg daily for 3 days. The RCT found that abciximab significantly reduced the combined outcome of mortality, MI, or target vessel revascularisation at 30 days compared with placebo (90/1012 [9%] with abciximab *v* 120/1010 [12%] with placebo; RR 0.75, 95% CI 0.58 to 0.97; P = 0.03). Subgroup analysis suggested that people with elevated troponin (>0.03 mg/L) especially benefited (67/513 [13%] with abciximab *v* 98/536 [18%] with placebo; RR 0.71, 95% CI 0.54 to 0.95; P = 0.02). [11]

Harms:

Intravenous glycoprotein IIb/IIIa inhibitors versus placebo:
The systematic review found that glycoprotein IIb/IIIa inhibitors significantly increased major bleeding compared with placebo at 30 days (AR: 445/18,297 [2%] with glycoprotein IIb/IIIa inhibitors *v* 180/13,105 [1%] with placebo; OR 1.6, 95% CI 1.4 to 1.9). It found no significant difference in stroke between groups at 30 days (AR: 137/18,297 [1%] with glycoprotein IIb/IIIa inhibitors *v* 91/13,105 [1%] with placebo; OR 1.11, 95% CI 0.8 to 1.5). [10]

Adding intravenous glycoprotein IIb/IIIa inhibitors to clopidogrel versus adding placebo:
The RCT found no significant difference in major or minor bleeding, or the need for blood transfusions between abciximab and placebo at 30 days (major bleeding: 14/1012 [1.4%] with abciximab *v* 14/1010 [1.4%] with placebo; RR 1.00, 95% CI 0.50 to 2.08; minor bleeding: 42/1012 [4%] with abciximab *v* 33/1010 [3%] with placebo; RR 1.27, 95% CI 0.81 to 1.99; need for blood transfusions: 25/1012 [2.5%] with abciximab *v* 20/1010 [2.0%] with placebo; RR 1.25, 95% CI 0.70 to 2.23). [11] Major bleeding was defined as >50 g/litre decrease in haemoglobin level or an absolute decrease in haematocrit of 15%; minor bleeding was defined as 30 to 50 g/litre decrease in haemoglobin level or an absolute decrease in haematocrit of 9% to 15%. An increase of profound thrombocytopenia was observed only in the people receiving abciximab, but this difference did not reach significance (8/1012 [0.8%] with abciximab *v* 0/1010 [0%] with placebo; P = 0.08).

Comment:

Clinical guide:
Intravenous glycoprotein IIb/IIIa inhibitors are recommended for people with high-risk acute coronary syndrome who do not have active bleeding. There are uncertainties associated with the use of intravenous glycoprotein IIb/IIIa inhibitors in people not routinely scheduled to have PCI and patients pre-treated with a thienopyridine, although there are limited data from one RCT that abciximab and clopidogrel further reduced the combined outcome of death, MI, or target vessel revascularisation in patients who had urgent PCI. [11] In patients who have PCI, heparin should be discontinued after the procedure.

QUESTION What are the effects of antithrombin treatments in people with non ST-elevation acute coronary syndrome?

OPTION UNFRACTIONATED HEPARIN

Cardiovascular events
Unfractionated heparin plus aspirin compared with aspirin alone Unfractionated heparin plus aspirin may be more effective at reducing the combined outcome of death or MI at 7 days in people with NSTE-ACS, but we don't know if benefits are sustained to 12 weeks (moderate-quality evidence).

Adverse effects
Unfractionated heparin plus aspirin compared with aspirin alone We don't know how unfractionated heparin plus aspirin and aspirin alone compare at reducing the risk of major bleeding in people with NSTE-ACS (moderate-quality evidence).

For GRADE evaluation of interventions for non ST-elevation acute coronary syndrome, see table, p 18 .

Benefits:

Unfractionated heparin plus aspirin versus aspirin alone:
We found three systematic reviews (search dates 1995, [12] not reported, [13] and 2002 [14]), which between them identified seven RCTs. Each review examined outcomes at different time points so they have all been reported here. The first two reviews included the same six RCTs in 1353 people with NSTE-ACS comparing unfractionated heparin versus placebo or no treatment for 2 to 7 days; one assessed outcomes at 12 weeks, [12] the other at 7 days. [13] The third review identified seven RCTs (1508 people), including the six RCTs identified by the first and second reviews and combined data for outcomes at 2 days to 12 weeks. [14] In all RCTs, all participants also received aspirin.

The first review found no significant difference in mortality or MI at 12 weeks between adding unfractionated heparin to aspirin and adding placebo to aspirin or no additional treatment (AR: 12% with unfractionated heparin plus aspirin *v* 14% with aspirin alone; RR 0.82, 95% CI 0.56 to 1.20). [12]

The second review found that adding unfractionated heparin to aspirin significantly reduced the risk of death or MI at 7 days compared with adding placebo or no additional treatment (AR: 55/698 [8%] with unfractionated heparin plus aspirin *v* 68/655 [10%] with aspirin alone; OR 0.67, 95% CI 0.45 to 0.99). [13]

The third review found no significant difference in the combined outcome of death or MI between adding unfractionated heparin to aspirin and adding placebo or no additional treatment at follow-up of 48 hours to 12 weeks (5 RCTs, 1225 people; 62/651 [10%] with unfractionated heparin plus aspirin *v* 66/574 [11%] with aspirin alone; RR 0.80, 95% CI 0.58 to 1.08). [14]

Unfractionated heparin versus low molecular weight heparin:
See benefits of low molecular weight heparin, p 7 .

Harms:

Unfractionated heparin plus aspirin versus aspirin alone:
The first review found no significant difference in major bleeding between unfractionated heparin plus aspirin and aspirin alone, but reported a wide CI (AR: 1.5% with unfractionated heparin *v* 0.4% with placebo or no treatment; RR 1.89, 95% CI 0.66 to 5.38; P = 0.68). [12]

The second review gave no information on adverse effects. [13]

The third review found no significant difference between adding unfractionated heparin to aspirin and adding placebo or no additional treatment in major bleeds (5 RCTs, 1225 people; 8/651 [1%] with unfractionated heparin plus aspirin *v* 3/574 [1%] with aspirin alone; RR 1.92, 95% CI 0.59 to 6.26) or minor bleeds, but also reported a wide CI (1 RCT, 107 people; 10/70 [14%] with unfractionated heparin plus aspirin *v* 0/37 [0%] with aspirin alone; RR 11.24, 95% CI 0.68 to 186.60). [14]

Unfractionated heparin versus low molecular weight heparin:
See harms of low molecular weight heparin, p 7 .

Comment: None.

OPTION LOW MOLECULAR WEIGHT HEPARIN

Mortality
Compared with unfractionated heparin Low molecular weight heparin (LMWH) may be no more effective at reducing mortality at 5 days to 3 months (high-quality evidence).

MI
Compared with unfractionated heparin LMWH is more effective at reducing MI at 5 days to 3 months (high-quality evidence).

Cardiovascular events
Compared with no heparin LMWH is more effective at reducing the combined outcome of death or MI when given up to day 7, but is not more effective when given up to day 90 (moderate-quality evidence).

Adverse effects
Compared with no heparin LMWH may not increase the risk of major bleeding when given up to day 7, but may increase the risk of major bleeding when given up to day 90 (low-quality evidence).

Compared with unfractionated heparin LMWH does not increase the risk of major bleeding at 5 days to 3 months (high-quality evidence).

For GRADE evaluation of interventions for non ST-elevation acute coronary syndrome, see table, p 18 .

Benefits:

LMWH versus no LMWH:
We found two systematic reviews (search dates not reported [13] and 2002 [14]) comparing LMWH versus placebo or no heparin treatment in people with NSTE-ACS. Both reviews identified the same two RCTs assessing shorter-term treatment with LMWH, but because the earlier review also evaluated five RCTs of longer-term treatment with LMWH, we have reported it here in preference to the more recent review.

The review (2 RCTs, 1639 people, all receiving aspirin) found that LMWH for <7 days significantly reduced the combined outcome of death or MI compared with control at the end of the treatment period (AR: 13/809 [2%] with LMWH *v* 43/830 [5%] with placebo; OR 0.34, 95% CI 0.20 to 0.58).

The systematic review identified 5 RCTs (12,099 people) comparing longer-term LMWH (from 7–90 days) versus placebo. It found that LMWH did not reduce death or MI at 90 days compared with placebo (AR: 228/5453 [4%] with LMWH *v* 257/6646 [3%] with placebo; OR 0.98, 95% CI 0.81 to 1.17). [13]

LMWH versus unfractionated heparin:
We found one systematic review (search date 2000; 7 RCTs, 11,092 people) comparing LMWH versus unfractionated heparin in people with NSTE-ACS. [15] The two largest RCTs used enoxaparin as LMWH (2 RCTs, 7045 people). The review found that LMWH significantly reduced MI compared with unfractionated heparin at 5 days to 3 months (AR: 233/5580 [4%] with LMWH *v* 276/5512 [5%] with unfractionated heparin; RR 0.83, 95% CI 0.70 to 0.99). However, it found no significant difference between treatments in mortality or recurrent angina at 5 days to 3 months (mortality: AR: 150/5580 [3%] with LMWH *v* 155/5512 [3%] with unfractionated heparin; RR 1.0, 95% CI 0.7 to 1.4; recurrent angina: 6 RCTs, 7209 people: 516/3642 [14%] with LMWH *v* 576/3576 [16%] with unfractionated heparin; RR 0.83, 95% CI 0.68 to 1.02).

LMWH versus factor Xa inhibitors:
See factor Xa inhibitors, p 9 .

Harms:

LMWH versus no LMWH:
The first systematic review found that LMWH did not significantly increase major bleeding compared with placebo or no treatment at 7 days (OR 1.48, 95% CI 0.45 to 4.84, absolute numbers not reported). However, long-term LMWH significantly increased the risk of major bleeding compared with placebo or no treatment at 90 days (OR 2.26, 95% CI 1.63 to 3.14, absolute numbers not reported) equivalent to an excess of 12 bleeds for every 1000 people treated. [13]

The second systematic review found no significant difference between LMWH plus aspirin and aspirin alone in major bleeding (2 RCTs, 1610 people; 6/814 [0.7%] with LMWH plus aspirin *v*

4/796 [0.5%] with aspirin alone; RR 1.53, 95% CI 0.43 to 5.39), but found that LMWH plus aspirin significantly increased the risk of minor bleeding compared with aspirin alone (2 RCTs, 1610 people; 62/814 [8%] with LMWH plus aspirin *v* 2/796 [0.3%] with aspirin alone; RR 9.96, 95% CI 0.56 to 177.8). [14]

LMWH versus unfractionated heparin:
The systematic review found no significant difference between LMWH and unfractionated heparin in major bleeding at 5 days to 3 months (AR: 156/5550 [3%] with LMWH *v* 153/5472 [3%] with unfractionated heparin; RR 1.0, 95% CI 0.80 to 1.24). [15]

Comment: The second review pooled data for LMWH and unfractionated heparin. Subgroup analysis demonstrated a significant reduction in recurrent angina and revascularisation procedures with LMWH, but this benefit was lost when analysis of both unfractionated heparin and LMWH were pooled together. This implies that high-risk NSTE-ACS patients experience an improved benefit-risk ratio compared with lower risk patients despite no reduction in mortality. [14]

Clinical guide
LMWH, more specifically enoxaparin, may be a more reasonable alternative to unfractionated heparin for routine short-term use. Coagulation monitoring is not required and it can be self-administered after discharge. A disadvantage in the catheterisation laboratory is a long half-life.

OPTION DIRECT THROMBIN INHIBITORS

Cardiovascular events
Compared with unfractionated heparin Direct thrombin inhibitors are more effective at reducing the combined outcome of death or MI at 30 days in people with NSTE-ACS (moderate-quality evidence).

Adverse effects
Compared with unfractionated heparin Direct thrombin inhibitors are more effective at reducing the risk of major bleeding (moderate-quality evidence).

For GRADE evaluation of interventions for non ST-elevation acute coronary syndrome, see table, p 18 .

Benefits: **Direct thrombin inhibitors versus unfractionated heparin:**
We found one systematic review (search date not reported, 11 RCTs, 35,070 people, 25,123 [72%] with NSTE-ACS) comparing 7 days' treatment with direct thrombin inhibitors (hirudin, argatroban, bivalirudin, efegatran, inogatran) versus unfractionated heparin. [16] It found that direct thrombin inhibitors significantly reduced the combined outcome of death or MI compared with unfractionated heparin at 30 days (AR: 7% with direct thrombin inhibitors *v* 8% with unfractionated heparin; RR 0.91, 95% CI 0.84 to 0.99). The review found no significant heterogeneity between STEMI and NSTE-ACS participants (P = 0.26).

Harms: **Direct thrombin inhibitors versus unfractionated heparin:**
The systematic review found that direct thrombin inhibitors significantly reduced major bleeding during treatment compared with unfractionated heparin (AR: 1.9% with direct thrombin inhibitors *v* 2.3% with heparin; OR 0.75, 95% CI 0.65 to 0.87). It found no significant difference in stroke between groups at 30 days (AR: 0.5% with direct thrombin inhibitors *v* 0.5% with heparin; OR 1.01, 95% CI 0.78 to 1.31). [16]

Comment: **Clinical guide:**
In heparin-allergic patients, direct thrombin inhibitors may produce similar clinical results, possibly with less death, MI, and bleeding. There was significant heterogeneity of RCTs in the systematic review, and different results were observed for the various agents.

OPTION WARFARIN

Cardiovascular events
Warfarin plus aspirin compared with aspirin alone Warfarin plus aspirin is no more effective at reducing the combined outcomes including mortality, MI, recurrent angina, or stroke at 12 weeks to 1 year in people with NSTE-ACS (high-quality evidence).

Adverse effects
Warfarin plus aspirin compared with aspirin alone Adding warfarin increases the risk of major bleeding at 5 months (high-quality evidence).

For GRADE evaluation of interventions for non ST-elevation acute coronary syndrome, see table, p 18 .

Benefits:

Warfarin plus aspirin versus aspirin alone:
We found no systematic review. We found five RCTs comparing warfarin plus usual treatment versus usual treatment alone in people with NSTE-ACS. [17] [18] [19] [20] Two of the RCTs were reported in the same journal article. [18]

The first RCT (214 people) compared warfarin plus aspirin versus aspirin alone. [17] It found that warfarin (target international normalised ratio [INR] 2.0–2.5) plus aspirin reduced the combined outcome of death, MI, or recurrent angina at 12 weeks compared with aspirin alone, but the difference did not reach significance (AR: 13% with warfarin plus aspirin *v* 25% with aspirin alone; P = 0.06).

The second RCT (309 people) compared warfarin (fixed dose 3 mg/day) plus aspirin versus aspirin alone. [18] It found no significant difference between warfarin plus aspirin and aspirin alone in the combined outcome of death, MI, or recurrent angina at 6 months (AR: 7% with warfarin plus aspirin *v* 4% with aspirin alone; RR 1.66, 95% CI 0.62 to 4.44). [18]

The third RCT (197 people) compared warfarin (target INR 2.0–2.5) plus aspirin versus aspirin alone. [18] It found no significant difference between treatments in the combined outcome of death, MI, or recurrent angina at 6 months (AR: 5% with warfarin plus aspirin *v* 12% with aspirin alone; RR 0.42, 95% CI 0.15 to 1.15).

The fourth RCT (3712 people) compared adding warfarin (target INR 2.0–2.5) to standard treatment versus standard treatment alone. [19] Standard treatment for most participants included aspirin; use of aspirin at 5 months was significantly higher among the group receiving standard treatment alone than in the group receiving warfarin plus standard treatment (AR: 83% in the warfarin group and 93% in the standard treatment group; P <0.001). The RCT found no significant difference between treatments in the combined outcome of death, MI, and stroke after 5 months (8% with warfarin *v* 8% with standard treatment alone; RR 0.90, 95% CI 0.72 to 1.14). [19]

The fifth RCT (135 people with NSTE-ACS who had received prior CABG) compared warfarin plus aspirin, warfarin plus placebo, and aspirin plus placebo. [20] It found no significant difference between treatments in the combined outcome of death, MI, or hospital admission for unstable angina after 1 year (AR: 11% with warfarin plus aspirin *v* 14% with warfarin plus placebo *v* 12% with aspirin plus placebo; P = 0.76 for overall comparison of the 3 treatment groups). [20]

Harms:

Warfarin plus aspirin versus aspirin alone:
In the fourth RCT, adding warfarin to standard treatment increased major bleeding compared with standard treatment alone (AR: 3% with warfarin plus standard treatment *v* 1% with standard treatment alone; RR 1.99, 95% CI 1.23 to 3.22; NNH 71; CI not reported). [19]

Comment:

Clinical guide:
In people with a high risk of thromboembolic events (i.e., those with atrial fibrillation, prosthetic heart valves, intracardiac thrombi, recurrent thromboembolic events, or anti-phospholipid syndrome), continuing warfarin should be at clinical discretion. If warfarin is to be used as part of the treatment regimen, the target INR for should be between 2 and 3. Warfarin should be withheld in people who have invasive treatment because it increases bleeding at the time of catheterisation.

OPTION FACTOR XA INHIBITORS New

Mortality
Compared with LMWH in people receiving a thienopyridine Fondaparinux and enoxaparin seem equally effective at reducing mortality in people with NSTE-ACS (moderate-quality evidence).

MI
Compared with LMWH in people receiving a thienopyridine Fondaparinux and enoxaparin seem equally effective at reducing MI in people with NSTE-ACS (moderate-quality evidence).

Adverse effects
Compared with LMWH Fondaparinux seems to be associated with a lower risk of major bleeding than enoxaparin in people with NSTE-ACS (moderate-quality evidence).

For GRADE evaluation of interventions for non ST-elevation acute coronary syndrome, see table, p 18 .

Benefits:

Factor Xa inhibitors versus LMWH in people receiving a thienopyridine:
We found no systematic review.

We found one RCT (20,078 people with NSTE-ACS) comparing fondaparinux versus LMWH (enoxaparin). [21] Administration of a thienopyridine or a glycoprotein IIb/IIIa inhibitor was at the discretion of the physician and about 90% of participants also received clopidogrel and around 40% received a glycoprotein IIb/IIIa inhibitor. Statins were also given to 84% of participants. The RCT found no significant difference between fondaparinux and enoxaparin in mortality at 9 days (37/3105 [1.2%] with fondaparinux *v* 38/3072 [1.2%] with enoxaparin; HR 0.96, 95% CI 0.61 to 1.52) or MI (160/3105 [5.2%] with fondaparinux *v* 154/3072 [5.0%] with enoxaparin; HR 1.03, 95% CI 0.82 to 1.28). It also found no significant difference in mortality or MI at 30 days (mortality: 62/3105 [2.0%] with fondaparinux *v* 65/3072 [2.1%] with enoxaparin; HR 0.94, 95% CI 0.67 to 1.34; MI: 177/3105 [5.7%] with fondaparinux *v* 168/3072 [5.5%] with enoxaparin; HR 1.04, 95% CI 0.84 to 1.29) or at 6 months (mortality: 99/3105 [3.2%] with fondaparinux *v* 107/3072 [3.5%] with enoxaparin; HR 0.92, 95% CI 0.70 to 1.20; MI: 230/3105 [7.4%] with fondaparinux *v* 210/3072 [6.8%] with enoxaparin; HR 1.09, 95% CI 0.90 to 1.31). [21]

A further report of the RCT [21] evaluated the effects of the concomitant treatment using either a glycoprotein IIb/IIIa inhibitor (3630 people) or a thienopyridine (13,532 people). [22] It found similar results to those reported when assessing the entire cohort. In people receiving a glycoprotein IIb/IIIa inhibitor, there was no significant difference in mortality or MI at 30 days between fondaparinux and enoxaparin (mortality: 3% with fondaparinux *v* 4% with enoxaparin; HR 0.85, 95% CI 0.59 to 1.23; MI: 6% with fondaparinux *v* 7% with enoxaparin; HR 0.83, 95% CI 0.67 to 1.10; absolute numbers not reported). In people receiving a thienopyridine, it found that fondaparinux significantly reduced mortality compared with enoxaparin (2.6% with fondaparinux *v* 3.2% with enoxaparin; HR 0.79, 95% CI 0.64 to 0.96; absolute numbers not reported), although there was no significant difference in MI between groups (4% with fondaparinux *v* 5% with enoxaparin; HR 0.95, 95% CI 0.81 to 1.12). [22]

Factor Xa inhibitors versus unfractionated heparin, direct thrombin inhibitors, or warfarin:
We found no systematic review or RCTs.

Harms:

Factor Xa inhibitors versus LMWH in people receiving a thienopyridine:
The RCT found that fondaparinux significantly reduced major bleeding compared with enoxaparin at 9 days, 30 days, and 6 months (9 days: 73/3105 [2%] with fondaparinux *v* 155/3072 [5%] with enoxaparin; HR 0.46, 95% CI 0.35 to 0.61; 30 days: 88/3105 [3%] with fondaparinux *v* 166/3072 [5%] with enoxaparin; HR 0.52, 95% CI 0.40 to 0.67; 6 months: 104/3105 [3%] with fondaparinux *v* 190/3072 [6%] with enoxaparin; HR 0.53, 95% CI 0.42 to 0.68). [21]

The first further report of the RCT [21] found that, in people receiving a glycoprotein IIb/IIIa inhibitor, fondaparinux plus significantly reduced major bleeding compared with enoxaparin (5% with fondaparinux *v* 8% with enoxaparin; HR 0.60, 95% CI 0.46 to 0.78; absolute numbers not reported). It also found that, in people receiving a thienopyridine, fondaparinux significantly reduced major bleeding compared with enoxaparin (3% with fondaparinux *v* 5% with enoxaparin; HR 0.62, 95% CI 0.52 to 0.73; absolute numbers not reported). [22]

Factor Xa inhibitors versus unfractionated heparin, direct thrombin inhibitors, or warfarin:
We found no RCTs.

Comment:

A second further report of the RCT [21] reported that major bleeding was associated with worse outcomes, with significantly increased mortality in people with major bleeding compared with no bleeding at 30 days and at 180 days (30 days: 65/771 [8%] with major bleeding *v* 512/18851 [3%] with no bleeding; HR 3.46, 95% CI 2.60 to 4.60; 180 days: 132/771 [14%] with major bleeding *v* 985/18,851 [5%] with no bleeding; HR 3.11, 95% CI 2.55 to 3.79). [23]

QUESTION What are the effects of anti-ischaemic treatments in people with non ST-elevation acute coronary syndrome?

OPTION BETA-BLOCKERS

Mortality
Compared with placebo We don't know whether beta-blockers are more effective at reducing mortality in people with acute coronary syndrome (low-quality evidence).

MI
Compared with placebo We don't know whether beta-blockers are more effective at reducing MI in people with acute coronary syndrome (low-quality evidence).

For GRADE evaluation of interventions for non ST-elevation acute coronary syndrome, see table, p 18 .

Benefits:

Beta-blockers versus placebo:
We found two RCTs. [24] [25] The first RCT (338 people with rest angina not already receiving a beta-blocker) compared metoprolol versus placebo. [24] It found no significant difference between metoprolol and placebo in MI at 48 hours (16% with metoprolol *v* 15% with placebo; RR 1.07, 95% CI 0.54 to 2.09; absolute numbers not reported).

The second RCT (81 people with unstable angina on "optimal doses" of nitrates and nifedipine) compared propranolol (at least 160 mg/day) versus placebo. [25] It found no significant difference in mortality between propranolol and placebo at 30 days (6/42 [14%] with propranolol *v* 3/39 [8%] with placebo; reported as not significant; RR, P, and CI values not reported). People taking propranolol had a lower cumulative probability of experiencing recurrent rest angina at 30 days (results presented graphically; P = 0.013).

Harms:

Beta-blockers versus placebo:
The first RCT gave no information on adverse effects. [24] The second RCT reported that bradycardia and hypotension were each reported by one person who received propranolol (1/42 with propranolol, rate in control group and significance data not reported). Potential adverse effects of beta-blockers in any patient population include bradycardia, exacerbation of reactive airways disease, and hypoglycaemia in people with diabetes. [25]

Comment:

We found no good evidence that beta-blockers prevent death in the first 6 months after NSTE-ACS (unstable angina or non-STEMI). Consensus suggests that, until further data are available, intravenous nitrates remain the preferred treatment for symptom control in people with NSTE- ACS.

OPTION NITRATES

Adverse effects
Compared with placebo Nitrates increase the risk of headache or drop in blood pressure (high-quality evidence).

Note:
We found no direct information from RCTs about nitrates in the reduction of mortality or MI in people with non-STEMI acute coronary syndrome.

For GRADE evaluation of interventions for non ST-elevation acute coronary syndrome, see table, p 18 .

Benefits:

Nitrates versus placebo:
We found two RCTs. [26] [27] The first RCT (162 people with non- STEMI) compared intravenous glyceryl trinitrate versus placebo for 48 hours. [26] It found that glyceryl trinitrate significantly reduced the proportion of people with more than two episodes of chest pain or one new episode lasting more than 20 minutes (18% with glyceryl trinitrate *v* 36% with placebo; RR 0.50, 95% CI 0.25 to 0.90), and the proportion of people needing more than two additional sublingual glyceryl trinitrate tablets (16% with glyceryl trinitrate *v* 31% with placebo; RR 0.52, 95% CI 0.26 to 0.97).

The second RCT (200 people hospitalised for unstable angina within 6 months of PTCA) compared intravenous glyceryl trinitrate alone, heparin alone, glyceryl trinitrate plus heparin, and placebo. [27] It found that recurrent angina occurred significantly less frequently in people treated with glyceryl trinitrate alone or glyceryl trinitrate plus heparin compared with placebo, but there was no benefit from heparin alone over placebo or additional benefit from combination treatment compared with glyceryl trinitrate alone (AR: 43% with glyceryl trinitrate alone *v* 42% with glyceryl trinitrate plus heparin *v* 75% with heparin alone *v* 75% with placebo; P <0.003 for glyceryl trinitrate alone and for glyceryl trinitrate plus heparin *v* placebo; P values for other comparisons not reported).

Harms:

Nitrates versus placebo:
The first RCT found that intravenous glyceryl trinitrate significantly increased adverse effects (headache or drop in blood pressure by >20%) compared with placebo (7/73 [10%] with glyceryl trinitrate *v* 0/70 [0%] with placebo; P <0.001) The second RCT gave no information on harms. A potential adverse effect of nitrates is symptomatic hypotension. Both older and more-recent large RCTs in people with other ischaemic conditions showed that nitrates were safe and well tolerated when used judiciously in clinically appropriate doses. [26]

Comment:

We found no good evidence that nitrates prevent death or MI, although consensus suggests that, until further data are available, intravenous nitrates remain the preferred treatment for symptom control in people with NSTE-ACS.

OPTION CALCIUM CHANNEL BLOCKERS

Mortality

Compared with placebo We don't know how calcium channel blockers and placebo compare for reducing mortality in people with unstable angina at 48 hours to 5 months (low-quality evidence).

Compared with beta-blockers We don't know how calcium channel blockers and beta-blockers compare for reducing mortality in people with unstable angina at 48 hours to 5 months (moderate-quality evidence).

MI

Compared with placebo We don't know how calcium channel blockers and placebo compare for reducing MI in people with unstable angina at 48 hours to 5 months (low-quality evidence).

Compared with beta-blockers We don't know how calcium channel blockers and beta-blockers compare for reducing MI in people with unstable angina at 48 hours to 5 months (low-quality evidence).

Note

Short-acting calcium channel blockers (such as nifedipine) have been associated with increased mortality in people with CHD.

For GRADE evaluation of interventions for non ST-elevation acute coronary syndrome, see table, p 18 .

Benefits:

We found one systematic review (search date not reported, 6 RCTs, 1109 people with unstable angina) comparing calcium channel blockers versus either a beta-blocker (propranolol, 3 RCTs) or placebo (3 RCTs). [28]

Calcium channel blockers versus placebo:

The review found that mortality and rates of MI were similar between calcium channel blockers and placebo at 48 hours to 5 months, but did not report significance (mortality: 8/439 [1.8%] with calcium channel blockers *v* 7/427 [1.6%] with placebo; MI: 89/409 [21.7%] with calcium channel blockers *v* 89/397 [22.4%] with placebo). [28] The review found no significant difference between calcium channel blockers and both controls combined (placebo and propranolol combined) in mortality or MI at 48 hours to 5 months (mortality: 14/591 [2%] with calcium channel blockers *v* 9/578 [2%] with control; MI: 110/561 [20%] with calcium channel blockers *v* 104/548 [19%] with control; OR and CI values presented graphically). One RCT included in the systematic review compared nifedipine, metoprolol, or both versus placebo. [24] It found no significant difference between nifedipine and placebo in MI, or combined MI and recurrent ischaemia at 48 hours (MI: RR 1.51, 95% CI 0.87 to 2.74; combined MI and recurrent ischaemia: RR 1.15, 95% CI 0.83 to 1.64; absolute numbers not reported).

Calcium channel blockers versus beta-blockers:

The review found that mortality and rates of MI were similar between calcium channel blockers and propranolol at 48 hours to 5 months, but did not report significance (mortality: 6/152 [3.9%] with calcium channel blockers *v* 2/151 [1%] with propranolol; MI: 21/152 [14%] with calcium channel blockers *v* 15/151 [10%] with propranolol; P values not reported). [28] One RCT included in the systematic review compared nifedipine, metoprolol, or both versus placebo. [24] It found that nifedipine significantly increased combined MI and recurrent ischaemia compared with metoprolol at 48 hours (RR 0.66, 95% CI 0.43 to 0.98; absolute numbers not reported). [24]

Harms:

Calcium channel blockers versus placebo or beta-blockers:

The systematic review gave no information on adverse effects. [28]

Observational studies have reported increased mortality with short-acting dihydropyridine calcium channel blockers (such as nifedipine) in people with CHD. [29] [30]

Comment:

We found no good evidence that calcium channel blockers prevent death or MI.

QUESTION What are the effects of lipid-lowering treatments in people with non ST-elevation acute coronary syndrome?

OPTION STATINS

Cardiovascular events

Compared with placebo We don't know whether statins are more effective at reducing the combined outcome of mortality or cardiovascular event in all people treated within 24 to 96 hours of NSTE-ACS, but they may be more effective in people undergoing percutaneous coronary intervention (PCI) (low-quality evidence).

Mortality

High-dose statins versus low-dose statins or no treatment Atorvastatin 80 mg daily may be no more effective than low-dose statins or no treatment in reducing death in people with NSTE-ACS (very low-quality evidence).

MI

High-dose statins versus low-dose statins or no treatment Atorvastatin 80 mg may be no more effective than low-dose statins or no treatment in reducing death in people with NSTE-ACS (very low-quality evidence).

Note

Observational data suggest that intensive lipid therapy is beneficial if initiated within 12 days of NSTE-ACS presentation and that statins improve clinical outcomes in the long term.

For GRADE evaluation of interventions for non ST-elevation acute coronary syndrome, see table, p 18 .

Benefits:

Statins versus placebo:

We found two RCTs. [31] [32] The first RCT (3086 people within 24–96 hours of NSTE-ACS) compared atorvastatin 80 mg versus placebo. [31] It found no significant difference in the combined outcome of mortality or non-fatal MI at 16 weeks (AR: 155/1538 [10%] with atorvastatin *v* 169/1548 [11%] with placebo; RR 0.92, 95% CI 0.75 to 1.13). However, it found that atorvastatin significantly reduced emergency hospital admission for recurrent myocardial ischaemia compared with placebo at 16 weeks (AR: 95/1538 [6%] with atorvastatin *v* 130/1548 [8%] with placebo; RR 0.74, 95% CI 0.57 to 0.95). [31]

The second RCT (171 people with NSTE-ACS undergoing percutaneous coronary intervention [PCI]) compared atorvastatin 80 mg given 12 hours before PCI plus a further 40 mg dose pre-procedure versus placebo. [32] All participants received long-term atorvastatin after the procedure. It found that atorvastatin significantly reduced the composite outcome of death, MI, or target vessel revascularisation compared with placebo at 30 days (4/86 [5%] with atorvastatin *v* 14/85 [17%] with placebo; P = 0.01). [32]

High-dose statins versus low-dose statins or no treatment:

We found one systematic review (search date 2006), which compared high-dose statins versus low-dose statins or no treatment in people with acute coronary syndrome (unstable angina, NSTEMI, and STEMI). [33] The review identified one RCT that met our inclusion criteria. [34] The RCT (81 people with unstable angina or non Q-wave MI) compared atorvastatin 80 mg daily given early after onset of NSTE-ACS versus low-dose statin or, if LDL levels were normal, no lipid-lowering treatment. It found no significant difference between high-dose statins and low-dose statins or no treatment in all-cause mortality or MI (all-cause mortality: 3/40 [7%] with high-dose statins *v* 4/41 [10%] with low-dose statins or no treatment; reported as not significant; P value not reported; MI: 4/40 [10%] with high-dose statins *v* 7/41 [17%] with low-dose statins or no treatment; reported as not significant; P value not reported). [34]

Harms:

Statins versus placebo:

The first RCT found that atorvastatin significantly increased the proportion of people with abnormal liver transaminase levels (at 3 times the upper limit of normal) compared with placebo at 16 weeks (AR: 38/1538 [3%] with atorvastatin *v* 9/1548 [1%] with placebo; P <0.001). Three of the people with abnormal LFTs from the atorvastatin group were hospitalised with a diagnosis of hepatitis. No one in either group was reported to have myositis. [31]

In the second RCT, one participant developed transaminitis that resulted in discontinuation of drug. [32]

High-dose statins versus low-dose statins or no treatment:

The systematic review reported a significantly increased risk of transaminitis with high-dose statins compared with low-dose statins or no treatment (2% with high-dose statins *v* 1% with low-dose statins or no treatment; OR 2.93, 95% CI 2.09 to 4.09). [33]

Comment:

While the first RCT, [31] despite its size, is likely to be underpowered to reliably estimate the effects of statins on mortality and MI because of its short follow-up, the systematic review [33] assessing high versus low-dose statins reported that in acute coronary syndrome (unstable angina, NSTEMI, and STEMI), intensive lipid therapy starts to be beneficial against major adverse events (including mortality) at about 24 months after initiation of treatment. There seems to be little harm in starting statins for secondary prevention on presentation, and observational data suggest that intensive lipid therapy is beneficial if initiated within 12 days of NSTE-ACS presentation. [33] There is stronger evidence that statins improve clinical outcomes in the long term (see review on secondary prevention of ischaemic cardiac events).

QUESTION **What are the effects of invasive treatments in people with non ST-elevation acute coronary syndrome?**

OPTION **ROUTINE EARLY CARDIAC CATHETERISATION AND REVASCULARISATION**

Mortality
Compared with medical management or delayed catheterisation and revascularisation Routine early catheterisation and revascularisation may be more effective at reducing mortality in people with NSTE-ACS (low-quality evidence).

MI
Compared with medical management or delayed catheterisation and revascularisation Routine early catheterisation and revascularisation may be more effective at reducing MI in people with NSTE-ACS (low-quality evidence).

Cardiovascular events
Compared with medical management or delayed catheterisation and revascularisation Routine early catheterisation and revascularisation seems more effective at reducing the composite outcome of death, MI, and readmission to hospital in men with NSTE-ACS, but seems no more effective in low-risk women (moderate-quality evidence).

Adverse effects
Compared with medical management or delayed catheterisation and revascularisation Routine early catheterisation and revascularisation seem to be associated with a higher risk of major bleeding (moderate-quality evidence).

For GRADE evaluation of interventions for non ST-elevation acute coronary syndrome, see table, p 18 .

Benefits:

Routine early cardiac catheterisation and revascularisation versus more conservative strategies (medical management or delayed surgical revascularisation):
We found three systematic reviews (search dates 2006, [35] 2007, [36] and 2008 [37]) comparing routine early percutaneous coronary intervention (PCI) versus more conservative strategies (medical management or delayed surgical revascularisation) in people with NSTE-ACS, which between them identified 10 RCTs. The first review identified six RCTs. [35] The second [36] and third reviews [37] both identified all six RCTs identified by the first review, [35] but we have retained the results of the first review because it included RCTs that used contemporary treatment protocols with established adjunct treatments, whereas the additional RCTs included in the later reviews used treatments that are not considered standard in current practice. We have reported both the second and third reviews, [36] [37] despite their identification of the same RCTs, because the third review reported subgroup analysis by sex.

The first review [35] (7 RCTs, 8375 people) compared routine early PCI versus more conservative strategies in people with non-STEMI. [35] Six of the RCTs identified compared early PCI versus medical management. In all the identified RCTs, a proportion of the medical management groups went on to have later PCI. The remaining RCT in the review compared immediate (within 6 hours) versus late (between 72–120 hours) PCI. The review found that routine early PCI significantly reduced mortality and non-fatal MI at 1 to 60 months compared with more conservative strategies (mortality: 5% with early PCI *v* 7% with more conservative strategies; RR 0.75, 95% CI 0.63 to 0.90; P = 0.001; non-fatal MI: 8% with early PCI *v* 9% with more conservative strategies; RR 0.83, 95% CI 0.72 to 0.96; P = 0.012; absolute numbers not reported). It also found that early PCI significantly reduced the proportion of people readmitted to hospital with unstable angina compared with more conservative strategies at 6 to 60 months (AR: 20% with early PCI *v* 29% with more conservative strategies; RR 0.69, 95% CI 0.65 to 0.74; P = 0.0001; absolute numbers not reported).

The second review (10 RCTs, 10,648 people with NSTE-ACS, mean age 62 years, median follow-up 16.5 months) compared early PCI versus conservative management. [36] A proportion of the people receiving conservative management went on to have later PCI in all of the trials if they had persistent or recurrent angina despite maximal medical treatment. The review found no significant difference between routine early PCI and medical management in the combined outcome of death or non-fatal MI (847/5330 [16%] with routine early PCI *v* 928/5318 [17%] with more conservative strategies; RR 0.90, 95% CI 0.74 to 1.08). When these outcomes were analysed separately, the review also found no significant difference in mortality or non-fatal MI (mortality: 438/5330 [8%] with routine early PCI *v* 463/5318 [9%] with more conservative strategies; RR 0.95, 95% CI 0.80 to 1.14; non-fatal MI: 490/5330 [9%] with routine early PCI *v* 569/5318 [11%] with more conservative strategies; RR 0.86, 95% CI 0.68 to 1.08). [36]

The third systematic review (8 RCTs, all identified by the second review; [36] 3075 women and 7075 men) compared early routine PCI versus more conservative strategies in people with NSTE-ACS, and performed subgroup analysis by sex. [37] While the review found that early routine PCI significantly reduced the composite outcome of death, MI, or readmission to hospital compared

with more conservative strategies in the total population (1075/5083 [21%] with routine early PCI *v* 1313/5067 [26%] with more conservative strategies; OR 0.78, 95% CI 0.61 to 0.98) and in men (751/3545 [21%] with routine early PCI *v* 928/3530 [26%] with more conservative strategies; OR 0.73, 95% CI 0.55 to 0.98), there was no significant difference between groups in women (324/1538 [21%] with routine early PCI *v* 385/1537 [25%] with more conservative strategies; OR 0.81, 95% CI 0.65 to 1.01). The composite benefit was driven mostly by reduction in readmission to hospital for acute coronary syndrome. [37]

Harms:

Routine early cardiac catheterisation and revascularisation versus more conservative strategies:
The systematic reviews gave no information on adverse effects. [35] [36] [37] One RCT identified by the reviews (2457 people with non-STEMI) found that early invasive treatment increased major bleeding, but not stroke, compared with non-invasive treatment (major bleeds: AR: 2% with invasive treatment *v* 1% with non-invasive treatment; NNH 111; CI values not reported). [38] A second RCT identified by the reviews (2220 people with non-STEMI) found that cardiac catheterisation increased bleeding compared with standard treatment (6% with cardiac catheterisation *v* 3% with standard treatment; P <0.01: NNH 34; CI values not reported). [39]

Comment:

Clinical guide:
There are conflicting results between systematic reviews. [35] [36] One systematic review compared routine early cardiac catheterisation and revascularisation versus more conservative management. [35] It found that routine early cardiac catheterisation and revascularisation significantly reduced the combined outcome of mortality and non-fatal MI. However, a larger systematic review found no benefit in early invasive treatment. [36] The possibility for this discrepancy might be the use of non-current treatments, skewing a true beneficial result.

A smaller, but thought-provoking, review demonstrated significant benefit in men and high-risk (biomarker-positive) women (data not presented) but not in all women. [37] It is possible that significant heterogeneity among RCTs identified by the systematic reviews eclipsed potential benefits highlighted by the sex-analysed systematic review. Revascularisation may be key in improving late outcomes, and the timing of the procedure may be less important. Adjunctive thienopyridines may enhance the safety of PCI by decreasing MI and death. Early invasive treatment improves survival but does increase the risk of bleeding. Continued attempts to decrease major bleeding during PCI remain a priority.

GLOSSARY

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

International normalised ratio (INR) A value derived from a standardised laboratory test that measures the effect of an anticoagulant. The laboratory materials used in the test are calibrated against internationally accepted standard reference preparations, so that variability between laboratories and different reagents is minimised. Normal blood has an INR of 1.0. Therapeutic anticoagulation often aims to achieve an INR value of 2.0 to 3.5.

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.

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

SUBSTANTIVE CHANGES

Factor Xa inhibitors: New option, for which we identified one RCT. [21] The RCT found no significant difference between fondaparinux and enoxaparin in mortality or MI at 30 days, 90 days, and 6 months. Fondaparinux was associated with less major bleeding compared with enoxaparin. A further report of the RCT [21] found no significant difference in mortality or MI at 30 days between fondaparinux and enoxaparin in people concomitantly treated with a glycoprotein IIb/IIIa inhibitor. However, in people concomitantly treated with a thienopyridine, fondaparinux reduced mortality compared with enoxaparin, although there was no significant difference in MI between the two groups. [22] Categorised as Likely to be beneficial.

Intravenous glycoprotein IIb/IIIa inhibitors One large RCT added, which found that adding abciximab to clopidogrel improved the composite outcome of mortality or MI at 30 days compared with placebo in people with high-risk NSTE-ACS undergoing urgent percutaneous coronary intervention (PCI). [11] Categorisation unchanged (Trade-off between benefits and harms).

Routine early cardiac catheterisation and revascularisation Two systematic reviews added. [36] [37] The results and conclusions of the reviews added at update [36] [37] conflict with a previously reported review. [35] The previously reported review found that routine early cardiac catheterisation and revascularisation reduced mortality and non-fatal

MI compared with conservative management. [35] However, a larger review found no significant difference between early cardiac catheterisation and conservative management for these outcomes. [36] One possible explanation for this discrepancy might be the inclusion of RCTs in the larger review [36] of treatments considered not to be standard practice, which could skew a true beneficial result. A smaller review that performed subgroup analyses by sex found that early cardiac catheterisation reduced the composite outcome of mortality, MI, and readmission to hospital in men but not in women. [37] Categorisation unchanged (Likely to be beneficial).

Statins One RCT [32] comparing statins versus placebo and one review [33] comparing high-dose versus low-dose statins added. The RCT found that two doses of atorvastatin given before percutaneous coronary intervention (PCI) reduced the composite outcome of death, MI, or target vessel revascularisation at 30 days compared with placebo. [32] The systematic review identified one RCT comparing high-dose statins versus low-dose statins or no treatment, and reported no significant difference between groups in mortality or MI. [33] Categorisation unchanged (Likely to be beneficial).

Unfractionated heparin One systematic review added, [14] which found no significant difference in the combined outcome of death or MI between unfractionated heparin plus aspirin and aspirin alone. It also found no significant difference between unfractionated heparin plus aspirin and aspirin alone in major or minor bleeding. Categorisation unchanged (Likely to be beneficial).

REFERENCES

1. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction): developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons: endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *Circulation* 2007;116:e14–e304.[PubMed]
2. Bugiardini R, Bugiardini R. Risk stratification in acute coronary syndrome: focus on unstable angina/non-ST segment elevation myocardial infarction. *Heart* 2004;90:729–731.
3. Das R, Kilcullen N, Morrell C, et al. The British Cardiac Society Working Group definition of myocardial infarction: implications for practice. *Heart* 2006;92:21–26.[PubMed]
4. Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. *JAMA* 2000;284:835–842.
5. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71–86. Search date 1997.[PubMed]
6. Yusuf S, Zhao F, Mehta S, et al. The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial. *N Engl J Med* 2001;345:494–502.[PubMed]
7. Peters RJ, Mehta SR, Fox KA, et al. Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) Trial Investigators. *Circulation* 2003;108:1682–1687.[PubMed]
8. Serebruany VL, Malinin AI, Eisert RM, et al. Risk of bleeding complications with antiplatelet agents: meta-analysis of 338 191 patients enrolled in 50 randomized controlled trials. *Am J Hematol* 2004;75:40–47.[PubMed]
9. Budaj A, Yusuf S, Mehta SR, et al. Benefit of clopidogrel in patients with acute coronary syndromes without ST-segment elevation in various risk groups. *Circulation* 2002;106:1622–1626.[PubMed]
10. Boersma E, Harrington RA, Moliterno DJ, et al. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials. *Lancet* 2002;359:189–198.
11. Kastrati A, Mehilli J, Neumann FJ, et al. Abciximab in patients with acute coronary syndromes undergoing percutaneous coronary intervention after clopidogrel pretreatment: the ISAR-REACT 2 randomized trial. *JAMA* 2006;295:1531–1538.[PubMed]
12. Oler A, Whooley MA, Oler J, et al. Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina: a meta-analysis. *JAMA* 1996;276:811–815. Search date 1995.[PubMed]
13. Eikelboom JW, Anand SS, Malmberg K, et al. Unfractionated heparin and low molecular weight heparin in acute coronary syndrome without ST elevation: a meta-analysis. *Lancet* 2000;355:1936–1942. Search date not reported.[PubMed]
14. Magee KD, Campbell SG, Moher D, et al. Heparin versus placebo for acute coronary syndromes. In: The Cochrane Library, Issue 4, 2009. Chichester, UK: John Wiley & Sons, Ltd. Search date 2002.
15. Magee KD, Sevcik W, Moher D, et al. Low molecular weight heparins versus unfractionated heparin for acute coronary syndromes. In: The Cochrane Library, Issue 4, 2009. Chichester, UK: John Wiley & Sons, Ltd. Search date 2000.
16. The Direct Thrombin Inhibitor Trialists' Collaborative Group. Direct thrombin inhibitors in acute coronary syndromes: principal results of a meta-analysis based on individual patients' data. *Lancet* 2002;359:294–302. Search date not reported.[PubMed]
17. Cohen M, Adams PC, Parry G, et al. Combination antithrombotic therapy in unstable rest angina and non-Q-wave infarction in nonprior aspirin users. Primary end points analysis from the ATACS trial. Antithrombotic Therapy in Acute Coronary Syndromes Research Group. *Circulation* 1994;89:81–88.[PubMed]
18. Anand SS, Yusuf S, Pogue J, et al. Long-term oral anticoagulant therapy in patients with unstable angina or suspected non-Q-wave myocardial infarction: organization to assess strategies for ischaemic syndromes (OASIS) pilot study results. *Circulation* 1998;98:1064–1070.[PubMed]
19. OASIS Investigators. Effects of long-term, moderate-intensity oral anticoagulation in addition to aspirin in unstable angina. *J Am Coll Cardiol* 2001;37:475–484.[PubMed]
20. Hunyh T, Theroux P, Bogaty P, et al. Aspirin, warfarin, or the combination for secondary prevention of coronary events in patients with acute coronary syndromes and prior coronary artery bypass surgery. *Circulation* 2001;103:3069–3074.[PubMed]
21. Mehta SR, Granger CB, Eikelboom JW, et al. Efficacy and safety of fondaparinux versus enoxaparin in patients with acute coronary syndromes undergoing percutaneous coronary intervention: results from the OASIS-5 trial. *J Am Coll Cardiol* 2007;50:1742–1751.[PubMed]
22. Jolly SS, Faxon DP, Fox KA, et al. Efficacy and safety of fondaparinux versus enoxaparin in patients with acute coronary syndromes treated with glycoprotein IIb/IIIa inhibitors or thienopyridines: results from the OASIS 5 (Fifth Organization to Assess Strategies in Ischemic Syndromes) trial. *J Am Coll Cardiol* 2009;54:468–476.[PubMed]
23. Budaj A, Eikelboom JW, Mehta SR, et al. Improving clinical outcomes by reducing bleeding in patients with non-ST-elevation acute coronary syndromes. *Eur Heart J* 2009;30:655–661.[PubMed]
24. HINT Research Group. Early treatment of unstable angina in the coronary care unit: a randomized, double blind, placebo controlled comparison of recurrent ischaemia in patients treated with nifedipine or metoprolol or both. *Br Heart J* 1986;56:400–413.[PubMed]
25. Gottlieb SO, Weisfeldt ML, Ouyang P, et al. Effect of the addition of propranolol to therapy with nifedipine for unstable angina pectoris: a randomized, double-blind, placebo-controlled trial. *Circulation* 1986;73:331–337.[PubMed]
26. Karlberg KE, Saldeen T, Wallin R, et al. Intravenous nitroglycerine reduces ischaemia in unstable angina pectoris: a double-blind placebo-controlled study. *J Intern Med* 1998;243:25–31.[PubMed]
27. Douchet S, Malekianpour M, Theroux P, et al. Randomized trial comparing intravenous nitroglycerin and heparin for treatment of unstable angina secondary or restenosis after coronary artery angioplasty. *Circulation* 2000;101:955–961.[PubMed]
28. Held PH, Yusuf S, Furberg CD. Calcium channel blockers in acute myocardial infarction and unstable angina: an overview. *BMJ* 1989;299:1187–1192. Search date not reported.[PubMed]
29. Furberg CD, Psaty BM, Meyer JV. Nifedipine: dose-related increase in mortality in patients with coronary heart disease. *Circulation* 1995;92:1326–1331. Search date not reported.[PubMed]
30. WHO-ISH Study. Ad hoc subcommittee of the liaison committee of the World Health Organization and the International Society of Hypertension: effects of calcium antagonists on the risks of coronary heart disease, cancer and bleeding. *J Hypertens* 1997:15:105–115.[PubMed]
31. Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA* 2001;285:1711–1718.[PubMed]
32. Patti G, Pasceri V, Colonna G, et al. Atorvastatin pretreatment improves outcomes in patients with acute coronary syndromes undergoing early percutaneous coronary intervention. Results of the ARMYDA-ACS Randomized Trial. *J Am Coll Cardiol* 2007;49:1272–1278.[PubMed]
33. Bavry AA, Mood GR, Kumbhani DJ, et al. Long-term benefit of statin therapy initiated during hospitalization for an acute coronary syndrome: a systematic review of randomized trials. *Am J Cardiovasc Drugs* 2007;7:135–141.[PubMed]
34. Colivicchi F, Guido V, Tubaro M, et al. Effects of atorvastatin 80 mg daily early after onset of unstable angina pectoris or non-Q-wave myocardial infarction. *Am J Cardiol* 2002;90:872–874.[PubMed]
35. Bavry AA, Kumbhani DJ, Rassi AN, et al. Benefit of early invasive therapy in acute coronary syndromes: a meta-analysis of contemporary randomized clinical trials. *J Am Coll Cardiol* 2006;48:1319–1325.[PubMed]
36. Qayyum R, Khalid MR, Adomaityte J, et al. Systematic review: comparing routine and selective invasive strategies for the acute coronary syndrome. *Ann Intern Med* 2008;148:186–196.[PubMed]
37. O'Donoghue M, Boden WE, Braunwald E, et al. Early invasive vs conservative treatment strategies in women and men with unstable angina and non-ST-segment elevation myocardial infarction: a meta-analysis. *JAMA* 2008;300:71–80.[PubMed]

38. FRISC II Investigators. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. Fragmin and Fast Revascularisation during Instability in Coronary artery disease Investigators. *Lancet* 1999;354:708–715.[PubMed]

39. Cannon CP, Weintraub WS, Demopoulos LA, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med* 2001;344:1879–1887. [PubMed]

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Disclaimer

TABLE GRADE evaluation of interventions for non ST-elevation acute coronary syndrome

Important outcomes	Mortality, MI, cardiovascular events, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of antiplatelet treatments in people with non ST-elevation acute coronary syndrome?									
12 (5031) [5]	Cardiovascular events	Aspirin *v* placebo	4	0	0	–1	0	Moderate	Directness point deducted for inclusion of different interventions
12 (5031) [5]	Adverse effects	Aspirin *v* placebo	4	0	0	–1	0	Moderate	Directness point deducted for inclusion of different interventions
1 (12,562) [6]	Cardiovascular events	Clopidogrel plus aspirin *v* aspirin alone	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (12,562) [6]	Adverse effects	Clopidogrel plus aspirin *v* aspirin alone	4	0	0	0	0	High	
What are the effects of antithrombin treatments in people with non ST-elevation acute coronary syndrome?									
6 (31,402) [10]	Cardiovascular events	Intravenous glycoprotein IIb/IIIa inhibitors *v* placebo in people not receiving a thienopyridine	4	0	0	–1	0	Moderate	Directness point deducted as around 40% of people in trial had undergone PCI or CABG by day 30 when outcome assessed
6 (31,402) [10]	Adverse effects	Intravenous glycoprotein IIb/IIIa inhibitors *v* placebo in people not receiving a thienopyridine	4	0	0	–1	0	Moderate	Directness point deducted as around 40% of people in trial had undergone PCI or CABG by day 30 when outcome assessed
1 (2022) [11]	Cardiovascular events	Intravenous glycoprotein IIb/IIIa inhibitors *v* placebo in people receiving a thienopyridine	4	0	0	–1	0	Moderate	Directness point deducted for narrow population (high-risk patients requiring surgery)
1 (2022) [11]	Adverse effects	Intravenous glycoprotein IIb/IIIa inhibitors *v* placebo in people receiving a thienopyridine	4	0	0	–1	0	Moderate	Directness point deducted for narrow population (high-risk patients requiring surgery)
7 (1508) [12] [13] [14]	Cardiovascular events	Unfractionated heparin plus aspirin *v* aspirin alone	4	0	–1	0	0	Moderate	Consistency point deducted for different results at different times
at least 5 RCTs (at least 1255 people) [12] [14]	Adverse effects	Unfractionated heparin plus aspirin *v* aspirin alone	4	0	0	–1	0	Moderate	Directness point deducted for low event rate
7 (13,738) [13] [14]	Cardiovascular events	LMWH *v* no heparin	4	0	–1	0	0	Moderate	Consistency point deducted for different results at different times
7 (13,738) [13] [14]	Adverse effects	LMWH *v* no heparin	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for different results at different times
7 (11,092) [15]	Mortality	LMWH *v* unfractionated heparin	4	0	0	0	0	High	
7 (11,092) [15]	MI	LMWH *v* unfractionated heparin	4	0	0	0	0	High	
7 (11,092) [15]	Adverse effects	LMWH *v* unfractionated heparin	4	0	0	0	0	High	
11 (35,070) [16]	Cardiovascular events	Direct thrombin inhibitors *v* unfractionated heparin	4	0	–1	0	0	Moderate	Consistency point deducted for heterogeneity of RCTs

Important outcomes	Mortality, MI, cardiovascular events, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
11 (35,070) [16]	Adverse effects	Direct thrombin inhibitors *v* unfractionated heparin	4	0	–1	0	0	Moderate	Consistency point deducted for heterogeneity of RCTs
5 (4567) [17] [18] [19] [20]	Cardiovascular events	Warfarin *v* aspirin alone	4	0	0	–1	0	Moderate	Directness point deducted for different definitions of combined outcome
1 (3712) [19]	Adverse effects	Warfarin *v* aspirin alone	4	0	0	0	0	High	
1 (20,078) [21]	Mortality	Factor Xa inhibitors *v* LMWH in people receiving a thienopyridine	4	0	0	–1	0	Moderate	Directness point deducted for use of co-interventions (glycoprotein IIb/IIIa inhibitors and statins)
1 (20,078) [21]	MI	Factor Xa inhibitors *v* LMWH in people receiving a thienopyridine	4	0	0	–1	0	Moderate	Directness point deducted for use of co-interventions (glycoprotein IIb/IIIa inhibitors and statins)
1 (20,078) [21]	Adverse effects	Factor Xa inhibitors *v* LMWH in people receiving a thienopyridine	4	0	0	–1	0	Moderate	Directness point deducted for use of co-interventions (glycoprotein IIb/IIIa inhibitors and statins)
What are the effects of anti-ischaemic treatments in people with non ST-elevation acute coronary syndrome?									
1 (338) [24]	MI	Beta-blockers *v* placebo	4	–2	0	–1	0	Very low	Quality points deducted for incomplete reporting of results and short follow-up. Directness point deducted for narrow range of beta-blockers studies
1 (81) [25]	Mortality	Beta-blockers *v* placebo	4	–2	0	–1	0	Very low	Quality points deducted for incomplete reporting of results and short follow-up. Directness point deducted for narrow range of beta-blockers studies
1 (162) [26]	Adverse effects	Nitrates *v* placebo	4	0	0	0	0	High	
6 (856) [28]	Mortality	Calcium channel blockers *v* placebo	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and inclusion of active comparator (propranolol) in analysis
6 (856) [28]	MI	Calcium channel blockers *v* placebo	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and inclusion of active comparator (propranolol) in analysis
6 (303) [28]	Mortality	Calcium channel blockers *v* beta-blockers	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and inclusion of placebo in analysis
6 (303) [28]	MI	Calcium channel blockers *v* beta-blockers	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and inclusion of placebo in analysis
What are the effects of lipid-lowering treatments in people with non ST-elevation acute coronary syndrome?									
2 (3257) [31] [32]	Cardiovascular events	Statins *v* placebo	4	0	–1	–1	0	Low	Consistency point deducted for major differences in absolute results in different trials. Directness point deducted for narrow range of interventions studied
1 (81) [34]	Mortality	High-dose statins *v* low-dose statins or no treatment	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for inclusion of "no treatment" in low-dose statin comparator group

Important outcomes	**Mortality, MI, cardiovascular events, adverse effects**								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
1 (81) [34]	MI	High-dose statins *v* low-dose statins or no treatment	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for inclusion of "no treatment" in low-dose statin comparator group
What are the effects of invasive treatments in people with non ST-elevation acute coronary syndrome?									
10 (10,648) [35] [36]	Mortality	Routine early catheterisation and revascularisation *v* more conservative management	4	0	0	–1	0	Moderate	Directness point deducted for inclusion of interventions not considered standard practice in one review
10 (10,648) [36]	MI	Routine early catheterisation and revascularisation *v* more conservative management	4	0	0	–1	0	Moderate	Directness point deducted for inclusion of interventions not considered standard practice
10 (10,648) [35] [36] [37]	Cardiovascular events	Routine early catheterisation and revascularisation *v* more conservative management	4	0	0	–1	0	Moderate	Directness point deducted for inclusion of interventions not considered standard practice in two reviews
2 (4677) [38] [39]	Adverse effects	Routine early catheterisation and revascularisation *v* more conservative management	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results

Type of evidence: 4 = RCT; 2 = Observational; Consistency: similarity of results across studies; Directness: generalisability of population or outcomes; Effect size: based on relative risk or odds ratio; LMWH, low molecular weight heparin.