Acute myocardial infarction

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QUESTIONS

INTERVENTIONS

See glossary G

Key Messages

Treatments in AMI

- **Angiotensin converting enzyme inhibitors** One systematic review in people treated within 14 days of acute myocardial infarction found that angiotensin converting enzyme inhibitors reduce mortality after 6 weeks compared with placebo. However, a non-systematic review found that angiotensin converting enzyme inhibitors increase persistent hypotension and renal dysfunction at 6 weeks compared with placebo.
- **Aspirin** One systematic review in people with acute myocardial infarction found that aspirin reduced mortality, reinfarction, and stroke at 1 month compared with placebo.
- **Beta-blockers** Two systematic reviews and one subsequent RCT found that beta-blockers reduced mortality compared with no beta-blockers. One RCT in people receiving thrombolytic treatment found that immediate treatment with metoprolol reduced rates of reinfarction and chest pain at 6 days compared with delayed treatment, but had no significant effect on mortality at 6 days or at 1 year.
- **Primary percutaneous transluminal coronary angioplasty versus thrombolysis (performed in specialist centres)** One systematic review found that primary percutaneous transluminal coronary angioplasty reduced a combined outcome of death, non-fatal reinfarction, and stroke compared with thrombolysis.
- **Thrombolysis** One non-systematic review of large RCTs in people with acute myocardial infarction and ST segment elevation or bundle branch block on their initial electrocardiogram found that prompt thrombolytic treatment (within 6 hours and perhaps up to 12 hours and longer after the onset of symptoms) reduced mortality compared with placebo. RCTs comparing different types of thrombolytic agents with each other found no significant difference in mortality. One non-systematic

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Acute myocardial infarction

review found that thrombolytic treatment increased the risk of stroke or major bleeding compared with control. The review also found that intracranial haemorrhage was more common in people of advanced age and low body weight, those with hypertension on admission, and those given tissue plasminogen activator rather than another thrombolytic agent. One non-systematic review found conflicting results for intracerebral haemorrhage with bolus treatment compared with infusion of thrombolytic agents. One systematic review found that thrombolysis was less effective at reducing a combined outcome of death, non-fatal reinfarction, and stroke compared with primary percutaneous transluminal coronary angioplasty.

- **Adding low molecular weight heparin (enoxaparin) to thrombolytics (reduces acute myocardial infarction rates)** One RCT found that adding enoxaparin (a low molecular weight heparin) to streptokinase reduced further acute myocardial infarction rates compared with adding placebo in people with early evidence of a developing infarction. One systematic review identified five RCTs comparing enoxaparin (a low molecular weight heparin) plus thrombolytic treatment versus unfractionated heparin plus thrombolytic treatment. Two of the RCTs identified by the review found that enoxaparin plus thrombolytics reduced further acute myocardial infarction rates compared with unfractionated heparin plus thrombolytics, whereas three RCTs found no significant difference between treatments. The review found no significant difference in mortality between enoxaparin and unfractionated heparin when added to thrombolytic treatment and no significant difference between added enoxaparin and added unfractionated heparin in the risk of intracranial or other major bleeding.
- **Nitrates (in the absence of thrombolysis)** One systematic review of the trials conducted in the prethrombolytic era found that nitrates reduced mortality in people with acute myocardial infarction compared with placebo.
- **Glycoprotein IIb/IIIa inhibitors** Two large RCTs found that combined treatment with half dose thrombolysis plus abciximab did not reduce mortality at 1 month in people with acute myocardial infarction compared with full dose thrombolysis, but one RCT found limited evidence that the combined treatment reduced non-fatal cardiovascular events. However, the RCTs found that combined treatment with abciximab increased bleeding complications, particularly extracranial haemorrhage. One meta-analysis of four RCTs with abciximab and one additional RCT in people treated with primary angioplasty found a reduction in the combined end point of death, reinfarction, and target vessel revascularisation at 30 days and 6 months compared with control, but found no significant reduction in death alone. The meta-analysis found an increased risk of major bleeding with abciximab compared with control. Two additional RCTs comparing early versus late administration of tirofiban in people undergoing primary coronary angioplasty found no significant difference in survival or morbidity outcomes between groups.
- **Adding unfractionated heparin to thrombolytics** Two RCTs found no significant difference in mortality or further acute myocardial infarction rates between unfractionated heparin plus thrombolytics and thrombolytics alone. One systematic review identified five RCTs comparing enoxaparin (a low molecular weight heparin) plus thrombolytic treatment versus unfractionated heparin plus thrombolytic treatment. Two of the RCTs identified by the review found that enoxaparin plus thrombolytics reduced further acute myocardial infarction rates compared with unfractionated heparin plus thrombolytics, whereas three RCTs found no significant difference between treatments. The review found no significant difference in mortality between enoxaparin and unfractionated heparin when added to thrombolytic treatment. The systematic review found no significant difference between added enoxaparin and added unfractionated heparin in the risk of intracranial or other major bleeding.
- **Nitrates (in addition to thrombolysis)** Two RCTs in people with acute myocardial infarction (after thrombolysis was introduced) found no significant difference in mortality between nitrates and placebo.
- **Calcium channel blockers** We found evidence that neither dihydropyridines nor verapamil reduce mortality compared with placebo. One RCT found limited evidence that, in people with left ventricular dysfunction, nifedipine given in the first few days after acute myocardial infarction may increase mortality compared with placebo.

Cardiogenic shock after AMI

- **Early invasive cardiac revascularisation** One large RCT found that early invasive cardiac revascularisation reduced mortality after 6 and 12 months compared with medical treatment alone in people with cardiogenic shock within 48 hours of acute myocardial infarction. A second, smaller RCT found similar results, although the difference was not significant.

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Acute myocardial infarction

- **Early cardiac surgery** We found no RCTs evaluating early surgical intervention for ventricular septal rupture, free wall rupture, or mitral valve regurgitation complicated by cardiogenic shock after acute myocardial infarction.
- **Intra-aortic balloon counterpulsation** An RCT presented only in abstract form found limited evidence of no significant difference in mortality at 6 months between intra-aortic balloon counterpulsation plus thrombolysis and thrombolysis alone in people with cardiogenic shock.
- **Positive inotropes** We found no RCTs comparing inotropes versus placebo.
- **Pulmonary artery catheterisation** We found no RCTs comparing pulmonary artery catheterisation versus no catheterisation.
- **Thrombolysis** Subgroup analysis of one RCT found no significant difference in mortality after 21 days between thrombolysis and no thrombolysis in people with cardiogenic shock.
- **Vasodilators** We found no RCTs comparing vasodilators versus placebo.
- **Ventricular assistance devices and cardiac transplantation** We found no RCTs evaluating either ventricular assistance devices or cardiac transplantation.

DEFINITION

Acute myocardial infarction (AMI): The sudden occlusion of a coronary artery leading to myocardial cell death. **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 (≥ 15 mm Hg).[1–3]

INCIDENCE/ PREVALENCE

AMI: Acute myocardial infarction 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 USA experience AMI, about 225 000 of whom die. About half of these people die within 1 hour of symptoms and before reaching a hospital emergency room.[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 AMI 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 AMI.[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 24–48 hours after their admission.[7]

AETIOLOGY/ RISK FACTORS

AMI: Identified major risk factors for cardiovascular disease include increasing age, male sex, raised low density lipoprotein cholesterol, reduced high density lipoprotein cholesterol, raised blood pressure, smoking, diabetes, family history of cardiovascular disease, obesity, and sedentary lifestyle. For many of these risk factors, observational studies show a continuous gradient of increasing risk of cardiovascular disease with increasing levels of the risk factor, with no obvious threshold level. The immediate mechanism of AMI 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 coronary heart disease 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 AMI usually follows a reduction in functional ventricular myocardium, and is caused by left ventricular infarction (79% of people with cardiogenic shock) more often than by right ventricular infarction (3% of people with cardiogenic shock).[8] Cardiogenic shock after AMI may also be caused by cardiac structural defects, such as mitral valve regurgitation due to papillary muscle dysfunction (7% of people with cardiogenic shock), ventricular septal rupture (4% of people with cardiogenic shock), or cardiac tamponade after free cardiac wall rupture (1% of people with cardiogenic shock). Major risk factors for cardiogenic shock after AMI are previous myocardial infarction, diabetes mellitus, advanced age, hypotension, tachycardia or bradycardia, congestive heart failure with Killip class II–III Ⓒ, and low left ventricular ejection fraction (ejection fraction < 35%).[7,8]

PROGNOSIS

AMI: 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 rates for people in hospital with cardiogenic shock after AMI vary between 50–80%.[2,3,6,7] Most deaths occur within 48 hours of the onset of shock (see figure 1, p 22).[9] People surviving until discharge from hospital have a reasonable long term prognosis (88% survival at 1 year).[10]

AIMS OF INTERVENTION

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

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Acute myocardial infarction

OUTCOMES **Efficacy outcomes:** Rates of major cardiovascular events, including death, recurrent acute myocardial infarction, refractory ischaemia, and stroke. **Safety outcomes:** Rates of major bleeding and intracranial haemorrhage.

METHODS *Clinical Evidence* search and appraisal August 2004.

QUESTION Which treatments improve outcomes in acute myocardial infarction?

OPTION ASPIRIN

One systematic review in people with acute myocardial infarction found that aspirin reduced mortality, reinfarction, and stroke at 1 month compared with placebo.

Benefits: **Versus placebo:** We found one systematic review (search date 1990, 9 RCTs, 18 773 people), which compared antiplatelet agents begun soon after the onset of acute myocardial infarction (AMI) and for at least 1 month afterwards versus placebo.[11] Almost all (> 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 (see figure 2, p 23).[11] The absolute and relative benefits found in the systematic review are shown in figure 2, p 22. The largest of the RCTs identified by the review (17 187 people with suspected AMI) compared aspirin 162.6 mg versus placebo chewed and swallowed on the day of AMI and continued daily for 1 month.[12] There was a 2.4% absolute reduction in vascular death at 35 days. The survival benefit was maintained for up to 4 years.[13] In the systematic review, the most widely tested aspirin regimens were 75–325 mg daily.[11] Doses throughout this range seemed similarly effective, with no evidence that "higher" doses were more effective (500–1500 mg/day aspirin *v* placebo; OR for all vascular events 21%, 95% CI 14% to 27%) than "medium" doses (160–325 mg/day aspirin *v* placebo; OR for all vascular events 28%, 95% CI 22% to 33%), or "lower" doses (75–160 mg/day aspirin *v* placebo; OR 26%, 95% CI 5% to 42%). 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 160–325 mg daily achieved a prompt antiplatelet effect.[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).[12] It also found a small absolute excess of "minor" bleeding (ARI 0.6%, CI not reported; $P < 0.01$).

Comment: None.

OPTION THROMBOLYSIS

One non-systematic review of large RCTs in people with acute myocardial infarction and ST segment elevation or bundle branch block on their initial electrocardiogram found that prompt thrombolytic treatment (within 6 hours and perhaps up to 12 hours and longer after the onset of symptoms) reduced mortality compared with placebo. RCTs comparing different types of thrombolytic agents with each other found no significant difference in mortality. One non-systematic review found that thrombolytic treatment increased the risk of stroke or major bleeding compared with control. The review also found that intracranial haemorrhage was more common in people of advanced age and low body weight, those with hypertension on admission, and those given tissue plasminogen activator rather than another thrombolytic agent. One non-systematic review found conflicting results for intracerebral haemorrhage with bolus treatment compared with infusion of thrombolytic agents. One systematic review found that thrombolysis was less effective at reducing a combined outcome of death, non-fatal reinfarction, and stroke compared with primary percutaneous transluminal coronary angioplasty.

Benefits: **Versus placebo:** We found one non-systematic review of high quality RCTs (9 RCTs, 58 600 people with suspected acute myocardial infarction [AMI]) 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

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rest. The review found that thrombolysis significantly reduced short term mortality compared with placebo (9.6% with thrombolysis *v* 11.5% with placebo; RR 0.82, 95% CI 0.77 to 0.87). The greatest benefit was found in the large subgroup of people presenting with ST elevation (RR 0.79, CI not reported) or bundle branch block (RR 0.75, CI not reported). Reduced death rates were seen in people with all types of infarction, but the benefit was several times greater in those with anterior infarction (ARR 3.7%) compared with those with inferior infarction (ARR 0.8%) or infarctions in other zones (ARR 2.7%). One of the RCTs included in the overview found that thrombolysis significantly reduced mortality after 12 years compared with placebo (36/107 [34%] died 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] **Timing of treatment:** The non-systematic review found that the earlier thrombolytic treatment was given after the onset of symptoms, the greater the absolute benefit of treatment (see figure 3, p 24).[15] For each hour of delay in thrombolytic treatment, the absolute risk reduction for death decreased by 0.16% (ARR for death if given within 6 hours of symptoms 3%; ARR for death if given 7–12 hours after onset of symptoms 2%).[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 tissue plasminogen activator (tPA):** We found one non-systematic review,[17] which found three RCTs[18–20] (see table 1, p 20) comparing streptokinase versus tPA. The first RCT, in people with ST segment elevation and symptoms of AMI for less than 6 hours, was unblinded.[18] People were first randomised to intravenous tPA 100 mg over 3 hours or streptokinase 1.5 MU over 1 hour and then further randomised to subcutaneous heparin 12 500 U twice daily beginning 12 hours later, or no heparin. There was no significant difference in mortality between tPA 100 mg and streptokinase (9.0% with tPA 100 mg *v* 8.6% with streptokinase; RR 1.05, 95% CI 0.95 to 1.16). In the second RCT, people with suspected AMI presenting within 24 hours of symptoms were first randomised to receive either streptokinase 1.5 MU over 1 hour, tPA 0.6 MU/kg every 4 hours, or anisoylated plasminogen streptokinase activator complex 30 U every 3 minutes, and then further randomised to subcutaneous heparin 12 500 U starting at 7 hours and continued for 7 days, or no heparin.[19] All people received aspirin on admission. The RCT found no significant difference between thrombolytic agents in mortality (AR of death: 10.6% with streptokinase *v* 10.5% with anisoylated plasminogen streptokinase activator complex *v* 10.3% with tPA). The third RCT was unblinded and included people with ST segment elevation presenting within 6 hours of symptom onset.[20] People were randomised to one of four regimens: streptokinase 1.5 MU over 1 hour plus subcutaneous heparin 12 500 U twice daily starting 4 hours after thrombolytic treatment; streptokinase 1.5 MU over 1 hour plus intravenous heparin 5000 U bolus followed by 1000 U every hour; accelerated tPA 15 mg bolus then 0.75 mg/kg over 30 minutes followed by 0.50 mg/kg over 60 minutes, plus intravenous heparin 5000 U bolus then 1000 U every hour; or tPA 1.0 mg/kg over 60 minutes, 10% given as a bolus, plus streptokinase 1.0 MU over 60 minutes.[20] Meta-analysis of the three 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%).[17] **tPA versus other thrombolytics:** We found two RCTs that compared tPA versus other thrombolytic agents in people with AMI (participants also received aspirin and heparin).[21,22] The first RCT (15 059 people from 20 different countries with AMI evolving for < 6 hours, with ST segment elevation or with the appearance of a new left bundle branch block on their electrocardiogram) compared tPA (accelerated iv administration according to the study regimen) versus reteplase (recombinant plasminogen activator; two 10 MU iv boluses, 30 minutes apart).[21] It found no significant difference in mortality after 30 days (OR 1.03, 95% CI 0.91 to 1.18). The second RCT (16 949 people; see comment below) compared tPA (accelerated iv administration) versus tenecteplase (a genetically engineered variant of tPA; 30–50 mg iv according to body weight as a single bolus).[22] It found

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Acute myocardial infarction

no significant difference between treatments in total mortality after 30 days (6% with tenecteplase *v* 6% with tPA; RR 1.0, 95% CI 0.91 to 1.10). **Thrombolysis versus primary percutaneous transluminal coronary angioplasty:** See benefits of primary percutaneous transluminal coronary angioplasty versus thrombolysis, p 13.

Harms:

Stroke/intracerebral haemorrhage: The overview found that thrombolytic treatment significantly increased the risk of stroke compared with control (ARI 0.4%, 95% CI 0.2% to 0.5%; NNH 250, 95% CI 200 to 500).[15] In the third RCT comparing streptokinase versus tPA, the overall incidence of stroke was 0.7%, of which 31% were severely disabling and 50% were intracerebral haemorrhages.[20] The RCT also found that tPA significantly increased the risk of haemorrhagic stroke compared with streptokinase plus subcutaneous heparin or streptokinase plus intravenous heparin (AR for combined streptokinase arms 0.52% *v* 0.72% with tPA; P = 0.03 for tPA compared with combined streptokinase arms). The RCT comparing reteplase versus tPA found that the incidence of stroke was similar with both treatments, and the odds ratio for the incidence of death or disabling stroke was 1.0.[21] The RCT comparing tenecteplase versus tPA found no significant difference between treatments in the rate of stroke or death (7% with tenecteplase *v* 7% with tPA; RR 1.01, 95% CI 0.91 to 1.13).[22] We found one non-systematic review that compared bolus thrombolytic treatment versus infusion treatment.[23] Meta-analysis of nine small phase II trials (3956 people) found no significant difference between bolus and standard infusion thrombolysis for intracerebral haemorrhage (bolus *v* infusion: OR 0.53, 95% CI 0.27 to 1.01). However, meta-analysis of six larger phase III trials (62 673 people) found that bolus treatment significantly increased the risk of intracerebral haemorrhage (OR 1.25, 95% CI 1.06 to 1.49). **Predictive factors for stroke/intracranial haemorrhage:** Multivariate analysis of data from a large database of people who experienced intracerebral haemorrhage after thrombolytic treatment identified four 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] Absolute risk of intracranial haemorrhage was 0.26% on streptokinase in the absence of risk factors and 0.96%, 1.32%, and 2.17% in people with one, two, and three risk factors, respectively.[24] Analysis of 592 strokes in 41 021 people from the trials found seven 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 overview also 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 (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty). Spontaneous bleeds were observed most often in the gastrointestinal tract.[20] **Thrombolysis versus primary percutaneous transluminal coronary angioplasty:** See harms of primary percutaneous transluminal coronary angioplasty versus thrombolysis, p 13.

Comment:

Extrapolation of the data from the overview (see figure 3, p 24) suggests that, at least for people suspected of having an AMI and with ST segment elevation on their electrocardiogram, there may be some net benefit of treatment between 12–18 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 should be used. 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 three trials can be questioned, as the selection criteria and protocols differed in important aspects.[17]

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OPTION ADDING ANTICOAGULANTS TO THROMBOLYTICS

Two RCTs found no significant difference in mortality or further acute myocardial infarction rates between unfractionated heparin plus thrombolytics and thrombolytics alone in people with early evidence of a developing infarction. One RCT found that adding enoxaparin (a low molecular weight heparin) to streptokinase reduced further acute myocardial infarction rates compared with adding placebo. One systematic review identified five RCTs comparing adding enoxaparin (a low molecular weight heparin) to thrombolytic treatment versus adding unfractionated heparin to thrombolytic treatment. Two of the RCTs identified by the review found that enoxaparin plus thrombolytics reduced further acute myocardial infarction rates compared with unfractionated heparin plus thrombolytics, whereas three RCTs found no significant difference between treatments. The review found no significant difference in mortality or bleeding complications between enoxaparin and unfractionated heparin when added to thrombolytic treatment.

Benefits:

Versus thrombolytics alone: We found three RCTs.[18,19,27] The first RCT (20 768 people with ST segment elevation and symptoms of acute myocardial infarction [AMI] for < 6 hours) was unblinded and compared streptokinase versus tissue plasminogen activator (tPA) with or without heparin.[18] People were first randomised to intravenous tPA 100 mg over 3 hours or streptokinase 1.5 >MU over 1 hour and then further randomised to subcutaneous heparin 12 500 U twice daily beginning 12 hours later, or no heparin. It found no significant difference in mortality or further AMI rate between thrombolytic plus heparin compared with thrombolytic alone (AR of death in hospital 8.5% with thrombolytic plus heparin *v* 8.9% with thrombolytic alone; RR 0.95, 95% CI 0.86 to 1.04; AR of further AMI 1.9% with thrombolytic plus heparin *v* 2.3% with thrombolytic alone; P reported as not significant). In the second RCT (about 27 000 people), people with suspected AMI presenting within 24 hours of symptoms were first randomised to receive either streptokinase 1.5 MU over 1 hour, tPA 0.6 MU/kg every 4 hours, or anisoylated plasminogen streptokinase activator complex 30 U every 3 minutes, and then further randomised to subcutaneous heparin 12 500 U starting at 7 hours and continued for 7 days, or no heparin.[19] All participants received aspirin on admission. The RCT found no significant difference in mortality or further AMI rate between thrombolytic plus heparin and thrombolytic alone (AR of death within 35 days: 10.3% with thrombolytic plus heparin *v* 10.6% with thrombolytic alone, P reported as not significant; AR of further AMI: 3.16% with thrombolytic plus heparin *v* 3.47% with thrombolytic alone, P = 0.09). The third RCT (496 people) compared streptokinase (1.5 MU over 1 hour) plus enoxaparin (a low molecular weight heparin; 30 mg iv bolus then subcutaneously every 12 hours) versus streptokinase plus placebo.[27] It found that streptokinase plus enoxaparin significantly reduced further AMI rates compared with streptokinase plus placebo after 30 days, although it found no significant difference in mortality rates between treatments (AR of further AMI: 6/253 [2.4%] with enoxaparin *v* 18/243 [7.4%] with placebo; OR 0.30, 95% CI 0.12 to 0.78; AR of death: 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 heparins versus thrombolytics plus unfractionated heparins: We found one systematic review (search date 2002; 5 RCTs, 5757 people) comparing thrombolytics plus enoxaparin (a low molecular weight heparin) or plus unfractionated heparin (see comment below).[28] Adjunctive thrombolytic treatment was tPA in one RCT, tenecteplase in two RCTs, streptokinase in one RCT, and either streptokinase, anistreplase, or tPA in one RCT. The first RCT (312 people) identified by the review found no significant difference between added enoxaparin and added heparin in mortality rates or combined mortality and further AMI rates after 30 days (AR for death: 13/154 [8.4%] with added heparin *v* 11/158 [7.0%] with added enoxaparin; OR 0.86, 95% CI 0.36 to 1.98; AR for death or further AMI: 23/154 [14.9%] with unfractionated heparin *v* 15/158 [9.5%] with enoxaparin; OR 0.63, 95% CI 0.32 to 1.23). The second RCT identified by the review[28] (6095 people treated within 6 hours of ST segment elevation AMI) compared three treatments: full dose tenecteplase (30–50 mg according to body weight) plus unfractionated heparin (60 U/kg bolus plus 12 U/kg/hour); full dose tenecteplase plus enoxaparin (30 mg immediately then 1 mg/kg every 12 hours); or half dose tenecteplase plus full dose abciximab (0.25 mg/kg

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bolus plus 0.125 μg/kg/minute for 12 hours).[29] It found that added enoxaparin significantly reduced further AMI rates compared with added unfractionated heparin plus tenecteplase after 30 days, although mortality rates were similar between treatments (AR for further AMI: 86/2038 [4.2%] with added heparin *v* 54/2040 [2.7%] with added enoxaparin; OR 0.62, 95% CI 0.44 to 0.87; AR for death: 122/2038 [6.0%] with added heparin *v* 109/2040 [5.4%] with added enoxaparin; OR 0.89, 95% CI 0.68 to 1.16).[28] The third RCT identified by the review[28] (300 people) compared thrombolytics (streptokinase, anistreplase, or t-PA; see comment below) plus enoxaparin or heparin. It found no significant difference between added enoxaparin and added heparin in mortality rates or further AMI rates after 90 days (AR for death: 16/151 [10.6%] with unfractionated heparin *v* 9/149 [6.0%] with enoxaparin; OR 0.54, 95% CI 0.23 to 1.27; AR for AMI: 30/151 [19.9%] with unfractionated heparin *v* 22/149 [14.8%] with enoxaparin; OR 0.70, 95% CI 0.38 to 1.28). The fourth RCT (483 people) identified by the review[28] compared enoxaparin versus heparin when added to either full dose tenecteplase (0.53 mg/kg) or half dose tenecteplase plus full dose abciximab (0.25 mg/kg bolus plus 0.125 μg/kg/minute for 12 hours).[30] It found that added enoxaparin significantly reduced further AMI rates compared with added heparin after 30 days, although mortality rates were similar between treatments (see comment below; AR for AMI: 6/324 [1.9%] with enoxaparin *v* 12/159 [7.5%] with unfractionated heparin; OR 0.23, 95% CI 0.09 to 0.63; AR for death: 10/324 [3.1%] with enoxaparin *v* 5/159 [3.1%] with unfractionated heparin; OR 0.98, 95% CI 0.33 to 2.92). The fifth RCT identified by the review[28] (400 people) found no significant difference between tPA plus enoxaparin and tPA plus unfractionated heparin in mortality rates or further AMI rates (AR for death: 10/200 [5.0%] with unfractionated heparin *v* 9/200 [4.5%] with enoxaparin; OR 0.90, 95% CI 0.36 to 2.5; AR for further AMI: 8/200 [4%] with unfractionated heparin *v* 8/200 [4%] with enoxaparin; OR 1.0, 95% CI 0.37 to 2.72).

Harms: **Thrombolytics plus low molecular weight heparins versus thrombolytics plus unfractionated heparins:** The systematic review comparing enoxaparin plus thrombolytic treatment versus unfractionated heparin plus thrombolytic treatment found no significant difference in the risk of intracranial bleeding between treatments (5 RCTs; OR 1.0, 95% CI not reported; P = 0.99).[28] It found no significant difference in the risk of major bleeding between treatments (5 RCTs; OR 1.34, 95% CI 0.97 to 1.87).[28]

Comment: **Thrombolytics plus low molecular weight heparins versus thrombolytics plus unfractionated heparins** There were methodological problems with the systematic review comparing enoxaparin plus thrombolytic treatment versus unfractionated heparin plus thrombolytic treatment.[28] Firstly, the review presented meta-analytic results for six RCTs, including a comparison of thrombolytic plus enoxaparin versus thrombolytic plus placebo, resulting in an unreliable comparison of enoxaparin versus unfractionated heparin. We have, therefore, presented the results for each relevant RCT separately. Secondly, in the third RCT identified by the review,[28] 66% of people had received streptokinase, 28% had received anistreplase, and 6% had received tPA, although treatment groups were balanced at baseline. Finally, in the presentation of the results for the fourth RCT, the systematic review pooled results that included a comparison of heparins added to tenecteplase alone and to tenecteplase plus abciximab. The results, therefore, do not strictly reflect the comparison of enoxaparin versus heparin added to a "pure" thrombolytic regimen.

OPTION GLYCOPROTEIN IIB/IIIA INHIBITORS

Two large RCTs found that combined treatment with half dose thrombolysis plus abciximab did not reduce mortality at 1 month in people with acute myocardial infarction compared with full dose thrombolysis, but one RCT found limited evidence that the combined treatment reduced non-fatal cardiovascular events. However, the RCTs found that combined treatment with abciximab increased bleeding complications, particularly extracranial haemorrhage. One meta-analysis of four RCTs with abciximab and one additional RCT in people treated with primary angioplasty found a reduction in the combined end point of death, reinfarction, and target vessel revascularisation at 30 days and 6 months compared with control, but found

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no significant reduction in death alone. The meta-analysis found an increased risk of major bleeding with abciximab compared with control. Two additional RCTs comparing early versus late administration of tirofiban in people undergoing primary coronary angioplasty found no significant difference in survival or morbidity outcomes between groups.

Benefits:

Added to thrombolytic: We found two RCTs.[29,31] The first RCT (16 588 people treated within 6 hours of ST segment elevation myocardial infarction; unblinded design) compared half dose reteplase plus abciximab (0.25 mg/kg bolus plus 0.125 μg/kg/minute for 12 hours) versus standard dose reteplase (total dose 20 U).[31] It found no significant difference in all cause mortality or stroke at 30 days between combined treatment and standard dose reteplase alone (mortality: AR 5.9% for reteplase alone *v* 5.6% for combined treatment; OR 0.95, 95% CI 0.83 to 1.08; any stroke: AR 0.9% for reteplase *v* 1.0% for combined treatment; OR 1.10, 95% CI 0.80 to 1.51). It found that combined treatment reduced the composite end point of mortality or non-fatal reinfarction at 30 days (AR 8.8% for thrombolysis alone *v* 7.4% for combined treatment; OR 0.83, 95% CI 0.74 to 0.93). At 1 year, there was no significant difference in mortality between combination treatment and standard dose reteplase (692/8260 [8.4%] with standard reteplase *v* 698/8328 [8.4%] with combined therapy; HR 1.00, 95% CI 0.90 to 1.11).[32] The second RCT (6095 people treated within 6 hours of ST segment elevation myocardial infarction; unblinded design) compared three treatments: full dose tenecteplase (30–50 mg according to body weight) plus unfractionated heparin (60 U/kg bolus plus 12 U/kg/hour); full dose tenecteplase plus enoxaparin (30 mg immediately then 1 mg/kg every 12 hours); or half dose tenecteplase plus full dose abciximab (0.25 mg/kg bolus plus 0.125 μg/kg/minute for 12 hours).[29] It found no significant difference among groups in mortality at 30 days (AR 6.0% with unfractionated heparin *v* 5.4% with enoxaparin *v* 6.6% with abciximab; P = 0.25). It found that added abciximab increased composite risk of death, non-fatal cardiovascular events, or haemorrhage at 30 days compared with added enoxaparin but reduced risk compared with added unfractionated heparin (AR 13.8% with enoxaparin, 14.2% with abciximab, and 17.0% with unfractionated heparin; P = 0.008). At 1 year, mortality was similar among the groups (7.9% in the heparin group, 8.1% in the enoxaparin group, and 9.3% in the abciximab group; P = 0.226).[33] **Primary percutaneous transluminal coronary angioplasty with or without glycoprotein IIb/IIIa inhibitors:** We found one systematic review (search date not stated, people with acute myocardial infarction) which included a meta-analysis of 4 RCTs adding abciximab or placebo/control in people undergoing primary percutaneous coronary intervention,[34] and we found one additional RCT in people with primary stenting.[35] The meta-analysis included 3266 people. The review found that abciximab therapy significantly reduced the 30 day composite end point of death, reinfarction, or urgent target revascularisation compared with control (OR 0.54, 95% CI 0.40 to 0.72).[34] It found no significant difference between groups in the outcomes of death (OR 0.73, 95% CI 0.46 to 1.16) and reinfarction (OR 0.72, 95% CI 0.39 to 1.34).[34] At 6 months, the composite end point of death, reinfarction, or urgent target revascularisation was significantly reduced with abciximab compared with control (OR 0.80, 95% CI 0.67 to 0.97); death or reinfarction was not significantly reduced (OR 0.85, 95% CI 0.65 to 1.15).[34] The additional RCT (400 people with acute myocardial infarction undergoing stenting) found that the primary composite end point of death, reinfarction, stroke, or target vessel revascularisation at 1 month was significantly reduced with abciximab compared with control (AR 4.5% stent plus abciximab *v* 10.5% stent without abciximab; P = 0.023).[35] Most of the difference was related to a decrease in reinfarction (AR 0.5% stent with abciximab *v* 4.5% stent without abciximab).[35] At 6 months, the combined end point of death or reinfarction was significantly lower in the abciximab group compared with control (AR 5.5% stent plus abciximab *v* 13.5% stent without abciximab; P = 0.006). It found no significant difference between groups in death (cumulative) alone at 6 months (4.5% *v* 8%; P = 0.148). **Timing of administration of glycoprotein IIb/IIIa inhibitors in people undergoing primary coronary angioplasty:** We found two other RCTs that assessed the efficacy of the administration of tirofiban before or during primary coronary angioplasty.[36,37] The first RCT (100 people with acute myocardial infarction in the past 12 hours referred for primary coronary angioplasty) compared tirofiban administered in the emergency room (early administration) versus tirofiban administered in the catheterisation laboratory after diagnostic angiography (late administration).[36] It found no significant difference between early or

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Acute myocardial infarction

late tirofiban administration in death, reinfarction, or rehospitalisation, although the study may have been too small to detect clinically significant differences (death rate: 2% with early *v* 2% with late; recurrent myocardial infarction: 0% with early *v* 2% with late; rehospitalisation: 4% with early *v* 6% with late; P > 0.05 for each outcome).[36] The second RCT compared prehospital initiation of tirofiban or initiation in the catheterisation laboratory in 507 people with acute myocardial infarction.[37] Angiographically normal coronary flow (TIMI 3 grade) was present in 19% of the early group compared with 15% of the later group. At 1 year follow up, the RCT found that the combined incidence of death or recurrent myocardial infarction was identical in the two groups (7.0% in early group *v* 7.0% in late group; P = 0.99).[37]

Harms: **Glycoprotein IIb/IIIa inhibitors plus thrombolysis versus thrombolysis alone:** The first RCT found that abciximab plus half dose thrombolysis significantly increased severe or moderate extracranial bleeding at 30 days compared with full dose thrombolysis (AR 4.6% with combined treatment *v* 2.3% 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). The second RCT found that rates of any stroke and of intracranial haemorrhage were similar for thrombolysis plus abciximab, enoxaparin, or unfractionated heparin (AR for any stroke about 1.5%; AR for intracranial haemorrhage about 0.9%).[28] **Primary percutaneous transluminal coronary angioplasty with or without glycoprotein IIb/IIIa inhibitors:** The systematic review in people undergoing primary percutaneous coronary intervention found a significantly increased risk of major bleeding associated with the use of abciximab compared with control (OR 1.74, 95% CI 1.11 to 2.72).[34] The additional RCT in people with stenting found that haemorrhagic complications requiring blood transfusion or vascular repair were observed in 3.5% of people with stent plus abciximab compared with 3.0% of people with stent without abciximab (P = 0.778).[35] **Timing of administration of glycoprotein IIb/IIIa inhibitors in people undergoing primary coronary angioplasty:** The first RCT comparing early versus late tirofiban administration before primary coronary angioplasty found similar rates of minor or major bleeding complications, although the study 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).[36] The second RCT found no significant difference between groups in the rates of non-CABG related major bleeding at 30 days (4.5% in early group *v* 3.2% in late group; P = 0.47).[37]

Comment: None.

OPTION BETA-BLOCKERS

Two systematic reviews and one subsequent RCT found that beta-blockers reduced mortality compared with no beta-blockers. One RCT in people receiving thrombolytic treatment found that immediate treatment with metoprolol reduced rates of reinfarction and chest pain at 6 days compared with delayed treatment, but had no significant effect on mortality at 6 days or at 1 year.

Benefits: **Versus no beta-blocker:** We found two systematic reviews (search date not stated, 16 RCTs short term with early oral use of beta-blockers, 31 RCTs with iv use of beta-blockers, 16 RCTs on long term use of beta-blockers;[38] search date 1997, 82 RCTs, 54 234 people)[39] and one subsequent RCT[40] of beta-blockers in people with acute myocardial infarction (AMI). The earlier review found that oral beta-blockers did not significantly reduce short term mortality compared with control (165/1900 [8.7%] with oral beta-blockers *v* 165/1711 [9.6%] without beta-blockers; P value not provided), and that 1 week mortality also did not significantly differ in people having received intravenous beta-blockers compared with those without intravenous beta-blockade (194/5676 [3.4%] with beta-blocker *v* 205/5633 [3.6%] without beta-blocker; P value not provided).[38] By contrast, it found that late mortality in long term trials was significantly reduced in people receiving beta-blockers compared with those without beta-blockers (827/10452 [7.9%] with beta-blocker *v* 986/9860 [10%] without beta-blocker; OR 0.77, 95% CI 0.7 to 0.85; P < 0.0001).[38] The more recent review separately

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analysed 51 short term RCTs (people within 6 weeks after the onset of pain) and 31 long term RCTs (people treated for up to 48 months after AMI).[39] In most of the RCTs, the participants did not receive thrombolysis. In the short term studies, seven RCTs reported no deaths and many reported only a few. The short term RCTs reporting at least one death found no significant difference in mortality between beta-blockers and no beta-blockers (ARR 0.4%; OR 0.96, 95% CI 0.85 to 1.08). In the longer term RCTs, beta-blockers significantly reduced mortality over 6 months to 4 years compared with no beta-blockers (OR 0.77, 95% CI 0.69 to 0.85). See beta-blockers under secondary prevention of ischaemic cardiac events, p 00. No significant difference in effectiveness was found between different types of beta-blocker (based on cardioselectivity or intrinsic sympathomimetic activity). Most evidence was obtained with propranolol, timolol, and metoprolol. The subsequent RCT (1959 people within 3–21 days of AMI and with left ventricular dysfunction, of whom 46% had received thrombolysis or percutaneous transluminal coronary angioplasty at the acute stage of their infarction and 97% had received angiotensin converting enzyme inhibitors) compared carvedilol (6.25 mg increased to a maximum of 25 mg over 4–6 weeks) versus placebo.[40] It found that carvedilol significantly reduced mortality and further non-fatal AMI compared with placebo (AR for death: 12% with carvedilol *v* 15% with placebo; HR 0.77, 95% CI 0.60 to 0.98; for non-fatal AMI: HR 0.59, 95% CI 0.39 to 0.90), but found no difference between treatments in the combined end point of total mortality and hospital admission for any cardiovascular event after a median of 1.3 years (HR 0.92, 95% CI 0.80 to 1.07). **Early versus delayed treatment:** We found one RCT (1434 people with AMI who had received tissue plasminogen activator thrombolysis), which compared early versus delayed metoprolol treatment.[41] Early treatment began on day 1 (iv 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 (AR for reinfarction: 2.7% with early treatment *v* 5.1% with delayed treatment; CI not reported; $P = 0.02$; AR for chest pain: 18.8% with early treatment *v* 24.1% 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 or 1 year.

Harms: People with asthma or severe congestive cardiac failure were excluded from most trials. One RCT found that people given immediate versus delayed beta-blockers after tissue plasminogen activator experienced increased frequency of heart failure during the initial admission to hospital, although the result was not statistically significant (15.3% with immediate *v* 12.2% with delayed; $P = 0.10$).[41] The presence of first degree heart block and bundle branch block was associated with more adverse events.

Comment: Until recently, trials involving the use of beta-blockers in AMI were conducted mostly 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 prethrombolytic 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 of beta-blockers when added to thrombolysis.[41]

OPTION ANGIOTENSIN CONVERTING ENZYME INHIBITORS

One systematic review in people treated within 14 days of acute myocardial infarction found that angiotensin converting enzyme inhibitors reduce mortality after 6 weeks compared with placebo. However, a non-systematic review found that angiotensin converting enzyme inhibitors increase persistent hypotension and renal dysfunction at 6 weeks compared with placebo.

Benefits: We found one systematic review (search date 1997, 15 RCTs with ≥ 6 weeks' follow up, 15 104 people), which compared angiotensin converting enzyme (ACE) inhibitors started within 14 days of acute myocardial infarction (AMI) versus placebo.[42] It found that ACE inhibitors decreased overall mortality and sudden cardiac death compared with placebo after 2–42 months (overall mortality: 1105/7658 [14.4%] with ACE inhibitors *v* 1251/7446 [16.8%] with placebo; OR 0.83, 95% CI 0.71 to 0.97; sudden cardiac death: OR 0.80, 95% CI 0.70 to 0.92).[42]

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Acute myocardial infarction

Harms: One non-systematic review of RCTs (search date not reported, 4 RCTs, 98 496 people within 36 hours of AMI) found that ACE inhibitors significantly increased persistent hypotension and renal dysfunction at 6 weeks compared with placebo (hypotension: AR 17.6% with ACE inhibitor *v* 9.3% with control; CI for difference not reported; $P < 0.01$; renal dysfunction: AR 1.3% *v* 0.6%; $P < 0.01$).[43] The relative and absolute risks of these adverse effects were uniformly distributed across both the high and lower cardiovascular risk groups. The systematic review did not report on harms.[42]

Comment: ACE inhibitors in people with AMI work best when treatment is started within 24 hours. The evidence does not answer the question of which people with an AMI should be offered ACE inhibitors, nor for how long after AMI 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.[44] 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 the benefits of ACE inhibitors also benefit people with normal left ventricular function after AMI.

OPTION NITRATES

One systematic review in people with acute myocardial infarction in the prethrombolytic era found that nitrates reduce mortality compared with placebo. Two RCTs in people with acute myocardial infarction (after thrombolysis was introduced) found no significant difference in mortality between nitrates and placebo.

Benefits: **Without thrombolysis:** We found one systematic review (search date not reported, 10 RCTs, 2000 people with acute myocardial infarction [AMI] who did not receive thrombolysis), which compared intravenous glyceryl trinitrate or sodium nitroprusside versus placebo.[45] The review found that nitrates significantly reduced mortality compared with placebo (RR 0.65, 95% CI 0.45 to 0.84). **With aspirin/thrombolysis:** We found two RCTs, which compared nitrates (given acutely) versus placebo in people with AMI, of whom 90% received aspirin and about 70% received thrombolytic treatment.[46,47] The first RCT (58 050 people with AMI) compared oral controlled release isosorbide mononitrate 30–60 mg daily versus placebo.[46] It found no significant difference in mortality between isosorbide mononitrate and placebo (ARR nitrates *v* placebo 0.20%; OR 0.97, 95% CI 0.91 to 1.03). The second RCT (17 817 people with AMI) compared intravenous glyceryl trinitrate for 24 hours, followed by transdermal glyceryl trinitrate, versus placebo. It found no significant difference in mortality between nitrates and placebo (ARR nitrates *v* placebo 0.4%; OR 0.94, 95% CI 0.84 to 1.05). Neither RCT found significant differences in mortality in subgroups of people with different risks of dying.

Harms: The systematic review and the large RCTs found no significant harm associated with routine use of nitrates.[45–47]

Comment: Results for the two large RCTs were limited because a large proportion of people took nitrates outside the study, 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 AMI.

OPTION CALCIUM CHANNEL BLOCKERS

We found evidence that neither dihydropyridines nor verapamil reduce mortality compared with placebo. One RCT found limited evidence that, in people with left ventricular dysfunction, nifedipine given in the first few days after acute myocardial infarction may increase mortality compared with placebo.

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Benefits: **Dihydropyridine calcium channel blockers:** We found two RCTs, which compared short acting nifedipine versus placebo within the first few days of acute myocardial infarction (AMI).[48,49] The first RCT (4491 people) was terminated prematurely because of concerns about safety.[48] It found that nifedipine increased mortality by 33% compared with placebo, although the increase did not reach statistical significance. The second RCT (1006 people) found no significant difference in mortality between nifedipine and placebo (18.7% with nifedipine *v* 15.6% with placebo; OR 1.60, 95% CI 0.86 to 3.00).[49] 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 AMI).[50] 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 AMI found non-significant increases in mortality of about 4% and 6%.[51,52] One RCT (2466 people with AMI) compared diltiazem (60 mg orally 4 times daily starting 3–15 days after AMI) versus placebo.[53] 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 PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY VERSUS THROMBOLYSIS

One systematic review found that primary percutaneous transluminal coronary angioplasty reduced a combined outcome of death, non-fatal reinfarction, and stroke compared with thrombolysis.

Benefits: We found one systematic review (search date not reported, 23 RCTs, 7739 people with or without cardiogenic shock), which compared primary percutaneous transluminal coronary angioplasty (PTCA) versus thrombolysis (streptokinase and fibrin specific agents) in people with acute ST segment myocardial infarction.[54] It found that PTCA significantly reduced the combined end point of death, non-fatal reinfarction, and stroke at 4–6 weeks compared with thrombolysis (253/3089 [8%] with PTCA *v* 442/3085 [14%] with thrombolysis; OR 0.53, 95% CI 0.45 to 0.63; no significant heterogeneity was detected; $P = 0.35$). It also found that PTCA significantly reduced the combined outcome at 6–18 months (approximately 11% *v* 20%, results presented graphically; $P < 0.0001$). Results were similar for PTCA compared with streptokinase and for PTCA compared with fibrin specific agents (PTCA *v* streptokinase, 8 RCTs, 1837 people: OR 0.40, 95% CI 0.28 to 0.58; PTCA *v* fibrin specific agents, 15 RCTs, 5902 people: OR 0.57, 95% CI 0.48 to 0.63). The review also found that emergency hospital transfer for primary PTCA (average delay 39 minutes) significantly reduced the combined outcome compared with on-site thrombolysis (5 RCTs, 2909 people: 8% with PTCA *v* 15% with thrombolysis, results presented graphically; $P < 0.0001$).

Harms: **Stroke:** The review found that PTCA reduced the risk of all types of stroke compared with thrombolysis (all stroke: 1.0% with PTCA *v* 2.0% with thrombolysis; $P < 0.001$; haemorrhagic stroke: 0.05% with PTCA *v* 1.1 % with thrombolysis; $P = 0.03$).[54] **Major bleeding:** The review also found that PTCA increased major bleeding at 4–6 weeks compared with thrombolysis (7% with PTCA *v* 5% with thrombolysis; OR 1.30, 95% CI 1.02 to 1.56).[54]

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, most of which may have inflated the benefit of PTCA.[55] RCTs comparing PTCA versus thrombolysis could not be easily blinded, and 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[56]) should be viewed as hypothesis

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generating, in that the composite 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 who 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.[57] The value of PTCA over thrombolysis in people presenting to hospital more than 12 hours after onset of chest pain remains to be tested. 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.[56] This may have been because the trials summarised above were in older people and used tissue plasminogen activator. 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 for cardiogenic shock after acute myocardial infarction?**

OPTION **EARLY INVASIVE CARDIAC REVASCULARISATION**

One large RCT found that early invasive cardiac revascularisation reduced mortality after 6 and 12 months compared with medical treatment alone in people with cardiogenic shock within 48 hours of acute myocardial infarction. A second, smaller RCT found similar results, although the difference was not significant.

Benefits: We found no systematic review. We found two RCTs in people with cardiogenic shock within 48 hours of acute myocardial infarction comparing early invasive cardiac revascularisation G versus initial medical treatment alone (see comment below).[2,3,58] The first RCT (302 people) found that early invasive cardiac revascularisation significantly reduced mortality after 6 and 12 months (see table 2, p 21).[2,58] The second RCT (55 people) found that early invasive cardiac revascularisation reduced mortality after 30 days and at 12 months, although the difference was not significant (see table 2, p 21).[3] **Percutaneous transluminal coronary angioplasty versus coronary artery bypass graft:** We found no RCTs in people with cardiogenic shock after acute myocardial infarction comparing percutaneous transluminal coronary angioplasty versus coronary artery bypass grafting.

Harms: 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).[2,58] The first RCT also found that acute renal failure (defined as a serum creatinine level > 265 μmol/L) was significantly more common in the medical treatment alone group than the early cardiac revascularisation group (36/150 [24%] *v* 20/152 [13%]; 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 G and thrombolytic treatment.[2,58] 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.[2,3,58]

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OPTION THROMBOLYSIS

Subgroup analysis of one RCT found no significant difference in mortality after 21 days between thrombolysis and no thrombolysis in people with cardiogenic shock.

Benefits: We found no systematic review. We found one RCT (11 806 people with acute myocardial infarction), which compared streptokinase versus no thrombolysis and performed a subgroup analysis on people with cardiogenic shock (see comment below).[59] 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 did not specifically report harms in the subgroup of people with cardiogenic shock.[59] 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 myocardial infarction, p 6.

Comment: The RCT was not blinded.[59] Data presented are from a retrospective subgroup analysis. Randomisation was not stratified by the presence of cardiogenic shock. One RCT in people with cardiogenic shock complicating acute myocardial infarction compared an emergency revascularisation strategy with initial medical stabilisation (See benefits of early invasive revascularisation, p 14).[2,58] A subsequent report of this RCT analysed the effects of thrombolytic therapy, with or without intra-aortic balloon counterpulsion, on 12 month survival.[60] 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 compared with no thrombolytic therapy (mortality hazard ratio adjusted for age and previous myocardial infarction 0.62, 95% CI 0.41 to 0.93).[60] In those people in the emergency revascularisation group, it found no significant difference in survival between thrombolytic therapy and no thrombolytic therapy (mortality hazard ratio adjusted for age and previous myocardial infarction 1.06, 95% CI 0.67 to 1.66).[60] Overall, it found a similar rate of severe bleeding between those receiving, and not receiving, thrombolytic therapy (31% *v* 26%; P = 0.37).[60] However, the administration of thrombolytic therapy (with or without IABP deployment) was not randomised, rather by protocol, and the analysis was *post hoc*.

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

We found no RCTs comparing inotropes versus placebo.

Benefits: We found no systematic review or RCTs. We found three non-systematic reviews, which did not include RCTs evaluating positive inotropes specifically in people with cardiogenic shock after acute myocardial infarction.[1,61,62]

Harms: Positive inotropes may worsen cardiac ischaemia and induce ventricular arrhythmias.[1,61,62] We found no studies of harms specifically in people with cardiogenic shock after acute myocardial infarction (see harms of positive inotropic drugs under heart failure, p 01).

Comment: There is consensus that positive inotropes are beneficial in cardiogenic shock after acute myocardial infarction. We found no evidence to confirm or reject this view.

OPTION VASODILATORS (ANGIOTENSIN CONVERTING ENZYME INHIBITORS, NITRATES)

We found no RCTs comparing vasodilators versus placebo.

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Acute myocardial infarction

Benefits: We found no systematic review or RCTs.

Harms: We found no systematic review or RCTs.

Comment: The risk of worsening hypotension has led to concern about treating acute cardiogenic shock with any vasodilator.[62]

OPTION PULMONARY ARTERY CATHETERISATION

We found no RCTs comparing pulmonary artery catheterisation versus no catheterisation.

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.[63] Harms such as major arrhythmias, injury to the lung, thromboembolism (see thromboembolism, p 00), and sepsis occur in 0.1–0.5% of people undergoing pulmonary artery catheterisation.[63]

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 myocardial infarction,[64,65] although we found no evidence to confirm or reject this view.

OPTION INTRA-AORTIC BALLOON COUNTERPULSATION

An RCT presented only in abstract form found limited evidence of no significant difference in mortality at 6 months between intra-aortic balloon counterpulsation plus thrombolysis and thrombolysis alone in people with cardiogenic shock.

Benefits: We found no systematic review. We found one abstract of an RCT (57 people), which compared intra-aortic balloon counterpulsation plus thrombolysis versus thrombolysis alone in people with cardiogenic shock after acute myocardial infarction (AMI; see comment below).[66] The RCT found no significant difference in mortality after 6 months (22/57 [39%] with thrombolysis plus balloon counterpulsation *v* 25/57 [43%] with thrombolysis alone; RR 0.90, 95% CI 0.57 to 1.37; P = 0.3).

Harms: Harms were not reported in the abstract of the RCT.[66]

Comment: The abstract did not describe detailed methods for the trial, making interpretation of results difficult.[62] We also found two additional small RCTs (30 people[67] and 20 people[68]), which compared intra-aortic balloon counterpulsation versus standard treatment in people after AMI. Neither RCT specifically recruited or identified data from people with cardiogenic shock after AMI. Neither RCT found a reduction in mortality with intra-aortic balloon counterpulsation. There is consensus that intra-aortic balloon counterpulsation is beneficial in people with cardiogenic shock after AMI. We found no evidence to confirm or reject this view.

OPTION VENTRICULAR ASSISTANCE DEVICES AND CARDIAC TRANSPLANTATION

We found no RCTs evaluating either ventricular assistance devices or cardiac transplantation.

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 myocardial infarction.

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Comment: Reviews of observational studies[1,62,69] and retrospective reports[70,71] 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 RCTs evaluating early surgical intervention for ventricular septal rupture, free wall rupture, or mitral valve regurgitation complicated by cardiogenic shock after acute myocardial infarction.

Benefits: We found no systematic review and no RCTs.

Harms: We found no evidence about the harms of surgery in people with cardiogenic shock caused by cardiac structural defects after acute myocardial infarction.

Comment: 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 24–48 hours.[1,62]

GLOSSARY

Cardiac index A measure of cardiac output derived from the formula: cardiac output/unit time divided by body surface area (L/minute/m^2).
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.
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 half way up the chest; Class III: crackles heard in all the lung fields; Class IV: cardiogenic shock.
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.

Substantive changes

Glycoprotein IIb/IIIa inhibitors (under question on improving outcomes in acute myocardial infarction): One systematic review added,[34] one extended follow up of an already reported RCT added,[33] and two RCTs added;[35,37] categorisation unchanged (trade off between benefits and harms).
Thrombolysis (under question on improving outcomes for cardiogenic shock after acute myocardial infarction): One further analysis of an already reported RCT added,[60] and evidence already reported reassessed; categorisation changed to Unknown effectiveness.

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Acute myocardial infarction

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

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 streptinokinase		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

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.[59] Plus-minus values are ± standard deviation. In all three trials, streptokinase was given in intravenous infusions of 1.5 MU over a period of 1 hour. AMI, acute myocardial infarction; iv, intravenous; tPA, tissue plasminogen activator; sc, subcutaneous. *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] Reproduced with permission from Collins R, Peto R, Baigent BM, et al.

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Aspirin, heparin and fibrinolytic therapy in suspected AMI. *N Engl J Med* 1997;336:847–860. Copyright © 1997 Massachusetts Medical Society. All rights reserved.

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 14).[2,3,58]**

Time after AMI	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[2,58]					
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

AMI, acute myocardial infarction; NA, not applicable.

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Acute myocardial infarction

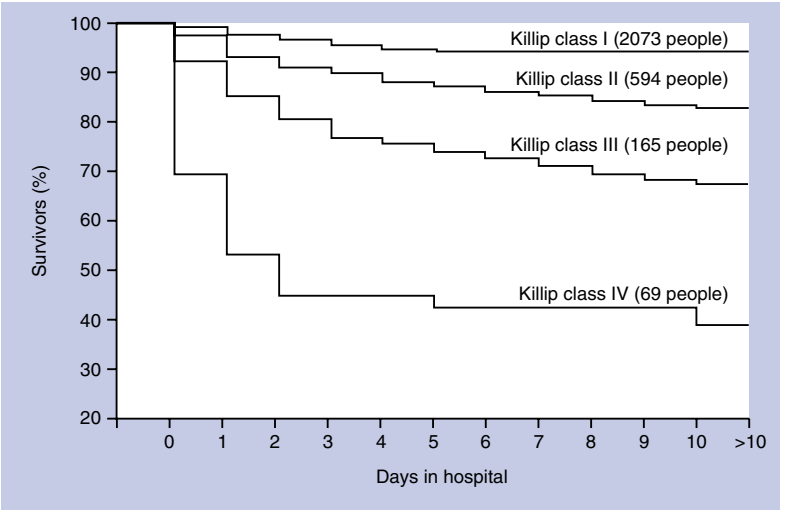

FIGURE 1 **The AMIS registry Kaplan–Meier survival curves as a function of Killip class at hospital admission for 3138 people (2901 evaluable) admitted in 50 Swiss hospitals between 1977 and 1998. Published with permission: Urban P, Bernstein MS, Costanza MC, et al, for the AMIS investigators. An internet-based registry of acute myocardial infarction in Switzerland. *Kardiovasc Med* 2000;3:430–441 (see text, p 3).[9]**

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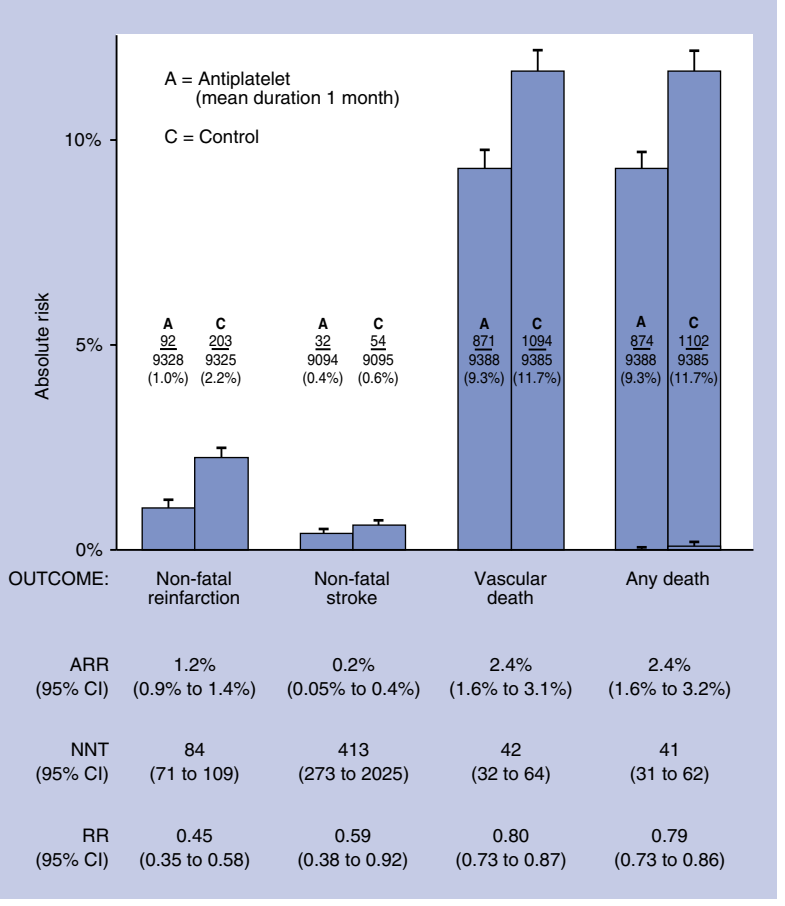

FIGURE 2 **Absolute effects of antiplatelet treatment on outcomes in people with a prior suspected or definite acute myocardial infarction (AMI).[11] The columns show the absolute risks over 1 month for each category; the error bars are the upper 95% confidence interval (CI). In the "any death" column, 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 4). Published with permission.[11]**

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Acute myocardial infarction

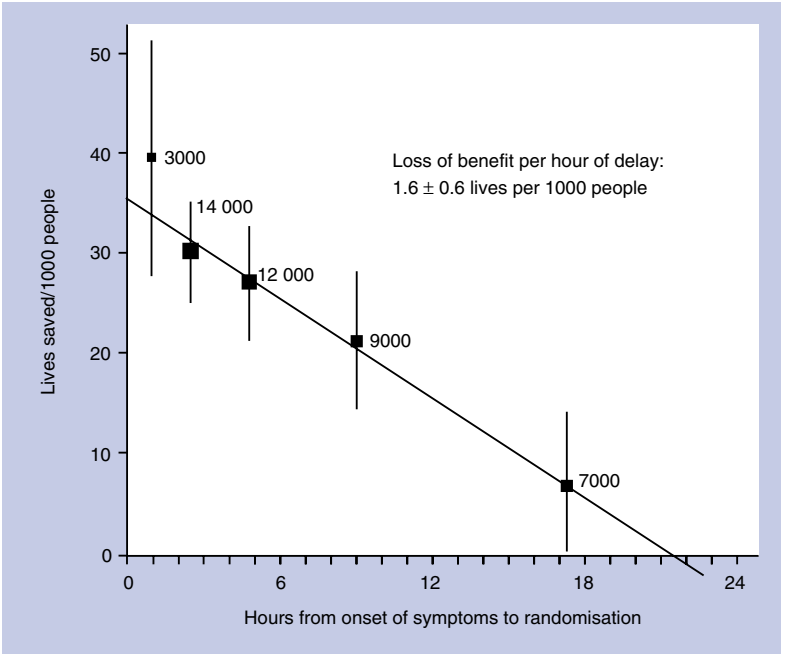

FIGURE 3 **Absolute number of lives saved at 1 month/1000 people receiving thrombolytic treatment plotted against the time from the onset of symptoms to randomisation among 45 000 people with ST segment elevation or bundle branch block.[15] Numbers along the curve are the number of people treated at 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.[17]**

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Angina (stable)

Search date December 2004

Laurence O'Toole

QUESTIONS

INTERVENTIONS

SINGLE DRUG TREATMENT
Likely to be beneficial

To be covered in future updates

Combination and adjunctive anti-anginal drug treatment
Coronary revascularisation treatments
Refractory angina

*Based on consensus
See glossary G

Key Messages

Single drug treatment

- **Beta Blockers*** One small RCT identified by a systematic review found no significant difference between a beta blocker (propranolol) and placebo in angina frequency or exercise duration after 6 months. However, this trial may have lacked power to detect a clinically important difference between groups. There is consensus that beta blockers are effective for treating the symptoms of stable angina. RCTs found no significant difference between beta blockers and calcium channel blockers in the frequency of angina attacks, exercise duration, mortality, or non-fatal cardiovascular events at 6 months to 3 years. However, these RCTs may have lacked power to detect clinically important differences between groups. One RCT also found no significant difference between beta blockers and calcium channel blockers in quality of life. We did not find any systematic reviews or RCTs that compared longer use of beta blockers with long acting nitrates or potassium channel openers.
- **Calcium channel blockers*** One small RCT identified by a systematic review found no significant difference between bepridil and placebo in the frequency of angina attacks. It found that bepridil increased exercise duration compared with placebo at 6 months. There is consensus that calcium channel blockers are effective for treating the symptoms of stable angina. RCTs identified by the review found no significant difference between calcium channel blockers and beta blockers in the frequency of angina attacks, exercise duration, mortality, or non-fatal cardiovascular events at between 6 months and 3 years. However, these RCTs may have lacked power to detect clinically important differences between groups. One RCT also found no significant difference between calcium channel blockers and beta blockers in quality of life. One RCT found no significant difference between amlodipine and isosorbide mononitrate in the frequency of angina attacks or in quality of life. It found that amlodipine increased exercise duration compared with isosorbide mononitrate at 6 months. The RCT found that peripheral oedema was more common with amlodipine than with isosorbide mononitrate, whereas headache was more common with isosorbide mononitrate. We found no systematic review or RCTs that compared long term calcium channel blockers with potassium channel openers.
- **Nitrates*** We found no RCTs comparing long term single drug treatment with nitrates versus placebo for stable angina. However, there is consensus that nitrates are effective for treating the symptoms of stable angina. One RCT found no significant difference between amlodipine and isosorbide mononitrate in the frequency of angina attacks or in quality of life. It found that amlodipine increased exercise duration compared with isosorbide mononitrate at 6 months. The RCT found that peripheral oedema was more common with amlodipine than with isosorbide mononitrate, whereas headache was more common with isosorbide mononitrate.

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Angina (stable)

- **Potassium channel openers*** We found no RCTs on the effects of long term single drug treatment with potassium channel openers for stable angina. However, there is consensus that potassium channel openers are effective for treating the symptoms of stable angina.

*Based on consensus

DEFINITION

Angina pectoris, often simply known as angina, is a clinical syndrome characterised by discomfort in the chest, shoulder, back, arm, or jaw.[1] Angina is usually caused by coronary artery atherosclerotic disease. Rarer causes include valvular heart disease, hypertrophic cardiomyopathy, uncontrolled hypertension, or vasospasm or endothelial dysfunction not related to atherosclerosis. The differential diagnosis of angina includes non-cardiac conditions affecting the chest wall, oesophagus, and lungs. Angina may be classified as stable or unstable. **Stable angina** is defined as regular or predictable angina symptoms that have been occurring for over 2 months. Symptoms are transient and are typically provoked by exertion, and alleviated by rest or nitroglycerin. Other precipitants include cold weather, eating, or emotional distress. This chapter deals specifically with long term treatment of stable angina caused by coronary artery atherosclerotic disease, and therefore, only includes RCTs with a follow up of more than 6 months. **Unstable angina** is diagnosed if there is a rapid decline in exercise capacity or if there are episodes of pain at rest. This is usually associated with atherosclerotic plaque instability and, as myocardial infarction and death may ensue, should be treated as a medical emergency, usually requiring hospital admission (see chapter on unstable angina, p 00).

INCIDENCE/ PREVALENCE

The prevalence of stable angina remains unclear.[1,2] Epidemiological studies in the UK estimate that 6–16% of men and 3–10% of women aged 65–74 years have experienced angina.[3–5] Annually, about 1% of the population visit their general practitioner with symptoms of angina[4] and 23 000 people with new anginal symptoms present to their general practitioner each year in the UK.[6] These studies did not distinguish between stable and unstable angina.[3–6]

AETIOLOGY/ RISK FACTORS

Stable angina resulting from coronary artery disease is characterised by focal atherosclerotic plaques in the intimal layer of the epicardial coronary artery. The plaques encroach on the coronary lumen and may limit blood flow to the myocardium, especially during periods of increased myocardial oxygen demand. The major risk factors that lead to the development of stable angina are similar to those that predispose to coronary heart disease. These risk factors include increasing age, male sex, overweight, hypertension, elevated serum cholesterol level, smoking, and relative physical inactivity.[7]

PROGNOSIS

Stable angina is a marker of underlying coronary heart disease, which accounts for 1 in 4 deaths in the UK.[8] People with angina are 2–5 times more likely to develop other manifestations of coronary heart disease than people who do not have angina.[7,9] One population based study (7100 men aged 51–59 years at entry) found that people with angina had higher mortality than people with no history of coronary artery disease at baseline (16 year survival rate: 53% with angina *v* 72% without coronary artery disease *v* 34% with a history of myocardial infarction).[10] Clinical trials in people with stable angina have tended to recruit participants who were not felt to be in need of coronary revascularisation and in these people prognosis is better, with an annual mortality of 1–2% and annual rate of non-fatal myocardial infarction of 2–3%.[11–14] Features that indicate a poorer prognosis include: more severe symptoms, male sex,[15] abnormal resting electrocardiogram[16] (present in about 50% of people with angina [17]), previous myocardial infarction,[10,18] left ventricular dysfunction,[19] easily provoked or widespread coronary ischaemia on stress testing (present in about one third of people referred to hospital with stable angina), and significant stenosis of all three major coronary arteries or the left main coronary artery.[6,19] In addition, the standard coronary risk factors continue to exert a detrimental and additive effect on prognosis in people with stable angina.[9,20,21] Control of these risk factors is dealt with in the *Clinical Evidence* chapter on secondary prevention of ischaemic cardiac events, p 01.

AIMS OF INTERVENTION

To prevent death and future cardiovascular events, and to improve symptoms, exercise capacity, and quality of life.

OUTCOMES

Primary outcomes: mortality, non-fatal myocardial infarction, and unstable angina. **Secondary outcomes:** anti-anginal efficacy (as determined by symptom frequency and total exercise time on treadmill testing), quality of life (assessed by questionnaire), and adverse effects of treatment.

METHODS

Clinical Evidence search and appraisal December 2004. The search was limited to RCTs with at least 6 months of follow up, which compared single drug anti-anginal treatment versus placebo or another single drug anti-anginal treatment, in people with stable angina believed to be caused by coronary artery atherosclerotic disease. All RCTs with a follow up of less than 6 months and with a population of less than 50 were excluded. The anti-anginal drug classes covered by the search were beta blockers, calcium channel blockers, long acting nitrate preparations, and potassium channel openers. We excluded RCTs where participants received combinations of anti-anginal drugs. Combination anti-anginal treatment will be dealt with in future updates.

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QUESTION What are the effects of long term single drug treatment for stable angina?

OPTION BETA BLOCKERS

One small RCT identified by a systematic review found no significant difference between a beta blocker (propranolol) and placebo in angina frequency or exercise duration after 6 months. However, this trial may have lacked power to detect a clinically important difference between groups. There is consensus that beta blockers are effective for treating the symptoms of stable angina. RCTs found no significant difference between beta blockers and calcium channel blockers in the frequency of angina attacks, exercise duration, mortality, or non-fatal cardiovascular events at 6 months to 3 years. However, these RCTs may have lacked power to detect clinically important differences between groups. One RCT also found no significant difference between beta blockers and calcium channel blockers in quality of life. We did not find any systematic reviews or RCTs that compared longer use of beta blockers with long acting nitrates or potassium channel openers.

Benefits:

We found one systematic review (search date 1996).[22] **Beta Blockers versus placebo:** The review[22] identified one RCT[23] (191 people aged < 70 years with abnormal exercise stress test G or previous myocardial infarction). It compared three treatments: beta blocker (propranolol; 78 people), calcium channel blocker (bepridil; 78 people), and placebo (35 people). It found no significant difference between propranolol and placebo in the reduction in frequency of angina attacks or improvement in duration of exercise at 6 months (mean reduction in weekly angina attacks from baseline: 71% with propranolol *v* 77% with placebo; P reported as not significant, increase in exercise duration from baseline: 24% with propranolol *v* 8% with placebo; P = 0.09). Serious cardiac events (cardiac death, myocardial infarction, or angina deterioration) were more common with propranolol than placebo, but the significance of this difference was not reported (AR for serious cardiac events: 8/78 [10.3%] with propranolol *v* 2/35 [5.7%] with placebo; P value not reported) **Beta blockers versus calcium channel blockers:** The systematic review[22] identified five RCTs that met our inclusion criteria (1818 people).[13,23–26] The first RCT (191 people aged < 70 years, with abnormal exercise stress test or previous myocardial infarction),[23] compared three treatments: beta blocker (propranolol 60–240 mg/day; 78 people), calcium channel blocker (bepridil 100–400 mg/day; 78 people), and placebo (35 people). It found no significant difference between propranolol and bepridil in the reduction in the frequency of angina attacks (reduction in weekly angina attacks from baseline: 69% with bepridil *v* 71% with propranolol; P reported as not significant) or improvement in duration of exercise at 6 months; (increase in exercise duration from baseline: 24% with propranolol *v* 31% with bepridil; P = 0.26). The incidence of serious cardiac events (cardiac death, myocardial infarction, or angina deterioration) was similar with propranolol and bepridil (AR for serious cardiac events: 8/78 [10.3%] with propranolol *v* 6/78 [7.7%] for bepridil; P value not reported). The second RCT (80 people aged ≤ 80 years with abnormal exercise stress test)[24] compared nadolol 40–160 mg once daily with amlodipine 2.5–10 mg once daily in people with stable angina. It found no significant difference in the reduction in frequency of angina attacks or change in exercise duration at 6 months (change in median number of angina attacks a week from baseline to 6 months: from 3.0 to 0.3 with nadolol *v* from 4.0 to 0.3 with amlodipine; P reported as not significant; change in total exercise treadmill time from baseline to 6 months: 490 seconds to 475 seconds [–3%] with nadolol *v* 454 seconds to 462 seconds [+2%] with amlodipine; P reported as not significant). The third RCT (56 people aged < 80 years with abnormal exercise stress test) compared metoprolol (100 mg twice daily; 26 people) with diltiazem (120 mg twice daily; 30 people) in people with stable angina.[25] It found no significant difference in the change in exercise capacity between groups at 32 weeks (39 people evaluable: 19 people with metoprolol *v* 20 people with diltiazem; analysis not by intention to treat; mean change in duration of exercise from baseline to 32 weeks: +0.2 minutes with metoprolol *v* +0.3 minutes with diltiazem; P reported as not significant). The effect of treatments on the frequency of angina symptoms was not reported. The fourth RCT (809 people aged < 70 years selected on the basis of typical clinical history and response to nitroglycerin or, if history was not typical, an abnormal stress test) compared a

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Angina (stable)

metoprolol (200 mg once daily) with verapamil (240 mg twice daily).[26] It found no significant difference in either mortality or the combined outcome of mortality or non-fatal cardiovascular event between metoprolol and verapamil after a median follow up of 3.4 years (mortality, AR: 22/406 [5.4%] with metoprolol *v* 25/403 [6.2%] with verapamil; OR 0.87, 95% CI 0.48 to 1.56; combined outcome of mortality or non-fatal cardiovascular event, AR: 128/406 [31.5%] with metoprolol *v* 123/403 [30.5%] with verapamil; OR 1.03, 95% CI 0.84 to 1.30). It also found no significant difference in three quality of life variables between metoprolol and verapamil (Cornell Medical Index psychomatic symptom index, score range 39–195, mean score change: –1.1 with metoprolol *v* –2.2 with verapamil; P = 0.34; overall life satisfaction, score range 0–120, mean score change: –3.0 with metoprolol *v* –2.5 with verapamil; P = 0.85; sleep disturbances, score range 9–36, mean score change: –0.7 with both treatments: P = 0.97). The fifth RCT (682 people with stable angina who were not immediately being considered for coronary revascularisation) compared three treatments: atenolol (50 mg twice daily), nifedipine (20 or 40 mg twice daily as tolerated), and atenolol plus nifedipine.[13] It found no significant difference between atenolol alone and nifedipine alone in the combined outcome of mortality, myocardial infarction, or unstable angina, after a mean follow up of 2 years (AR for combined death, myocardial infarction, or unstable angina: 29/226 [12.8%] with atenolol *v* 25/232 [10.8%] with nifedipine; log rank P = 0.32). **Beta blockers versus nitrates or potassium channel openers:** We found no systematic review or RCTs.

Harms:

Beta blockers versus placebo: The RCT identified by the review found no significant difference between propranolol and placebo in the proportion of people experiencing at least one non-cardiac adverse effect (AR: 23/78 [29.5%] with propranolol *v* 6/35 [17.1%] with placebo; P = 0.08).[23] There was no significant difference between groups in treatment withdrawal owing to lack of efficacy or severe adverse effects (17/78 [21.8%] with propranolol *v* 6/35 [17.1%] with placebo; P = 0.58).[23] **Beta blockers versus calcium channel blockers:** The first RCT identified by the review found that the proportion of people experiencing at least one non-cardiac adverse event was significantly higher with propranolol than with bepridil (AR for at least 1 non-cardiac adverse event: 23/78 [29.5%] with propranolol *v* 9/78 [11.5%] with bepridil; P = 0.003).[23] This was mostly because of an increased incidence of fatigue in the propranolol group (14/78 [17.9%] with propranolol *v* 6/78 [7.7%] with bepridil; P = 0.05). However, there was no significant difference between groups in treatment withdrawal owing to lack of efficacy or severe adverse effects (17/78 [21.8%] with propranolol *v* 15/78 [19.2%] with bepridil; P = 0.69). The second RCT found that significantly more people taking nadolol experienced adverse effects than people taking amlodipine (AR 33/40 [82.5%] with nadolol *v* 17/40 [42.5%] with amlodipine; P < 0.0001).[24] However, similar numbers of people were withdrawn owing to adverse effects in both groups (4/40 [10.0%] with nadolol *v* 3/40 [7.5%] with amlodipine; P value not reported). The third RCT reported that most adverse events were mild and that there was no significant difference in the incidence of adverse events with metoprolol and diltiazem (figures not reported, P reported as not significant).[25] The fourth RCT found that significantly fewer people withdrew from the study because of gastrointestinal upset with metoprolol than with verapamil (AR 10/406 [2.5%] with metoprolol *v* 22/403 [5.5%] with verapamil; P = 0.029). However, it found no significant difference in overall withdrawal owing to adverse effects between the two treatments (AR: 45/406 [11.1%] with metoprolol *v* 59/403 [14.6%] with verapamil; P = 0.13).[26] The fifth RCT found that, over an average of 2 years' follow up, significantly fewer people discontinued treatment because of adverse effects in the atenolol group than in the nifedipine group (AR: 60/226 [26.5%] with atenolol *v* 93/232 [40.0%] with nifedipine; log rank P = 0.001).[13] **Beta blockers versus nitrates or potassium channel openers:** We found no systematic review or RCTs.

Comment:

There is consensus that beta blockers are effective for treating the symptoms of stable angina. Many of the RCTs included in the review may not have been sufficiently powered to detect a clinically important difference between groups. [22]

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OPTION CALCIUM CHANNEL BLOCKERS

One small RCT identified by a systematic review found no significant difference between bepridil and placebo in the frequency of angina attacks. It found that bepridil increased exercise duration compared with placebo at 6 months. There is consensus that calcium channel blockers are effective for treating the symptoms of stable angina. RCTs identified by the review found no significant difference between calcium channel blockers and beta blockers in the frequency of angina attacks, exercise duration, mortality, or non-fatal cardiovascular events at between 6 months and 3 years. However, these RCTs may have lacked power to detect clinically important differences between groups. One RCT also found no significant difference between calcium channel blockers and beta blockers in quality of life. One RCT found no significant difference between amlodipine and isosorbide mononitrate in the frequency of angina attacks or in quality of life. It found that amlodipine increased exercise duration compared with isosorbide mononitrate at 6 months. The RCT found that peripheral oedema was more common with amlodipine than with isosorbide mononitrate, whereas headache was more common with isosorbide mononitrate. We found no systematic review or RCTs that compared long term calcium channel blockers with potassium channel openers.

Benefits:

We found one systematic review (search date 1996).[22] **Calcium channel blockers versus placebo:** The review[22] identified one RCT (191 people aged < 70 years with abnormal exercise stress test Ⓔ or previous myocardial infarction).[23] It compared three treatments: calcium channel blocker (bepridil; 78 people), beta blocker (propranolol; 78 people), and placebo (35 people). It found no significant difference between bepridil and placebo in the reduction in frequency of angina attacks at 6 months (mean reduction in weekly angina attacks from baseline: 69% with bepridil *v* 77% with placebo; P reported as not significant). It found that bepridil significantly increased duration of exercise compared with placebo at 6 months (increase in exercise duration from baseline: 31% with bepridil *v* 8% with placebo; P = 0.03). It found that the rate of serious cardiac events (defined as death, myocardial infarction, or unstable angina) was higher with bepridil than placebo, but the significance of this difference was not reported (AR for major cardiac events: 6/78 [7.7%] with bepridil *v* 2/35 [5.7%] with placebo; P value not reported). **Calcium channel blockers versus beta blockers:** See benefits of beta blockers versus calcium channel blockers, p 3. **Calcium channel blockers versus nitrates:** The systematic review did not find any RCTs.[22] We found one subsequent RCT (196 people, aged ≥ 65 years with an abnormal exercise stress test) comparing amlodipine (5–10 mg once daily) versus isosorbide mononitrate (25–50 mg once daily).[27] It found no significant difference either in the number of weekly anginal attacks or in quality of life (assessed using the short form-36 [SF-36] questionnaire Ⓔ between amlodipine and isosorbide mononitrate at 6 months (median weekly number of angina attacks: 0 for both groups; ; mean improvement in SF-36 bodily pains scale score from baseline: about 5 for both groups; mean improvement in SF-36 health transition score from baseline: about 11 for both groups; all differences reported as not significant). It found a significant improvement in exercise duration with amlodipine compared with isosorbide mononitrate at 6 months (mean change in exercise duration from baseline to 6 months: from 436 seconds to 548 seconds [+112 seconds] with amlodipine *v* from 462 seconds to 494 seconds [+32 seconds] with isosorbide mononitrate; P = 0.016). **Calcium channel blockers versus potassium channel openers:** We found no systematic review or RCTs.

Harms:

Calcium channel blockers versus placebo: The RCT found no significant difference between bepridil and placebo in the proportion of people experiencing at least one non-cardiac adverse effect at 6 months (AR: 9/78 [11.5%] with bepridil *v* 6/35 [17.1%] with placebo; P = 0.22).[23] **Calcium channel blockers versus beta blockers:** See harms of beta blockers versus calcium channel blockers, p 4. **Calcium channel blockers versus nitrates:** The RCT found no significant difference between amlodipine and isosorbide mononitrate in the proportion of people reporting any adverse event at 6 months: (AR: 58% with amlodipine *v* 53% with isosorbide mononitrate; reported as not significant). The proportion of people with serious adverse effects was also similar in both groups (AR: about 7% in both groups; P value not reported, significance assessment not performed).[27] About 8% of people in the amlodipine group and 18% of people

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in the isosorbide mononitrate group discontinued the study because of adverse events (significance assessment not performed). Only two withdrawals (2%; both owing to oedema) in the amlodipine group and seven withdrawals (7.3%; all owing to headache) in the isosorbide mononitrate group were considered to be treatment related (significance assessment not performed). The RCT found that peripheral oedema was more common with amlodipine than with isosorbide mononitrate (AR: 14% with amlodipine *v* 0% with isosorbide mononitrate), whereas headache was more common with isosorbide mononitrate than with amlodipine (AR: 13% with isosorbide mononitrate *v* 2% with amlodipine; P value not reported for either comparison). **Calcium channel blockers versus potassium channel openers:** We found no systematic review or RCTs.

Comment: There is consensus that calcium channel blockers are effective for treating the symptoms of stable angina.

OPTION NITRATES

We found no RCTs comparing long term single drug treatment with nitrates versus placebo for stable angina. However, there is consensus that nitrates are effective for treating the symptoms of stable angina. One RCT found no significant difference between amlodipine and isosorbide mononitrate in the frequency of angina attacks or in quality of life. It found that amlodipine increased exercise duration compared with isosorbide mononitrate at 6 months. The RCT found that peripheral oedema was more common with amlodipine than with isosorbide mononitrate, whereas headache was more common with isosorbide mononitrate.

Benefits: **Nitrates versus placebo, beta blockers, or potassium channel openers:** We found no systematic review or RCTs (see comment below). **Nitrates versus calcium channel blockers:** See benefits of calcium channel blockers versus nitrates, p 5.

Harms: **Nitrates versus placebo, beta blockers, or potassium channel openers:** We found no systematic review or RCTs. **Nitrates versus calcium channel blockers:** See harms of calcium channel blockers versus nitrates, p 5.

Comment: There is consensus that nitrates are effective for treating the symptoms of stable angina.

OPTION POTASSIUM CHANNEL OPENERS

We found no RCTs on the effects of long term single drug treatment with potassium channel openers for stable angina. However, there is consensus that potassium channel openers are effective for treating the symptoms of stable angina.

Benefits: **Potassium channel openers versus placebo, beta blockers, calcium channel blockers, or nitrates:** We found no systematic review or RCTs (see comment below).

Harms: **Potassium channel openers versus placebo, beta blockers, calcium channel blockers, or nitrates:** We found no systematic review or RCTs.

Comment: There is consensus that potassium channel openers are effective for treating the symptoms of stable angina.

GLOSSARY

Exercise stress testing is widely used in the evaluation of people with chest pain. The person walks on a treadmill, the speed and slope of which is varied according to protocol, while being monitored by electrocardiogram. Exercise induced horizontal or down-sloping ST segment depression is strongly suggestive of myocardial ischaemia, particularly when associated with typical chest pain. ST segment depression at a low workload usually indicates severe coronary artery disease, as may exercise induced ventricular arrhythmia or a fall in blood pressure.

SF-36 Short form-36 questionnaire is a generic quality of life assessment tool which is well documented as reproducible and sensitive. It includes 36 questions over nine domains/areas which are converted to an overall score from 0 to 100.

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Competing interests: LOT has attended international cardiological conferences as a guest of a number of pharmaceutical companies. He has been paid by Novartis and Pfizer for running educational programmes and has recieved research funds from Sanofi-Synthelabo.

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Angina (unstable)

Search date March 2004

Madhu Natarajan

QUESTIONS

INTERVENTIONS

See glossary

Key Messages

Antiplatelets

- **Aspirin** One systematic review found that antiplatelet treatment, mostly medium dose aspirin 75–325 mg/day, reduced the risk of death, myocardial infarction, and stroke compared with placebo in people with unstable angina. The evidence suggested no added cardiovascular benefit, and possible added harm, from doses of aspirin over 325 mg daily.
- **Clopidogrel/ticlopidine** Two RCTs found that adding clopidogrel to aspirin or ticlopidine to conventional treatment reduced mortality and myocardial infarction compared with aspirin alone or conventional treatment alone. One of the RCTs found that adding clopidogrel to aspirin increased major bleeding, but not haemorrhagic strokes, compared with aspirin alone after 6–9 months. Ticlopidine may cause reversible neutropenia. These drugs may be an alternative in people who are intolerant of or allergic to aspirin.
- **Intravenous glycoprotein IIb/IIIa inhibitors** One systematic review found that intravenous glycoprotein IIb/IIIa inhibitors reduced death or myocardial infarction at up to 6 months compared with placebo, but increased major bleeding complications. Longer term follow up of one of the RCTs included in the review found no significant difference between abciximab and placebo in mortality at 1 year.
- **Oral glycoprotein IIb/IIIa inhibitors** One RCT identified by a systematic review found that the oral glycoprotein IIb/IIIa inhibitor sibrafiban did not significantly reduce the combined outcome of death, myocardial infarction, or recurrent ischaemia compared with aspirin at 90 days. However, the review found that oral glycoprotein IIb/IIIa inhibitors with or without aspirin increased bleeding compared with aspirin alone.

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Angina (unstable)

Antithrombin treatments

- **Direct thrombin inhibitors** One systematic review found that treatment with direct thrombin inhibitors for 7 days reduced death and myocardial infarction compared with heparin after 30 days.
- **Low molecular weight heparin** One systematic review in people taking aspirin found that adding low molecular weight heparin reduced death and myocardial infarction, and did not significantly increase bleeding complications in the first 7 days after unstable angina compared with adding placebo or no treatment. However, it found that longer term treatment with low molecular weight heparin (up to 90 days) did not significantly reduce death or myocardial infarction after 90 days compared with placebo. One systematic review found that low molecular weight heparin reduced myocardial infarction but not mortality, recurrent angina, or major bleeding compared with unfractionated heparin.
- **Unfractionated heparin** One systematic review found that adding unfractionated heparin to aspirin for 7 days in people with unstable angina reduced death or myocardial infarction at 1 week. However, a second review found no significant effect on death or myocardial infarction after 12 weeks. One systematic review found that unfractionated heparin was less effective than low molecular weight heparin at reducing myocardial infarction, but found no significant difference between treatments in mortality, recurrent angina or major bleeding.
- **Warfarin** Five RCTs found no significant effect of adding warfarin to usual treatment (usually aspirin) for recurrent angina, myocardial infarction, or death at up to 1 year. One of the RCTs found that warfarin was associated with an increase in major bleeding compared with usual treatment alone.

Anti-ischaemic treatments

- **Beta-blockers (for myocardial infarction or death)** We found insufficient evidence on the effects of beta-blockers on mortality or myocardial infarction, although one RCT suggested that beta-blockers may reduce the frequency and severity of chest pain.
- **Nitrates (for myocardial infarction or death)** We found insufficient evidence on the effects of nitrates on mortality or myocardial infarction, although RCTs suggested that nitrates may reduce the frequency and severity of chest pain.
- **Calcium channel blockers** One systematic review found no significant difference between calcium channel blockers and either placebo or standard treatment in mortality or myocardial infarction. Observational studies suggest that short acting dihydropyridine calcium channel blockers may increase mortality.

Invasive treatments

- **Routine early cardiac catheterisation and revascularisation** We found five RCTs that reported on different composite outcomes at different time points. Two RCTs found that early invasive treatment reduced death and other cardiac events or hospital readmission compared with conservative treatment at 4–6 months. However, three RCTs found no significant difference in death or other cardiac events between early invasive treatment and conservative treatment at 12 or more months.

DEFINITION	Unstable angina is distinguished from stable angina, acute myocardial infarction, and non-cardiac pain by the pattern of symptoms (characteristic pain present at rest or on lower levels of activity), the severity of symptoms (recently increasing intensity, frequency, or duration), and the absence of persistent ST segment elevation on a resting electrocardiogram. Unstable angina includes a variety of different clinical patterns: angina at rest of up to 1 week of duration; angina increasing in severity to moderate or severe pain; non-Q wave myocardial infarction; and post-myocardial infarction angina continuing for longer than 24 hours. Unstable angina and non-ST segment elevation myocardial infarction (non-STEMI) are clinically overlapping entities in terms of diagnosis and treatment strategies. Unstable angina, broadly defined as new or persistent chest pain, becomes classified as non-STEMI if in addition to chest pain there is elevation of cardiac enzymes, such as troponin, or persistent ST depression on electrocardiogram. Many trials include people with either unstable angina or non-STEMI. We have included RCTs in a mixed population of people with unstable angina or non-STEMI, as well as RCTs solely in people with unstable angina.
INCIDENCE/ PREVALENCE	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 cardiovascular disease, diabetes mellitus, smoking cigarettes, hypertension, hypercholesterolaemia, male sex, and a family history of ischaemic heart disease (see Appendix 1). Unstable angina can also occur in association with other disorders of the circulation, including heart valve disease, arrhythmia, and cardiomyopathy.

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Angina (unstable)

PROGNOSIS

In people with unstable angina taking aspirin, the incidence of serious adverse outcomes (such as death, acute myocardial infarction, or refractory angina requiring emergency revascularisation) is 5–10% within the first 7 days and about 15% at 30 days. Between 5% and 14% of people with unstable angina die in the year after diagnosis, with about half of these deaths occurring within 4 weeks of diagnosis. No single factor identifies people at higher risk of an adverse event. Risk factors include severity of presentation (e.g. duration of pain, speed of progression, evidence of heart failure), medical history (e.g. previous unstable angina, acute myocardial infarction, left ventricular dysfunction), other clinical parameters (e.g. age, diabetes), electrocardiogram changes (e.g. severity of ST segment depression, deep T wave inversion, transient ST segment elevation), biochemical parameters (e.g. troponin concentration), and change in clinical status (e.g. recurrent chest pain, silent ischaemia, haemodynamic instability).

AIMS OF INTERVENTION

To relieve pain and ischaemia; to prevent death and myocardial infarction; 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, myocardial infarction, and recurrent ischaemia after discharge from hospital, with minimum adverse effects.

OUTCOMES

Rate of death or myocardial infarction (often measured at 2, 7, and 30 days, and 6 months after randomisation); and adverse effects of treatment. Some RCTs include rates of refractory ischaemia or readmission for unstable angina.

METHODS

Clinical Evidence search and appraisal March 2004.

QUESTION What are the effects of antiplatelet treatments?

OPTION ASPIRIN

One systematic review found that antiplatelet treatment, mostly medium dose aspirin 75–325 mg/day, reduced the risk of death, myocardial infarction, and stroke compared with placebo in people with unstable angina. The evidence suggested no added cardiovascular benefit, and possible added harm, from doses of aspirin over 325 mg daily.

Benefits:

One systematic review (search date 1997, 287 RCTs, 135 000 people at high risk of vascular events) compared antiplatelet treatment versus placebo.[1] Twelve of these trials included a total of 5031 people with unstable angina. The review found that, in people with unstable angina, antiplatelet treatment (mostly medium dose aspirin, 75–325 mg/day) reduced the combined outcome of vascular death, myocardial infarction, or stroke at up to 12 months compared with placebo (AR 199/2497 [8%] with antiplatelet treatment *v* 336/2534 [13%] with placebo; OR 0.54, 95% CI showing significance displayed graphically; $P < 0.0001$). Individual trials within the systematic review found consistent benefit from daily aspirin in terms of reduced deaths and myocardial infarction.

Harms:

Overall, the review found no increase in non-vascular mortality with antiplatelet treatment compared with 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). There was an increase in major extracranial bleeding with antiplatelet treatment 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).[1] The review concluded that the sum of the evidence suggests no added cardiovascular benefit, and greater incidence of adverse effects, for aspirin doses greater than 325 mg daily. Some people are allergic to aspirin.

Comment:

People with unstable angina who are allergic or who do not respond to aspirin will need alternative antiplatelet treatment.

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Angina (unstable)

OPTION CLOPIDOGREL/TICLOPIDINE

Two RCTs found that adding clopidogrel to aspirin or ticlopidine to conventional treatment reduced mortality and myocardial infarction compared with aspirin alone or conventional treatment alone. One of the RCTs found that adding clopidogrel to aspirin increased major bleeding, but not haemorrhagic strokes, compared with aspirin alone after 6–9 months. Ticlopidine may cause reversible neutropenia. These drugs may be an alternative in people who are intolerant of or allergic to aspirin.

Benefits: We found no systematic review. We found two RCTs comparing clopidogrel or ticlopidine versus placebo or conventional treatment.[2,3] The first RCT (12 562 people) compared clopidogrel (300 mg orally within 24 hours of onset of symptoms followed by 75 mg/day) versus placebo.[2] All participants received aspirin (75–325 mg daily). It found that clopidogrel significantly reduced the combined outcome of death, myocardial infarction, and stroke after 9 months compared with placebo (AR 9% with clopidogrel *v* 11% with placebo; OR 0.8, 95% CI 0.7 to 0.9; see comment). The second RCT (652 people) found that ticlopidine plus conventional treatment significantly reduced the combined outcome of vascular deaths and myocardial infarction after 6 months compared with conventional treatment alone (RR 0.5, 95% CI 0.2 to 0.9; NNT 16, 95% CI 9 to 62).[3]

Harms: In the first RCT, adding clopidogrel to aspirin increased major bleeding complications compared with adding placebo, but not haemorrhagic strokes (major bleeding 3.7% with clopidogrel *v* 2.7% with placebo; RR 1.4, 95% CI 1.1 to 1.7; haemorrhagic stroke 0.1% with clopidogrel *v* 0.1% with placebo).[2] Post-hoc subgroup analysis of this RCT showed increasing aspirin dose increased the risk of major bleeding, with little corresponding reduction in cardiovascular risk.[4] The study concluded that the optimum daily dose of aspirin for use in combination with clopidogrel was 75–100 mg. One systematic review (search date 2002) of RCTs of antiplatelet agents for different indications, including unstable angina, found that the weighted mean rate of major bleeding with ticlopidine or clopidogrel was 2.1% (95% CI 1.9% to 2.3%; 8 RCTs, 18 574 people) and the rate of minor bleeding was 5.1% (95% CI 4.6% to 5.7%; 1 RCT, 6259 people).[5] Reversible neutropenia has been reported in 1–2% of people taking ticlopidine. Clopidogrel and ticlopidine are also associated with other adverse effects, including diarrhoea and rash.

Comment: Post-hoc subgroup analysis of the first RCT found that the reduction in death, myocardial infarction, and stroke with clopidogrel was seen across all risk groups (low, medium, and high, as classified by Thrombolysis In Myocardial Infarction [TIMI] risk score) of unstable angina.[6]

OPTION INTRAVENOUS GLYCOPROTEIN IIB/IIIA PLATELET RECEPTOR INHIBITORS

One systematic review found that intravenous glycoprotein IIb/IIIa inhibitors reduced death or myocardial infarction at up to 6 months compared with placebo, but increased major bleeding complications. Longer term follow up of one of the RCTs included in the review found no significant difference between abciximab and placebo in mortality at 1 year.

Benefits: We found one systematic review (search date 2001, 8 RCTs, 30 006 people) comparing intravenous glycoprotein IIb/IIIa inhibitors (abciximab, eptifibatide, lamifiban, and tirofiban) versus placebo.[7] It found that intravenous glycoprotein IIb/IIIa inhibitors significantly reduced the combined outcome of death and myocardial infarction at 30 days and 6 months compared with placebo (at 30 days: 8 RCTs, AR 10.8% with inhibitors *v* 11.8% with placebo; RR 0.92, 95% CI 0.87 to 0.99; at 6 months: 4 RCTs, 18 538 people, AR 13.3% with inhibitors *v* 14.6% with placebo; RR 0.92, 95% CI 0.83 to 0.96).[7] Longer term follow up of one of the RCTs (7800 people) included in the review found no significant difference between abciximab (24 or 48 hour infusion) and placebo in mortality at 1 year (AR 9.0% with 48 hour abciximab infusion *v* 8.2% with 24 hour abciximab infusion *v* 7.8% with placebo; 48 hour abciximab *v* placebo HR 1.20, 95% CI 0.95 to 1.41; 24 hour abciximab *v* placebo HR 1.10, 95% CI 0.86 to 1.29).[8]

Harms: The systematic review found that intravenous glycoprotein IIb/IIIa inhibitors (abciximab, eptifibatide, lamifiban, and tirofiban) increased major bleeding complications at 30 days compared with placebo (8 RCTs, 29 920 people, AR 4.2% with inhibitors *v* 3.2% with placebo; RR 1.24, 95% CI 1.11 to 1.39).[7]

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Comment: One small trial found limited evidence that in people receiving standard treatment, a "dose ceiling" may exist, beyond which dose escalation of added glycoprotein IIb/IIIa inhibitor increases bleeding complications with no increase in efficacy.[9] A second systematic review (search date 2001; 6 RCTs, all identified by the first systematic review;[7] 29 570 people) conducted subgroup analysis according to whether surgical treatment was received during the index hospitalisation.[10] It suggested that the reduction in mortality and myocardial infarction with intravenous glycoprotein IIb/IIIa inhibitors was restricted to people who received percutaneous coronary intervention during the index hospitalisation, rather than those who received medical management only (6337 people received percutaneous coronary intervention, AR 10.7% with inhibitors *v* 12.7% with placebo; OR 0.82, 95% CI 0.71 to 0.96; 20 054 people received medical management, AR 9.3% with inhibitors *v* 9.7% with placebo; OR 0.95, 95% CI 0.86 to 1.04).

OPTION ORAL GLYCOPROTEIN IIB/IIIA PLATELET RECEPTOR INHIBITORS

One RCT identified by a systematic review found that the oral glycoprotein IIb/IIIa inhibitor sibrafiban did not significantly reduce the combined outcome of death, myocardial infarction, or recurrent ischaemia compared with aspirin at 90 days. However, the review found that oral glycoprotein IIb/IIIa inhibitors with or without aspirin increased bleeding compared with aspirin alone.

Benefits: We found one systematic review (search date 2000, 4 RCTs, 26 462 people) comparing oral glycoprotein IIb/IIIa inhibitors with or without aspirin versus aspirin alone.[9] Three of the RCTs were reported as abstracts only (see comment below). The fully published RCT (9233 people) identified by the review[9] found that sibrafiban (low or high dose) did not reduce the combined outcome of death, myocardial infarction, and severe ischaemia compared with aspirin alone after 90 days (AR 10.1% with high dose sibrafiban *v* 10.1% with low dose sibrafiban *v* 9.8% with aspirin; sibrafiban low or high dose *v* aspirin: OR 1.03, 95% CI 0.87 to 1.21).[11]

Harms: The fully reported RCT identified by the review[9] found that sibrafiban significantly increased bleeding compared with aspirin (AR for any bleeding episode 27.3% with low dose sibrafiban *v* 36.2% with high dose sibrafiban *v* 18.5% with aspirin; low dose sibrafiban *v* aspirin OR 1.65, 95% CI 1.46 to 1.86; high dose sibrafiban *v* aspirin OR 2.49, 95% CI 2.21 to 2.80).[11]

Comment: The first RCT identified by the review in abstract form compared sibrafiban plus aspirin versus placebo plus aspirin and was stopped early after the fully reported RCT[11] found no benefit with sibrafiban.[9] The second RCT reported in abstract form, which compared adding high dose orbofiban, tapering dose orbofiban, or placebo to aspirin was stopped early because adding orbofiban increased mortality at 30 days and also increased bleeding.[9] The third RCT reported in abstract form compared adding different doses of lefradafiban or placebo to aspirin plus heparin, and stopped recruiting to the high dose lefradafiban group because of increased bleeding.[9]

QUESTION What are the effects of antithrombin treatments?

OPTION UNFRACTIONATED HEPARIN

One systematic review found that adding unfractionated heparin to aspirin for 7 days in people with unstable angina reduced death or myocardial infarction at 1 week. However, a second review found no significant effect on death or myocardial infarction after 12 weeks. One systematic review found that unfractionated heparin was less effective than low molecular weight heparin at reducing myocardial infarction, but found no significant difference between treatments in mortality, recurrent angina or major bleeding.

Benefits: **Versus no heparin:** We found two systematic reviews (search dates 1995[12] and not stated[13]), which examined outcomes at different time points (7 days and 12 weeks). Both included the same six RCTs in 1353 people with unstable angina who were treated

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Angina (unstable)

with either unfractionated heparin plus aspirin or aspirin alone for 2–7 days. The first review found that unfractionated heparin plus aspirin reduced the risk of death or myocardial infarction after 7 days compared with aspirin alone (AR 55/698 [7.9%] with unfractionated heparin plus aspirin *v* 68/655 [10.4%] with aspirin alone; OR 0.67, 95% CI 0.45 to 0.99).[13] The second review found that heparin plus aspirin did not reduce death or myocardial infarction after 12 weeks compared with aspirin alone (AR 12% with unfractionated heparin plus aspirin *v* 14% with aspirin; RR 0.82, 95% CI 0.56 to 1.20).[12] **Versus low molecular weight heparin:** See benefits of low molecular weight heparin, p 6.

Harms: The second systematic review found that adding unfractionated heparin to aspirin did not significantly increase major bleeding compared with aspirin alone (AR 1.5% with unfractionated heparin plus aspirin *v* 0.4% with aspirin; RR 1.99, 95% CI 0.52 to 7.65).[12] **Versus low molecular weight heparin:** See harms of low molecular weight heparin, p 6.

Comment: None.

OPTION **LOW MOLECULAR WEIGHT HEPARIN**

One systematic review in people taking aspirin found that adding low molecular weight heparin reduced death and myocardial infarction, and did not significantly increase bleeding complications in the first 7 days after unstable angina compared with adding placebo or no treatment. However, it found that longer term treatment with low molecular weight heparin (up to 90 days) did not significantly reduce death or myocardial infarction after 90 days compared with placebo. One systematic review found that low molecular weight heparin reduced myocardial infarction but not mortality, recurrent angina, or major bleeding compared with unfractionated heparin.

Benefits: **Versus no heparin:** We found one systematic review (search date not stated, 7 RCTs) comparing low molecular weight heparin (LMWH) versus placebo or no heparin treatment.[13] The systematic review found two RCTs (1639 people already taking aspirin) comparing adding short term LMWH (≤ 7 days) versus no added heparin or adding placebo. It found that short term LMWH reduced death and myocardial infarction compared with no heparin or placebo during treatment (AR 13/809 [1.6%] with short term LMWH *v* 43/830 [5.2%] with placebo; OR 0.34, 95% CI 0.20 to 0.58). The systematic review found five RCTs (12 099 people) comparing longer term LMWH (> 7 days but ≤ 90 days) versus placebo. It found that LMWH did not reduce death or myocardial infarction after 90 days compared with placebo (AR 228/5453 [4.2%] with longer term LMWH *v* 257/6646 [3.9%] with placebo; OR 0.98, 95% CI 0.81 to 1.17). **Versus unfractionated heparin:** We found one systematic review (search date 2000; 7 RCTs, 11 092 people with unstable angina or non-ST segment elevation myocardial infarction), which compared LMWH versus unfractionated heparin.[14] It found no significant difference between treatments in mortality or recurrent angina (mortality: AR 150/5580 [2.8%] with LMWH *v* 155/5512 [2.8%] with unfractionated heparin; RR 1.0, 95% CI 0.69 to 1.44; recurrent angina, 6 RCTs, 7209 people: 516/3642 [14.2%] with LMWH *v* 576/3576 [16.1%] with unfractionated heparin; RR 0.83, 95% CI 0.68 to 1.02). However, it found that LWMH significantly reduced myocardial infarction compared with unfractionated heparin (AR 233/5580 [4.2%] with LMWH *v* 276/5512 [5.0%] with unfractionated heparin; RR 0.83, 95% CI 0.70 to 0.99).

Harms: **Versus placebo or no heparin treatment:** Short term LMWH did not significantly increase major bleeding compared with placebo or no treatment (OR 1.48, 95% CI 0.45 to 4.84). However, long term LMWH significantly increased the risk of major bleeding compared with placebo or no treatment (OR 2.26, 95% CI 1.63 to 3.14); equivalent to an excess of 12 bleeds for every 1000 people treated.[13] **Versus unfractionated heparin:** The systematic review found no significant difference between LMWH and unfractionated heparin in major bleeds (AR 156/5550 [2.8%] with LMWH *v* 153/5472 [2.8%] with unfractionated heparin; RR 1.0, 95% CI 0.80 to 1.24).[14] (see harms of unfractionated heparin, p 6).

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Comment: LMWH may be more attractive than unfractionated heparin for routine short term use because coagulation monitoring is not required and it can be self administered after discharge.

OPTION DIRECT THROMBIN INHIBITORS

One systematic review found that treatment with direct thrombin inhibitors for 7 days reduced death and myocardial infarction compared with heparin after 30 days.

Benefits: We found one systematic review (search date not stated, 11 RCTs, 35 070 people) comparing 7 days' treatment with direct thrombin inhibitors (hirudin, argatroban, bivalirudin, efegatran, inogatran) versus heparin.[15] It found that direct thrombin inhibitors reduced the combined outcome of death or myocardial infarction compared with heparin after 30 days (AR 7.4% with direct thrombin inhibitors *v* 8.2% with heparin; RR 0.91, 95% CI 0.84 to 0.99).

Harms: The systematic review found that direct thrombin inhibitors reduced major bleeding during treatment compared with heparin (AR 1.9% with direct thrombin inhibitors *v* 2.3% with heparin; OR 0.75, 95% CI 0.65 to 0.87), but found no significant difference in the risk of stroke at 30 days (AR 0.6% with direct thrombin inhibitors *v* 0.6% with heparin; OR 1.01, 95% CI 0.78 to 1.31).[15]

Comment: None.

OPTION WARFARIN

Five RCTs found no significant effect of adding warfarin to usual treatment (usually aspirin) for recurrent angina, myocardial infarction, or death at up to 1 year. One of the RCTs found that warfarin was associated with an increase in major bleeding compared with usual treatment alone.

Benefits: We found no systematic review. We found five RCTs comparing warfarin plus usual treatment versus usual treatment alone.[16–19] Two of the RCTs were reported in the same journal article.[17] The first RCT (214 people) compared warfarin plus aspirin versus aspirin alone.[16] It found that warfarin (target international normalised ratio Ⓖ 2.0–2.5) plus aspirin reduced the combined outcome of recurrent angina, myocardial infarction, or death after 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.[17] It found no significant difference between warfarin plus aspirin and aspirin alone in the combined outcome of refractory angina, myocardial infarction, or death after 6 months (AR 7% with warfarin plus aspirin *v* 4% with aspirin alone; RR 1.66, 95% CI 0.62 to 4.44).[17] The third RCT (197 people) compared warfarin (target international normalised ratio 2.0–2.5) plus aspirin versus aspirin alone.[17] It found no significant difference between treatments in the combined outcome of refractory angina, myocardial infarction, and death after 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 international normalised ratio 2.0–2.5) to standard treatment versus standard treatment alone.[18] 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 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, myocardial infarction, and stroke after 5 months (8% with warfarin *v* 8% with standard treatment alone; RR 0.90, 95% CI 0.72 to 1.14).[18] The fifth RCT (135 people with prior coronary artery bypass grafts) compared warfarin plus aspirin, warfarin plus placebo, and aspirin plus placebo.[19] It found no significant difference between treatments in the combined outcome of death, myocardial infarction, 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 three treatment groups).[19]

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Angina (unstable)

Harms: In the fourth RCT, adding warfarin to standard treatment increased major bleeding compared with standard treatment alone (AR 2.7% with warfarin plus standard treatment *v* 1.3% with standard treatment alone; RR 1.99, 95% CI 1.23 to 3.22; NNH 71; CI not provided).[18]

Comment: None.

QUESTION **What are the effects of anti-ischaemic treatments?**

OPTION **NITRATES, BETA-BLOCKERS, AND CALCIUM CHANNEL BLOCKERS**

We found insufficient evidence on the effects of nitrates and beta-blockers on mortality or myocardial infarction, although RCTs suggested that these interventions may reduce the frequency and severity of chest pain. One systematic review found no significant difference between calcium channel blockers and either placebo or standard treatment in mortality or myocardial infarction. Observational studies suggest that short acting dihydropyridine calcium channel blockers may increase mortality in people with coronary heart disease.

Benefits: We found no systematic review. **Nitrates:** We found two RCTs.[20,21] The first RCT (162 people) compared intravenous glyceryl trinitrate versus placebo for 48 hours.[20] 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 within 6 months of percutaneous transluminal coronary angioplasty) compared intravenous glyceryl trinitrate alone, heparin alone, glyceryl trinitrate plus heparin, and placebo.[21] 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 42.6% with glyceryl trinitrate alone *v* 41.7% 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). **Beta-blockers:** We found two RCTs.[22,23] The first RCT (338 people with rest angina not already receiving a beta-blocker) compared nifedipine, metoprolol, or both versus placebo.[22] It found that metoprolol significantly reduced the composite outcome of recurrent angina and myocardial infarction within 48 hours compared with nifedipine (28% with metoprolol *v* 47% with nifedipine; RR 0.66, 95% CI 0.43 to 0.98). The second RCT (81 people with unstable angina on "optimal doses" of nitrates and nifedipine) compared propranolol (≥ 160 mg/day) versus placebo.[23] It found no significant difference in the combined outcome of death, myocardial infarction, and requirement for coronary artery bypass grafting or percutaneous coronary interventions at 30 days (38% with propranolol *v* 46% with placebo; RR 0.83, 95% CI 0.44 to 1.30). People taking propranolol had a lower cumulative probability of experiencing recurrent rest angina over the first 4 days of the trial. The mean number of clinical episodes of angina and the duration of angina was also lower. **Calcium channel blockers:** We found one systematic review (search date not stated, 6 RCTs, 1109 people)[24] comparing calcium channel blockers versus control treatment (3 RCTs used propranolol as a control and 3 used placebo) and one additional RCT.[22] The duration of the RCTs included in the review ranged from 48 hours (4 RCTs) to 4 months (2 RCTs). The review found no significant difference between calcium channel blockers and control in rates of myocardial infarction or death. The additional RCT compared nifedipine, metoprolol, or both, versus placebo.[22] It found that nifedipine was less effective at reducing recurrent angina and myocardial infarction within 48 hours compared with metoprolol (see benefits of beta-blockers above).[22]

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Harms: **Nitrates:** Hypotension is a potential adverse effect of nitrates. 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. **Beta-blockers:** Potential adverse effects of beta-blockers include bradycardia, exacerbation of reactive airways disease, and hypoglycaemia in people with diabetes. **Calcium channel blockers:** Observational studies have reported increased mortality with short acting dihydropyridine calcium channel blockers (such as nifedipine) in people with coronary heart disease.[25,26]

Comment: We found no good evidence that anti-ischaemic drugs (nitrates, beta-blockers, calcium channel blockers) prevent death or myocardial infarction. Consensus suggests that until further data are available, intravenous nitrates remain the preferred treatment, together with heparin and aspirin in unstable angina.

QUESTION What are the effects of invasive treatments?

OPTION ROUTINE EARLY CARDIAC CATHETERISATION AND REVASCULARISATION

We found five RCTs that reported on different composite outcomes at different time points. Two RCTs found that early invasive treatment reduced death and other cardiac events or hospital readmission compared with conservative treatment at 4–6 months. However, three RCTs found no significant difference in death or other cardiac events between early invasive treatment and conservative treatment at 12 or more months.

Benefits: We found no systematic review. We found five RCTs (6 articles) comparing early routine angiography and revascularisation (if appropriate) versus medical treatment alone.[27–32] The first RCT (2457 people) compared invasive treatment within the first 7 days versus non-invasive treatment plus planned coronary angiography.[27] Invasive treatment significantly reduced the combined outcome of death and myocardial infarction compared with non-invasive treatment after 6 months (AR 9% with invasive treatment *v* 12% with non-invasive treatment; RR 0.78, 95% CI 0.62 to 0.98; NNT 38; CI not provided). The second RCT (2220 people) compared cardiac catheterisation at 4–48 hours and revascularisation (if appropriate) versus standard treatment.[28] It found that cardiac catheterisation reduced the combined outcome of death, myocardial infarction, and readmission for unstable angina after 6 months (AR 16% with catheterisation *v* 19% with standard treatment; OR 0.78, 95% CI 0.62 to 0.97; NNT 34; CI not reported). The third RCT (1473 people) compared early cardiac catheterisation at 18–48 hours versus standard treatment.[29,30] Early cardiac catheterisation did not significantly reduce death or myocardial infarction but did reduce hospital admissions after 1 year (death or myocardial infarction: 11% with cardiac catheterisation *v* 12% with standard treatment; $P = 0.42$; hospital admissions: 26% with cardiac catheterisation *v* 33% with standard treatment; $P < 0.005$; NNT 14; CI not reported). The fourth RCT (920 people) compared invasive versus conservative treatment.[31] Invasive treatment did not significantly reduce the combined outcome of death or myocardial infarction compared with conservative treatment after 12–44 months (HR 0.87, 95% CI 0.68 to 1.10). The fifth RCT (1810 people) found that early invasive intervention (angiography followed by revascularisation) significantly reduced the composite outcome of death, non-fatal myocardial infarction, or refractory angina compared with conservative treatment at 4 months (86/895 [9.6%] with early intervention *v* 133/915 [14.5%] with conservative treatment; RR 0.66, 95% CI 0.51 to 0.85).[32] The difference was mainly due to reduced refractory angina with early intervention. The RCT found no significant difference in the combined outcome of death or myocardial infarction between early intervention and conservative treatment at 1 year (68/895 [7.6%] with early intervention *v* 76/915 [8.3%] with conservative treatment; RR 0.91, 95% CI 0.67 to 1.25).[32]

Harms: The first RCT found that early invasive treatment increased major bleeding, but not stroke, compared with non-invasive treatment (major bleeds: AR 1.6% with invasive treatment *v* 0.7% with non-invasive treatment; NNH 111; CI not reported).[27] The second RCT found that cardiac catheterisation increased bleeding compared with standard treatment (6% with cardiac catheterisation *v* 3% with standard treatment; $P < 0.01$:

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Angina (unstable)

NNH 34; CI not reported).[28] The third RCT found that early cardiac catheterisation did not increase complication rates (death, myocardial infarction, emergency coronary artery bypass grafting, abrupt vessel closure, haemorrhage, serious hypotension) compared with conservative treatment (AR 14% with cardiac catheterisation *v* 13% with conservative treatment; P = 0.38; NNH 100; CI not reported).[29,30] The fourth RCT did not report on harms.[31] The fifth RCT found that early intervention increased bleeding events during the index admission, but the significance of this increase was not reported (8% with early intervention *v* 4% with conservative treatment).

Comment: All trials have reported only short term and medium term follow up, so we cannot exclude a long term difference in effect between early invasive and early non-invasive strategies. There may be subgroups of people who benefit particularly from either invasive or conservative treatment. Advances in catheterisation and revascularisation technology and periprocedural management may reduce the early risks of invasive treatment in the future.

GLOSSARY

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 international normalised ratio of 1.0. Therapeutic anticoagulation often aims to achieve an international normalised ratio value of 2.0–3.5.

Substantive changes

Aspirin Systematic review updated;[1] categorisation unchanged.
Clopidogrel/ticlopidine One systematic review and post hoc analysis of an RCT added;[4,5] harms data enhanced but categorisation unchanged.
Intravenous glycoprotein IIb/IIIa platelet receptor inhibitors Long term follow up of one RCT added;[8] categorisation unchanged.
Oral glycoprotein IIb/IIIa platelet receptor inhibitors Further details of one RCT added;[11] categorisation unchanged.
Low molecular weight heparin One systematic review added;[14] categorisation unchanged.

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Atrial fibrillation (recent onset)

Search date October 2004

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QUESTIONS

INTERVENTIONS

Key Messages

Prevention of embolism

- **Antithrombotic treatment before cardioversion** We found no RCTs on use of aspirin, heparin, or warfarin as thromboprophylaxis before attempted cardioversion in acute atrial fibrillation.

Rhythm conversion

- **Flecainide** Five RCTs found that intravenous flecainide increased the proportion of people who reverted to sinus rhythm within 1–24 hours compared with placebo. Flecainide was associated with serious adverse events such as severe hypotension and torsades de pointes. Two RCTs found that oral flecainide increased the proportion of people who reverted to sinus rhythm within 8 hours compared with intravenous amiodarone. We found insufficient evidence to draw any conclusions about comparisons between intravenous flecainide and intravenous amiodarone and between flecainide and quinidine. Three RCTs found no significant difference in rates of conversion to sinus rhythm between flecainide and propafenone. Flecainide and propafenone are not used in people with known or suspected ischaemic heart disease because they may cause arrhythmias.

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Atrial fibrillation (recent onset)

- **Propafenone** One systematic review and subsequent RCTs found that propafenone increased the proportion of people converting to sinus rhythm within 1–24 hours compared with placebo. Two RCTs found a faster rate of conversion to sinus rhythm with propafenone, but no significant difference between amiodarone and propafenone after 12 hours. One RCT found that propafenone increased conversion to sinus rhythm after 8 hours compared with amiodarone. One RCT found no significant difference between conversion to sinus rhythm between amiodarone and propafenone at 1 hour. One RCT found no significant difference in conversion to sinus rhythm between propafenone and digoxin at 1 hour. Three RCTs found insufficient evidence to compare rates of conversion to sinus rhythm between propafenone and flecainide. Propafenone and flecainide are not used in people with known or suspected ischaemic heart disease because they may cause arrhythmias.
- **Amiodarone** We found insufficient evidence from four RCTs about the effects of amiodarone as a single agent compared with placebo for conversion to sinus rhythm in people with acute atrial fibrillation who are haemodynamically stable. Four small RCTs found no significant difference in rate of conversion to sinus rhythm at 24–48 hours for amiodarone compared with digoxin, although the studies may have lacked power to exclude clinically important differences. One RCT found that amiodarone increased rate of cardioversion compared with verapamil at 3 hours. Two RCTs found a faster rate of conversion to sinus rhythm with propafenone, but no significant difference between amiodarone and propafenone after 12 hours. One RCT found that propafenone increased conversion to sinus rhythm after 8 hours compared with amiodarone. One RCT found no significant difference between conversion to sinus rhythm between amiodarone and propafenone at 1 hour. Two RCTs found that intravenous amiodarone reduced the proportion of people who reverted to sinus rhythm within 8 hours compared with oral flecainide. We found insufficient evidence to draw any conclusion between intravenous flecainide and intravenous amiodarone. We found no RCTs comparing amiodarone with DC cardioversion.
- **DC cardioversion** We found no RCTs of DC cardioversion in acute atrial fibrillation in people who are haemodynamically stable.
- **Quinidine** We found no RCTs of DC cardioversion that compared quinidine versus placebo. One small RCT in people with onset of atrial fibrillation of less than 48 hours found that quinidine plus digoxin increased the proportion of people converting to sinus rhythm within 12 hours compared with sotalol. We found insufficient evidence to draw any conclusions about comparisons between flecainide and quinidine.
- **Sotalol** We found no RCTs comparing sotalol versus placebo. One small RCT in people with onset of atrial fibrillation of less than 48 hours found that quinidine plus digoxin increased the proportion of people who converted to sinus rhythm within 12 hours compared with sotalol.
- **Digoxin** We found no placebo controlled RCTs limited to people with acute atrial fibrillation. Four RCTs in people with atrial fibrillation of up to 7 days' duration found no significant difference between digoxin and placebo in conversion to sinus rhythm. Four RCTs found no significant difference between amiodarone and digoxin in conversion to sinus rhythm at 24–48 hours, although these trials may have lacked power to detect clinically important differences. One RCT found no significant difference in conversion to sinus rhythm between propafenone and digoxin at 1 hour.
- **Verapamil** One RCT found that amiodarone increased rate of cardioversion compared with verapamil at 3 hours.

Rate control

- **Digoxin** We found no placebo controlled RCTs limited to people with acute atrial fibrillation. Two RCTs found that intravenous digoxin reduced ventricular rate compared with placebo after 30 minutes and after 2 hours in people with atrial fibrillation of up to 7 days' duration. One RCT found that, compared with intravenous digoxin, intravenous diltiazem reduced heart rate within 5 minutes in people with acute atrial fibrillation and atrial flutter.

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Atrial fibrillation (recent onset)

- **Diltiazem** One RCT in people with atrial fibrillation (of unspecified duration) or atrial flutter found that intravenous diltiazem reduced heart rate in people within 15 minutes compared with placebo. One RCT found that in people with acute atrial fibrillation and atrial flutter, intravenous diltiazem reduced heart rate within 5 minutes compared with intravenous digoxin. One RCT found no significant difference between intravenous verapamil and intravenous diltiazem in rate control or measures of systolic function in people with acute atrial fibrillation or atrial flutter, but verapamil caused hypotension in some people.
- **Timolol** We found no RCTs limited to people with acute atrial fibrillation. One small RCT in people with atrial fibrillation of unspecified duration found that intravenous timolol (a β blocker) reduced ventricular rate within 20 minutes compared with placebo.
- **Verapamil** Two RCTs found that intravenous verapamil reduced heart rate at 10 or 30 minutes compared with placebo in people with atrial fibrillation or atrial flutter. One RCT in people with atrial fibrillation or acute atrial flutter found no significant difference between intravenous verapamil and intravenous diltiazem in rate control or measures of systolic function, but verapamil caused hypotension in some people.
- **Amiodarone** We found no systematic review or RCTs on the effects of amiodarone to control heart rate in people with acute atrial fibrillation who are haemodynamically stable.
- **Sotalol** We found no systematic review or RCTs on the effects of sotalol to control heart rate in people with acute atrial fibrillation who are haemodynamically stable.

DEFINITION

Acute atrial fibrillation is rapid, irregular, and chaotic atrial activity of less than 48 hours' duration. It includes both the first symptomatic onset of chronic or persistent atrial fibrillation G and episodes of paroxysmal atrial fibrillation G. It is sometimes difficult to distinguish new onset of atrial fibrillation from long standing atrial fibrillation that was previously undiagnosed. Atrial fibrillation within 72 hours of onset is sometimes called recent onset atrial fibrillation. By contrast, chronic atrial fibrillation G is more sustained and can be described as paroxysmal (with spontaneous termination and sinus rhythm between recurrences), persistent, or permanent atrial fibrillation G. This review deals only with people with acute atrial fibrillation who are haemodynamically stable. The consensus is that people who are not haemodynamically stable should be treated with immediate DC cardioversion. We have excluded studies in people with atrial fibrillation arising during or soon after cardiac surgery.

INCIDENCE/ PREVALENCE

We found limited evidence of the incidence or prevalence of acute atrial fibrillation. Extrapolation from the Framingham study suggests an incidence in men of 3/1000 person years at age 55 years, rising to 38/1000 person years at 94 years.[1] In women, the incidence was 2/1000 person years at age 55 years and 32.5/1000 person years at 94 years. The prevalence of atrial fibrillation ranged from 0.5% for people aged 50–59 years to 9% in people aged 80–89 years. Among acute emergency medical admissions in the UK, 3–6% had atrial fibrillation, and about 40% were newly diagnosed.[2,3] Among acute hospital admissions in New Zealand, 10% (95% CI 9% to 12%) had documented atrial fibrillation.[4]

AETIOLOGY/ RISK FACTORS

Common precipitants of acute atrial fibrillation are acute myocardial infarction and the acute effects of alcohol. Age increases the risk of developing acute atrial fibrillation. Men are more likely to develop atrial fibrillation than women (38 years' follow up from the Framingham Study, RR after adjustment for age and known predisposing conditions 1.5).[5] Atrial fibrillation can occur in association with underlying disease (both cardiac and non-cardiac) or can arise in the absence of any other condition. Epidemiological surveys found that risk factors for the development of acute atrial fibrillation include ischaemic heart disease, hypertension, heart failure, valve disease, diabetes, alcohol abuse, thyroid disorders, and disorders of the lung and pleura.[1] In a British survey of acute hospital admissions of people with atrial fibrillation, a history of ischaemic heart disease was present in 33%, heart failure in 24%, hypertension in 26%, and rheumatic heart disease in 7%.[3] In some populations, the acute effects of alcohol explain a large proportion of the incidence of acute atrial fibrillation. Paroxysms of atrial fibrillation are more common in athletes.[6]

PROGNOSIS

Spontaneous reversion: Observational studies and placebo arms of RCTs found that more than 50% of people with acute atrial fibrillation revert spontaneously

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Atrial fibrillation (recent onset)

within 24–48 hours, especially if atrial fibrillation is associated with an identifiable precipitant such as alcohol or myocardial infarction. **Progression to chronic atrial fibrillation:** We found no evidence about the proportion of people with acute atrial fibrillation who develop more chronic forms of atrial fibrillation (e.g. paroxysmal, persistent, or permanent atrial fibrillation). **Mortality:** We found little evidence about the effects on mortality and morbidity of acute atrial fibrillation where no underlying cause is found. Acute atrial fibrillation during myocardial infarction is an independent predictor of both short term and long term mortality.[7] **Heart failure:** Onset of atrial fibrillation reduces cardiac output by 10–20% irrespective of the underlying ventricular rate[8,9] and can contribute to heart failure. People with acute atrial fibrillation who present with heart failure have worse prognoses. **Stroke:** Acute atrial fibrillation is associated with a risk of imminent stroke.[10–13] One case series used transoesophageal echocardiography in people who had developed acute atrial fibrillation within the preceding 48 hours; 15% had atrial thrombi.[14] An ischaemic stroke associated with atrial fibrillation is more likely to be fatal, have a recurrence, and leave a serious functional deficit among survivors than a stroke not associated with atrial fibrillation.[15]

AIMS OF INTERVENTION To reduce symptoms, morbidity, and mortality, with minimum adverse effects.

OUTCOMES Major outcomes include measures of symptoms, recurrent strokes, or transient ischaemic attacks; thromboembolism; mortality; and major bleeding. Proxy measures include heart rhythm, ventricular rate, and time to restoration of sinus rhythm. Frequent spontaneous reversion to sinus rhythm makes it difficult to interpret short term studies of rhythm; treatments may accelerate restoration of sinus rhythm without increasing the proportion of people who eventually convert. The clinical importance of changes in mean heart rate is also unclear.

METHODS *Clinical Evidence* search and appraisal October 2004. Current contents, textbooks, review articles, and recent abstracts were reviewed. Many studies were not solely in people with acute atrial fibrillation. The text indicates where results have been extrapolated from studies of paroxysmal, persistent, or permanent atrial fibrillation. Atrial fibrillation that follows coronary surgery was excluded. We found no RCTs that reported on quality of life, functional capacity, or mortality.

QUESTION **What are the effects of interventions to prevent embolism in people with recent onset atrial fibrillation who are haemodynamically stable?**

OPTION ANTITHROMBOTIC TREATMENT BEFORE CARDIOVERSION

We found no RCTs on use of aspirin, heparin, or warfarin as thromboprophylaxis before attempted cardioversion in acute atrial fibrillation.

Benefits: We found no RCTs on use of aspirin, heparin, or warfarin as thromboprophylaxis before cardioversion in acute atrial fibrillation.

Harms: We found no RCTs.

Comment: There is consensus to give heparin to people who have cardioversion within 48 hours of the onset of arrhythmia, but we found insufficient evidence from trials. The decision to give anticoagulation both in the short term and after cardioversion is usually based on an individual's intrinsic risk of thromboembolism.[16] Warfarin is not used as an anticoagulant in acute atrial fibrillation because of its slow onset of action. One transoesophageal echocardiography study in people with a recent embolic event found left atrial thrombus in 15% of people with acute atrial fibrillation of less than 3 days' duration.[14] This would suggest that such people may benefit from formal anticoagulation or need to be evaluated by transoesophageal echocardiography before safe cardioversion. One ongoing trial is assessing the feasibility and effects of such a strategy by comparing low molecular weight and unfractionated heparin in people with atrial fibrillation of more than 2 days' duration who have transoesophageal echocardiographically guided early electrical or chemical cardioversion.[17]

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Atrial fibrillation (recent onset)

QUESTION **What are the effects of interventions for conversion to sinus rhythm in people with recent onset atrial fibrillation who are haemodynamically stable?**

OPTION DC CARDIOVERSION

We found no RCTs of DC cardioversion in acute atrial fibrillation in people who are haemodynamically stable.

Benefits: We found no systematic review. **Versus no cardioversion or chemical conversion:** We found no RCTs.

Harms: Adverse events from synchronised DC cardioversion include those associated with a general anaesthetic, generation of a more serious arrhythmia, superficial burns, and thromboembolism.

Comment: It might be unethical to conduct RCTs of DC cardioversion in people with acute atrial fibrillation and haemodynamic compromise. The only evidence for DC cardioversion in acute atrial fibrillation is extrapolated from its use in chronic atrial fibrillation G. DC cardioversion has been used for the treatment of atrial fibrillation since the 1960s.[18] Consensus is that immediate DC cardioversion for acute atrial fibrillation should be attempted only if there are signs of haemodynamic compromise.[16] Otherwise, full anticoagulation is recommended (warfarin for 3 weeks before and 4 weeks after cardioversion) to reduce the risk of thromboembolism in people with acute atrial fibrillation of more than 48 hours' duration.[16] We found insufficient evidence on whether cardioversion or rate control is superior for the treatment of acute atrial fibrillation.

OPTION AMIODARONE

We found insufficient evidence from four RCTs about the effects of amiodarone as a single agent compared with placebo for conversion to sinus rhythm in people with acute atrial fibrillation who are haemodynamically stable. Four small RCTs found no significant difference in rate of conversion to sinus rhythm at 24–48 hours for amiodarone compared with digoxin, although the studies may have lacked power to exclude clinically important differences. One RCT found that amiodarone increased rate of cardioversion compared with verapamil at 3 hours. Two RCTs found a faster rate of conversion to sinus rhythm with propafenone, but no significant difference between amiodarone and propafenone after 12 hours. One RCT found that propafenone increased conversion to sinus rhythm after 8 hours compared with amiodarone. One RCT found no significant difference between conversion to sinus rhythm between amiodarone and propafenone at 1 hour. Two RCTs found that intravenous amiodarone reduced the proportion of people who reverted to sinus rhythm within 8 hours compared with oral flecainide. We found insufficient evidence to draw any conclusion between intravenous flecainide and intravenous amiodarone. We found no RCTs comparing amiodarone with DC cardioversion.

Benefits: **Versus placebo:** We found two systematic reviews (search dates 2001, 2 RCTs that compared amiodarone as a single agent with placebo, 104 people with acute onset atrial fibrillation),[19,20] one additional RCT,[21] and one subsequent RCT.[22] Both RCTs included in the reviews found no significant difference in rates of conversion from atrial fibrillation to sinus rhythm between intravenous amiodarone and placebo at 8 hours (first RCT: 40 people; cardioversion rate: 37% with amiodarone 5 mg/kg bolus plus 1800 mg/day *v* 48% with placebo; P value reported as not significant, CI not reported; second RCT: 64 people; cardioversion rate: 59% with amiodarone 7 mg/kg bolus *v* 56%

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Atrial fibrillation (recent onset)

with placebo; P value reported as not significant, CI not reported).[23,24] The additional RCT (417 people with recent onset atrial fibrillation ≤ 7 days) compared five treatments: intravenous amiodarone (5 mg/kg bolus followed by 1.8 g/24 hours); intravenous propafenone (2 mg/kg bolus followed by 0.0078 g/kg/minute); oral propafenone 600 mg single dose; oral flecainide 300 mg single dose; or placebo. It found that intravenous amiodarone significantly increased rates of conversion to sinus rhythm compared with placebo at 8 hours (cardioversion rate: 57% with amiodarone *v* 37% with placebo; reported as significant).[21] The subsequent RCT (72 people) found higher cardioversion rates with oral amiodarone compared with placebo at 8 hours (cardioversion rate: 50% with amiodarone 30 mg/kg/day *v* 20% with placebo; P < 0.0001).[22] **Versus digoxin:** We found two systematic reviews (search date 2001, 3 RCTs, 148 people with acute onset atrial fibrillation;[19] search date 2001, 3 RCTs, 114 people, no statistical pooling of results[20]). Together, the reviews identified four small RCTs (34, 45, 50, and 30 people).[25–28] None found any statistically significant difference in rates of conversion to sinus rhythm between amiodarone and digoxin at 24–48 hours. **Versus flecainide:** See benefits of flecainide, p 8. **Versus verapamil:** We found two systematic reviews (search dates 2001, 1 RCT, 24 people).[19,20] The RCT found that amiodarone increased conversion to sinus rhythm compared with verapamil at 3 hours (AR for cardioversion: 77% with intravenous amiodarone *v* 0% with intravenous verapamil; P < 0.05).[29] **Versus propafenone:** See benefits of propafenone, p 11. **Versus DC cardioversion:** We found no systematic review or RCTs.

Harms:

Versus placebo: One systematic review found that the most common adverse effects of intravenous amiodarone were phlebitis, hypotension, and bradycardia.[20] Pooled adverse event rates were higher with amiodarone than placebo (AR for any adverse effect: 17% with amiodarone *v* 11% with placebo). Other reported adverse effects of amiodarone in the acute setting include heart failure and arrhythmia. The additional RCT found no serious adverse effects in the intravenous amiodarone group.[21] The subsequent RCT reported a similar proportion of people with adverse events with amiodarone and placebo (rapid ventricular response, diarrhoea, nausea, fainting 6/31 [19%] with amiodarone; diarrhoea, nausea, sinus arrest, transient ischaemic attack 6/31 [19%] with placebo).[22] **Versus digoxin:** No adverse events were reported in one of the RCTs (0/15 [0%] with amiodarone *v* 0/15 [0%] with digoxin).[26] Two RCTs reported more adverse events with amiodarone than with digoxin (1/18 [6%] with amiodarone *v* 0/16 [0%] with digoxin; 3/26 [12%] with amiodarone *v* 0/24 [0%] with digoxin).[25,27] One RCT reported more adverse events with digoxin than with amiodarone (major adverse events: 3/39 [8%] with amiodarone *v* 8/36 [22%] with digoxin).[28] **Versus flecainide:** See harms of flecainide, p 10. **Versus verapamil:** The RCT reported slowing of ventricular response to 45 beats/minute and transitory hypotension in one person receiving verapamil, and hypotension without bradycardia, lasting for about 4 minutes, in one person receiving amiodarone.[29] **Versus propafenone:** See harms of propafenone, p 13. **Versus DC cardioversion:** We found no systematic review or RCTs.

Comment:

The RCTs were small. Those that found no significant difference between treatments may have lacked power to detect clinically important effects.

OPTION DIGOXIN

We found no placebo controlled RCTs limited to people with acute atrial fibrillation. Four RCTs in people with atrial fibrillation of up to 7 days' duration found no significant difference between digoxin and placebo in conversion to

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sinus rhythm. Four RCTs found no significant difference between amiodarone and digoxin in conversion to sinus rhythm at 24–48 hours, although these trials may have lacked power to detect clinically important differences. One RCT found no significant difference in conversion to sinus rhythm between propafenone and digoxin at 1 hour.

Benefits: We found no systematic review. We found no RCTs limited to people with acute atrial fibrillation. **Versus placebo:** We found four RCTs in people with atrial fibrillation of up to 7 days' duration.[30–33] The first RCT (239 people within 7 days of onset of atrial fibrillation, mean age 66 years, mean ventricular rate 122 beats/minute) found that intravenous digoxin (mean 0.88 mg) did not increase the restoration of sinus rhythm at 16 hours compared with placebo (51% with digoxin *v* 46% with placebo).[30] The second RCT (40 people within 7 days of the onset of atrial fibrillation, mean age 64 years, 23 men) compared high dose intravenous digoxin 1.25 mg versus placebo.[31] Restoration to sinus rhythm was not significantly different (9/19 [47%] with digoxin *v* 8/20 [40%] with placebo; P = 0.6). The third RCT (36 people within 7 days of the onset of atrial fibrillation) compared oral digoxin (doses of 0.6, 0.4, 0.2, and 0.2 mg at 0, 4, 8, and 14 hours, or until conversion to sinus rhythm, whichever occurred first) versus placebo. Conversion to sinus rhythm at 18 hours was not significantly different (50% with digoxin *v* 44% with placebo; ARR +6%, 95% CI −11% to +22%).[32] The fourth RCT (123 people aged 18–75 years, onset of atrial fibrillation < 72 hours) compared three treatments given as a 10 minute infusion: propafenone 2 mg/kg; digoxin 0.007 mg/kg; or placebo. It found no significant difference in rate of conversion to sinus rhythm between digoxin and placebo within 1 hour (13/40 [33%] with digoxin *v* 6/42 [14%] with placebo; RR 2.28, 95% CI 0.96 to 5.40).[33] **Versus amiodarone:** See benefits of amiodarone, p 5. **Versus propafenone:** See benefits of propafenone, p 11.

Harms: **Versus placebo:** In the first RCT, some people developed asymptomatic bradycardia and one person with previously undiagnosed hypertrophic cardiomyopathy suffered circulatory distress.[30] In the second RCT, two people developed bradyarrhythmias.[31] No adverse effects were stated in the third RCT.[32] Digoxin at toxic doses could result in visual, gastrointestinal, and neurological symptoms; heart block; and arrhythmias. The fourth RCT reported hypotension in four people receiving propafenone and it reported asymptomatic atrial flutter Ⓡ with 2 : 1 atrioventricular conduction (ventricular rates between 105 beats/minute and 130 beats/minute) in three people: one receiving propafenone as first treatment, one receiving propafenone after digoxin, and one receiving digoxin after propafenone.[33] **Versus amiodarone:** See harms of amiodarone, p 6. **Versus propafenone:** See harms of propafenone, p 13.

Comment: The evidence suggests that digoxin is no better than placebo for restoring sinus rhythm in people with recent onset atrial fibrillation. The peak action of digoxin is delayed for up to 6–12 hours.

OPTION FLECAINIDE

Five RCTs found that intravenous flecainide increased the proportion of people who reverted to sinus rhythm within 1–24 hours compared with placebo. Flecainide was associated with serious adverse events such as severe hypotension and torsades de pointes. Two RCTs found that oral flecainide increased the proportion of people who reverted to sinus rhythm within 8 hours compared with intravenous amiodarone. We found insufficient evidence to draw any conclusions about comparisons between intravenous flecainide and intravenous amiodarone and between flecainide and quinidine.

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Atrial fibrillation (recent onset)

Three RCTs found no significant difference in rates of conversion to sinus rhythm between flecainide and propafenone. Flecainide and propafenone are not used in people with known or suspected ischaemic heart disease because they may cause arrhythmias.

Benefits:

We found no systematic review. **Versus placebo:** We found five RCTs.[21,23,24,34,35] The first RCT (62 people aged > 75 years, onset of atrial fibrillation ≤ 7 days) compared three treatments: oral flecainide (300 mg single dose); intravenous amiodarone (5 mg/kg bolus followed by 1.8 g/day); or placebo. It found that oral flecainide significantly increased the rate of conversion to sinus rhythm compared with placebo at 8 hours (conversion rate: 20/22 [91%] with flecainide *v* 10/21 [48%] with placebo; $P < 0.01$).[23] The second RCT (98 people, onset of atrial fibrillation ≤ 72 hours) compared three treatments: intravenous flecainide (2 mg/kg, maximum dose 150 mg); intravenous amiodarone 7 mg/kg; or placebo. It found that intravenous flecainide significantly increased conversion to sinus rhythm compared with placebo within 2 hours (20/34 [59%] with flecainide *v* 7/32 [22%] with placebo; RR 2.69, 95% CI 1.32 to 5.48).[24] The third RCT (102 people with recent onset atrial fibrillation [< 72 hours]) also found that intravenous flecainide significantly increased the proportion of people who reverted to sinus rhythm within 1 hour and in whom the sinus rhythm was maintained after 6 hours (reversion to sinus rhythm within 1 hour of starting treatment: 29/51 [57%] with flecainide *v* 7/51 [14%] with placebo; OR 8.3, 95% CI 2.9 to 24.8; maintenance of sinus rhythm after 6 hours: 34/51 [67%] with flecainide *v* 18/51 [35%] with placebo; OR 3.67, 95% CI 1.50 to 9.10). Participants were randomised to receive flecainide 2 mg/kg over 30 minutes (maximum dose 150 mg) or placebo and were monitored in intensive care or coronary care units. Intravenous digoxin 500 μg over 30 minutes was given to all people who had not previously received digoxin.[34] The fourth RCT (417 people admitted to hospital with recent onset atrial fibrillation ≤ 7 days) compared five treatments: intravenous amiodarone (5 mg/kg bolus followed by 1.8 g/24 hours); intravenous propafenone (2 mg/kg bolus followed by 0.0078 mg/kg/minute); oral propafenone 600 mg single dose; oral flecainide 300 mg single dose; or placebo. It found that oral flecainide increased rate of conversion to sinus rhythm compared with placebo at 8 hours (cardioversion rate: 75% with flecainide *v* 37% with placebo; significance not reported).[21] The fifth RCT (352 people with recent onset atrial fibrillation < 72 hours) compared three treatments: flecainide; propafenone; or control. It found that flecainide significantly increased the rate of conversion to sinus rhythm compared with control at 1, 3, 6, and 24 hours (at 1 hour: 72.5% with flecainide *v* 22.2% with control; $P < 0.0001$; at 3 hours: 80.4% with flecainide *v* 27.8% with control; $P < 0.0001$; at 6 hours: 86.2% with flecainide *v* 35.2% with control; $P < 0.0005$; at 24 hours: 89.8% with flecainide *v* 46.3% with control; $P < 0.0001$).[35] **Versus amiodarone or propafenone:** We found five RCTs.[21,23,24,35,36] The first RCT (417 people admitted to hospital with recent onset atrial fibrillation ≤ 7 days) compared five treatments: intravenous amiodarone (5 mg/kg bolus followed by 1.8 g/24 hours); intravenous propafenone (2 mg/kg bolus followed by 0.0078 mg/kg/minute); oral propafenone 600 mg single dose; oral flecainide 300 mg single dose; or placebo. It found no significant difference between oral flecainide and intravenous amiodarone in the proportion of people who converted to sinus rhythm at 1 and 3 hours but found a higher rate of conversion to sinus rhythm with oral flecainide at 8 hours (conversion to sinus rhythm at 1 hour: 9/69 [13%] with oral flecainide *v* 3/51 [6%] with intravenous amiodarone; RR 2.2, 95% CI 0.6 to 7.8; at 3 hours: 39/69 [57%] with oral flecainide *v* 13/51 [25%] with intravenous amiodarone; RR 2.20, 95% CI 0.96 to 1.51; at

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8 hours: 52/69 [75%] with oral flecainide *v* 29/51 [57%] with intravenous amiodarone; RR 1.30, 95% CI 1.01 to 1.74).[21] It found no significant difference between oral flecainide and oral propafenone in the proportion of people who converted to sinus rhythm at 1, 3, or 12 hours (at 1 hour: 9/69 [13%] with oral flecainide *v* 10/119 [8%] with oral propafenone; RR 1.55, 95% CI 0.66 to 3.63; at 3 hours: 39/69 [57%] with oral flecainide *v* 54/119 [45%] with oral propafenone; RR 1.25, 95% CI 0.94 to 1.66; at 8 hours: 52/69 [75%] with oral flecainide *v* 91/119 [76%] with oral propafenone; RR 0.99, 95% CI 0.83 to 1.17).[21] It found that intravenous propafenone increased rate of conversion to sinus rhythm within 1 hour, but it found similar conversion rates at 3 and 8 hours (conversion rate of about 75% at 8 hours).[21] The second RCT (62 people aged > 75 years, onset of atrial fibrillation ≤ 7 days) compared three treatments: oral flecainide 300 mg single dose; amiodarone (5 mg/kg bolus followed by 1.8 g/day); or placebo. It found that oral flecainide significantly increased the proportion of people who converted to sinus rhythm at 8 hours compared with intravenous amiodarone (20/22 [91%] with flecainide *v* 7/19 [37%] with amiodarone; RR 2.47, 95% CI 1.35 to 4.51).[23] The third RCT (98 people, onset of atrial fibrillation ≤ 72 hours) compared three treatments: intravenous flecainide (2 mg/kg, maximum dose 150 mg); intravenous amiodarone 7 mg/kg; or placebo. It found no significant difference between intravenous flecainide and intravenous amiodarone in the proportion of people who converted to sinus rhythm within 2 hours (20/34 [59%] with flecainide *v* 11/32 [34%] with amiodarone; RR 1.71, 95% CI 0.98 to 2.98).[24] The fourth RCT (352 people with recent onset atrial fibrillation < 72 hours) compared three treatments: flecainide; propafenone; or control. It found significantly faster conversion to sinus rhythm with intravenous flecainide within 1 hour after treatment compared with propafenone (72.5% with flecainide *v* 54.3% with propafenone; P = 0.05; absolute numbers not reported).[35] The fifth RCT (150 people, onset of atrial fibrillation ≤ 48 hours) compared three treatments: flecainide (2 mg/kg bolus in 20 minutes); propafenone (2 mg/kg bolus in 20 minutes); or amiodarone (5 mg/kg in 20 minutes followed by continuous infusion of 50 mg/hour). It found that intravenous flecainide significantly increased the proportion of people who converted to sinus rhythm at 1, 8, and 12 hours compared with intravenous amiodarone (at 1 hour: 29/50 [58%] with flecainide *v* 7/50 [14%] with amiodarone; RR 4.14, 95% CI 2.00 to 8.57; at 8 hours: 41/50 [82%] with flecainide *v* 21/50 [42%] with amiodarone; RR 1.95, 95% CI 1.38 to 2.77; at 12 hours: 45/50 [90%] with flecainide *v* 32/50 [64%] with amiodarone; RR 1.41, 95% CI 1.12 to 1.77).[36] The RCT found no significant difference between intravenous flecainide and intravenous propafenone in the proportion of people who converted to sinus rhythm at 1 and 8 hours. It found a significantly higher conversion rate at 12 hours with flecainide compared with propafenone (at 1 hour: 29/50 [58%] with flecainide *v* 30/50 [60%] with propafenone; RR 0.97, 95% CI 0.70 to 1.34; at 8 hours: 41/50 [82%] with flecainide *v* 34/50 [68%] with propafenone; RR 1.21, 95% CI 0.96 to 1.51; at 12 hours: 45/50 [90%] with flecainide *v* 36/50 [72%] with propafenone; RR 1.25, 95% CI 1.03 to 1.52).[36] **Versus quinidine:** One small RCT found insufficient evidence to draw any conclusions about the effectiveness of flecainide compared with quinidine for conversion to sinus rhythm (60 people aged 16–92 years, of whom 36 people had atrial fibrillation < 10 days; conversion to sinus rhythm [time period not reported]: 18/21 [86%] with flecainide *v* 12/15 [80%] with quinidine; RR 1.07, 95% CI 0.79 to 1.46).[37]

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Atrial fibrillation (recent onset)

Harms:

Versus placebo: The first RCT reported an asymptomatic pause of 9.3 seconds in a person who took flecainide.[23] The second RCT reported hypotension during the study period but this was not significantly different between flecainide and placebo (8/34 [24%] of people in the flecainide group *v* 8/32 [25%] with placebo).[24] The third RCT found that a higher proportion of people developed severe hypotension (a decrease in systolic arterial pressure by ≥33%) with flecainide compared with placebo (11/51 [22%] with flecainide *v* 3/51 [6%] with placebo; OR 4.40, 95% CI 1.03 to 18.60). One person in the flecainide group with no history of ventricular arrhythmia and a normal QT interval developed torsades de pointes G.[34] The fourth RCT reported adverse effects of flecainide in three people, one with left ventricular decompensation, and two with atrial flutter G with rapid ventricular response. One person with placebo had atrial flutter with rapid ventricular response.[21] The fifth RCT found more adverse effects with flecainide compared with control (10% with flecainide *v* 4% with control; significance not reported).[35] **Versus amiodarone or propafenone:** The first RCT reported left ventricular decompensation in one person receiving flecainide and one person receiving intravenous propafenone, and atrial flutter with rapid ventricular response in two people receiving flecainide.[21] The second RCT reported no major adverse effects leading to interruption of the study. It reported superficial phlebitis in two people receiving amiodarone, and mild light-headedness in one person receiving flecainide.[23] The third RCT found that a higher proportion of people developed severe hypotension with flecainide compared with amiodarone (8/34 [24%] with flecainide *v* 5/32 [16%] with amiodarone). It found that, overall, adverse effects were more common with flecainide.[24] The fourth RCT found similar adverse effects with flecainide and propafenone (10% with flecainide *v* 10% with propafenone; significance not reported).[35] The fifth RCT found no significant difference in adverse events between flecainide, amiodarone, and propafenone (transient junctional rhythm, symptomatic hypotension: 6/50 [12%] with flecainide; rash, symptomatic hypotension: 3/50 [6%] with amiodarone; transient junctional rhythm, atrial tachycardia: 7/50 [14%] with propafenone; reported as non-significant).[36] **Versus quinidine:** The RCT reported adverse effects of flecainide in two people, one with severe bradycardia after the loading dose, which responded to atropine treatment, and one with first degree atrioventricular block and left bundle branch block during the intravenous loading dose, which resolved as soon as sinus rhythm was restored. Adverse effects of quinidine treatment consisted of transient gastrointestinal disturbances (nausea, abdominal pain, and diarrhoea; numbers not reported).[37]

Comment:

Following the increased mortality observed in post-myocardial infarction patients randomised to flecainide or encainide in the Cardiac Arrhythmia Suppression Trial, flecainide is not used for the treatment of atrial fibrillation in people with known ischaemic heart disease because of the risk of proarrhythmia.[38]

OPTION PROPAFENONE

One systematic review and subsequent RCTs found that propafenone increased the proportion of people converting to sinus rhythm within 1–24 hours compared with placebo. Two RCTs found a faster rate of conversion to sinus rhythm with propafenone, but no significant difference between amiodarone and propafenone after 12 hours. One RCT found that propafenone increased conversion to sinus rhythm after 8 hours compared with amiodarone. One RCT found no significant difference between conversion to sinus rhythm between amiodarone and propafenone at 1 hour. One RCT found no significant difference in conversion to sinus rhythm between propafenone and digoxin at 1 hour. Three RCTs found insufficient evidence to

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compare rates of conversion to sinus rhythm between propafenone and flecainide. Propafenone and flecainide are not used in people with known or suspected ischaemic heart disease because they may cause arrhythmias.

Benefits:

Versus placebo: We found one systematic review (search date 1997, 27 controlled clinical trials including some non-randomised trials, 1843 people),[39] one additional RCT,[40] and eight subsequent RCTs (see table 1, p 22).[21,33,35,41–45] The systematic review found that people treated with propafenone were more likely to convert to sinus rhythm at 4 and 8 hours after initial treatment compared with placebo but the difference between the groups did not remain significant after 24 hours (at 4 hours: ARR 31.5%, 95% CI 24.5% to 38.5%; at 8 hours: ARR 32.9%, 95% CI 24.3% to 41.5%; P < 0.01 for both time points; at 24 hours: ARR +11.0%, 95% CI –0.6% to +22.4%; absolute numbers not reported).[39] In the trials included in the systematic review, propafenone was given either intravenously (2 mg/kg as initial bolus followed by infusion) or orally (450–600 mg).[39] The systematic review included people with either acute or chronic fibrillation, but it did not stratify the data. The number of RCTs was not reported clearly. All of the five subsequent RCTs found propafenone to be more effective than placebo in terms of conversion to sinus rhythm within 6 hours (see table 1, p 22). The additional RCT (75 people aged 18–75 years, onset of atrial fibrillation < 72 hours) found that intravenous propafenone significantly increased the proportion of people who converted to sinus rhythm within 3 hours compared with placebo (24/41 [58.5%] with propafenone *v* 10/34 [29.4%] with placebo; OR 3.2, 95% CI 1.3 to 7.9; see table 1, p 22).[40] The first subsequent multicentre RCT (240 people, mean age 59 years with atrial fibrillation duration < 7 days) found that propafenone significantly increased the proportion of people in sinus rhythm at 3 and 8 hours after treatment compared with placebo (at 3 hours: 54/119 [45%] with propafenone *v* 22/121 [18%] with placebo; ARR 27%, 95% CI 17% to 39%; RR 2.5, 95% CI 1.6 to 3.8; at 8 hours: 91/119 [76%] with propafenone *v* 45/121 [37%] with placebo; ARR 39%, 95% CI 29% to 52%; RR 2.1, 95% CI 1.6 to 2.6; see table 1, p 22).[41] After stratification by age (≤ 60 years or > 60 years of age), the RCT found that conversion to sinus rhythm with propafenone was more likely in people aged under 60 years old compared with older people (in people ≤ 60 years of age: OR 3.78, 95% CI 1.80 to 7.92 at 3 hours *v* OR 4.74, 95% CI 2.12 to 10.54 at 8 hours; in people aged > 60 years of age: OR 5.03, 95% CI 2.08 to 12.12 at 3 hours *v* OR 6.75, 95% CI 3.38 to 73.86 at 8 hours).[46] The second subsequent RCT (55 people, mean age 59 years, duration of atrial fibrillation < 7 days) found that a significantly higher proportion of people converted to sinus rhythm within 2 hours with propafenone compared with placebo, and the significant difference was maintained up to 6 hours but not at 12 or 24 hours (at 2 hours: 12/29 [41%] with propafenone *v* 2/26 [8%] with placebo; P = 0.005; at 6 hours: 65% with propafenone *v* 31% with placebo; P = 0.015; at 12 hours: 69% with propafenone *v* 31% with placebo; P = 0.06; at 24 hours: 79% with propafenone *v* 73% with placebo; P = 0.75; see table 1, p 22).[42] The third subsequent RCT (156 people aged 18–80 years, onset of atrial fibrillation < 72 hours) found that intravenous propafenone significantly increased the proportion of people who converted to sinus rhythm within 2 hours compared with placebo: 57/81 [70.3%] with propafenone *v* 13/75 [17.3%] with placebo; ARR 53%, 95% CI 42% to 68%; RR 4.06, 95% CI 2.43 to 6.79 (see table 1, p 22).[43] The fourth subsequent RCT (123 people, onset of atrial fibrillation < 72 hours) found that intravenous or oral propafenone significantly increased the proportion of people who converted to sinus rhythm within 1 and 4 hours but not at 8 hours after initial treatment compared with placebo (within 1 hour: 25/81 [31%] with propafenone *v* 7/42 with placebo [17%]; RR 1.85, 95% CI 0.87 to 3.92; within 4

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Atrial fibrillation (recent onset)

hours: 49/81 [61%] with propafenone *v* 14/42 [33%] with placebo; RR 1.82, 95% CI 1.14 to 2.88; within 8 hours: 53/81 [65%] with propafenone *v* 20/42 [48%] with placebo; RR 1.37, 95% CI 0.96 to 1.96; see table 1, p 22).[44] The RCT also found that the time to conversion to sinus rhythm was significantly shorter with intravenous propafenone compared with oral propafenone (1 hour: 19/40 [48%] with intravenous propafenone *v* 6/41 [15%] with oral propafenone; RR 3.25, 95% CI 1.45 to 7.28; within 4 hours: 20/40 [50%] with intravenous propafenone *v* 29/41 [71%] with oral propafenone; RR 0.71, 95% CI 0.49 to 1.02; see table 1, p 22).[44] The fifth subsequent RCT (123 people aged 18–75 years, onset of atrial fibrillation < 72 hours) compared three treatments given as a 10 minute infusion: propafenone 2 mg/kg; digoxin 0.007 mg/kg; or placebo. It found that a significantly higher proportion of people converted to sinus rhythm with propafenone compared with placebo within 1 hour (20/41 [49%] with propafenone *v* 6/42 [14%] with placebo; RR 3.42, 95% CI 1.53 to 7.63; see table 1, p 22).[33] After 1 hour, people who had not converted to sinus rhythm were switched to the alternative drug (see table 1, p 22).[33] The sixth subsequent RCT (77 men, mean age 63 years, recent onset atrial fibrillation ≤ 48 hours) compared three treatments: intravenous propafenone (2 mg/kg over 15 minutes followed by 10 mg/kg over next 24 hours); intravenous amiodarone (300 mg over 1 hour followed by 20 mg/kg over next 24 hours plus 1800 mg/day orally); or placebo. It found that intravenous propafenone significantly increased the rate of conversion to sinus rhythm at 1 hour compared with placebo (36/46 [78.2%] with propafenone *v* 27/49 [55.1%] with placebo; RR 1.42, 95% CI 1.06 to 1.91).[45] Intravenous digoxin was given to all people who had not previously received digoxin.[45] The seventh subsequent RCT (417 people with recent onset atrial fibrillation ≤ 7 days) compared five treatments: intravenous amiodarone (5 mg/kg bolus followed by 1.8 g/24 hours); intravenous propafenone (2 mg/kg bolus followed by 0.0078 mg/kg/minute); oral propafenone 600 mg single dose; oral flecainide 300 mg single dose; or placebo.[21] Propafenone significantly increased rate of conversion to sinus rhythm at 8 hours (76% with propafenone *v* 37% with placebo; $P < 0.05$). The eighth subsequent RCT (352 people with recent onset atrial fibrillation < 72 hours) compared three treatments: flecainide; propafenone; or control. It found that propafenone significantly increased rate of conversion to sinus rhythm compared with control at 1, 3, 6, and 24 hours (at 1 hour: 54.3% with propafenone *v* 22.2% with control; $P < 0.001$; at 3 hours: 68.3% with propafenone *v* 27.8% with control; $P < 0.001$; at 6 hours: 75.0% with propafenone *v* 35.2% with control; $P < 0.0005$; at 24 hours: 92.1% with propafenone *v* 46.3% with control; $P < 0.0001$).[35]

Versus digoxin: We found one RCT (123 people aged 18–75 years, onset of atrial fibrillation < 72 hours), which compared three treatments given as a 10 minute infusion: propafenone 2 mg/kg; digoxin 0.007 mg/kg; or placebo. It found no significant difference in rate of conversion to sinus rhythm between propafenone and digoxin at 1 hour (49% with propafenone *v* 32% with digoxin; OR 1.50, 95% CI 0.87 to 2.59).[33]

Versus amiodarone: We found no systematic review. We found four RCTs.[21,36,45,47] The first RCT (77 men, mean age 63 years, recent onset atrial fibrillation ≤ 48 hours) compared three treatments: intravenous propafenone (2 mg/kg over 15 minutes followed by 10 mg/kg over next 24 hours); intravenous amiodarone (300 mg over 1 hour followed by 20 mg/kg over next 24 hours plus 1800 mg/day orally); or placebo. It found no significant difference between intravenous propafenone and amiodarone in the proportion of people who converted to sinus rhythm within 1 hour (36/46 [78.2%] with propafenone *v* 40/48 [83.3%] with amiodarone; RR 0.94, 95% CI 0.77 to 1.15).[45] The second RCT (86 people, onset of atrial fibrillation < 2 weeks) found a

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faster rate of conversion to sinus rhythm with oral propafenone compared with amiodarone but no significant difference in the proportion of people who converted to sinus rhythm at 24 and 48 hours (median time to sinus rhythm: 2.4 hours with propafenone *v* 6.9 hours with amiodarone; P = 0.05; conversion to sinus rhythm at 24 hours: 56% with propafenone *v* 47% with amiodarone; reported as not significant, results presented graphically).[47] The third RCT (417 people with recent onset atrial fibrillation ≤ 7 days) compared five treatments: intravenous amiodarone (5 mg/kg bolus followed by 1.8 g/24 hours); intravenous propafenone (2 mg/kg bolus followed by 0.0078 mg/kg/minute); oral propafenone 600 mg single dose; oral flecainide 300 mg single dose; or placebo.[21] It found that intravenous propafenone increased rate of conversion to sinus rhythm compared with amiodarone at 8 hours (75% with propafenone *v* 57% with amiodarone; significance not reported). The fourth RCT (150 people, onset of atrial fibrillation ≤ 48 hours) compared three treatments: flecainide (2 mg/kg bolus in 20 minutes); propafenone (2 mg/kg bolus in 20 minutes); or amiodarone (5 mg/kg in 20 minutes followed by continuous infusion of 50 mg/hour). It found no significant difference in rate of conversion to sinus rhythm between propafenone and amiodarone at 12 hours (36/50 [72%] with propafenone *v* 32/50 [64%] with amiodarone; P = 0.39). It found that propafenone significantly reduced median time to conversion to sinus rhythm compared with amiodarone (30 minutes with propafenone *v* 333 minutes with amiodarone; P < 0.001).[36] **Versus flecainide:** See benefits of flecainide, p 8.

Harms:

Versus placebo: The systematic review did not comment on adverse events.[39] The first subsequent RCT that included people with structural heart disease and hypertension found no significant difference between propafenone and placebo in terms of adverse events (sustained atrial flutter Ⓖ or tachycardia lasting > 1 minute: 8/119 [7%] with propafenone *v* 7/121 [6%] with placebo; P > 0.2; pauses of > 2 seconds: 1/119 [1%] with propafenone *v* 3/121 [2%] with placebo; P > 0.2). No cases of ventricular proarrhythmia were reported.[41] The sixth subsequent RCT reported discontinuation of propafenone in two people because of excessive QRS widening.[45] The seventh subsequent RCT reported left ventricular depression in one person receiving propafenone, and atrial flutter with rapid ventricular response in one person receiving placebo.[21] The eighth subsequent RCT found more adverse effects with propafenone compared with control (10% with propafenone *v* 4% with control; significance not reported).[35] The other five RCTs that compared propafenone versus placebo reported no serious adverse events.[33,40,42–44] **Versus digoxin:** The RCT found no significant difference in hypotension between propafenone and digoxin (P = 0.12). It reported asymptomatic atrial flutter with 2 : 1 atrioventricular conduction (ventricular rates between 105 beats/minute and 130 beats/minute) in three people: one receiving propafenone as first treatment, one receiving propafenone after digoxin, and one receiving digoxin after propafenone.[33] **Versus amiodarone:** The first RCT that compared amiodarone versus propafenone found no serious adverse events.[47] The second RCT reported discontinuation of propafenone in two people because of excessive QRS widening, and discontinuation of amiodarone in one person because of allergy.[45] The third RCT reported left ventricular decompensation in one person receiving propafenone.[21] The fourth RCT found no significant difference in adverse events between amiodarone and propafenone (rash, symptomatic hypotension: 3/50 [6%] with amiodarone; transient junctional rhythm, atrial tachycardia: 7/50 [14%] with propafenone; reported as non-significant).[36] **Versus flecainide:** See harms of flecainide, p 10. **Other comparisons:** We found one RCT (246 people with onset of atrial fibrillation < 48 hours) that evaluated the safety of an oral loading dose of propafenone (600 mg for > 60 kg

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Atrial fibrillation (recent onset)

body weight, then 300 mg if persistent) compared with that of digoxin plus propafenone, digoxin plus quinidine, or placebo.[48] The RCT found no serious adverse events. The RCT found transient atrial flutter (13/66 [20%] with propafenone *v* 12/70 [17%] with digoxin plus propafenone *v* 9/70 [13%] with digoxin plus quinidine *v* 3/40 [8%] with placebo), asymptomatic salvos of up to four ventricular beats (4/70 [6%] with digoxin plus propafenone *v* 1/70 [1%] with digoxin plus quinidine), transient left bundle branch block (3/66 [5%] with propafenone *v* 2/70 [3%] with digoxin plus propafenone *v* 2/70 [3%] digoxin plus quinidine), transient Weinkebach 2 : 1 heart block (2/66 [3%] with propafenone *v* 2/70 [3%] with digoxin plus quinidine), and transient mild hypotension (5/66 [8%] propafenone *v* 1/70 [1%] digoxin plus quinidine). The RCT found no significant difference between groups for non-cardiac adverse events such as nausea, headache, gastrointestinal disturbance, dizziness, and paraesthesia.[48]

Comment: Extrapolation of the results of the cardiac arrhythmia suppression trial mean that other class 1c antiarrhythmic agents including propafenone tend not to be used in people with ischaemic heart disease because of concerns over a possible increase in proarrhythmic effects in this group of people.[38] In addition, the increased frequency of cardiac adverse events with long term propafenone noted in people with structural heart disease means that trials in acute atrial fibrillation have, for the main part, excluded people with significant heart disease.[49]

OPTION QUINIDINE

We found no RCTs of DC cardioversion that compared quinidine versus placebo. One small RCT in people with onset of atrial fibrillation of less than 48 hours found that quinidine plus digoxin increased the proportion of people converting to sinus rhythm within 12 hours compared with sotalol. We found insufficient evidence to draw any conclusions about comparisons between flecainide and quinidine.

Benefits: We found no systematic review. **Versus placebo:** We found no RCTs that compared quinidine versus placebo. **Quinidine plus digoxin versus sotalol:** One small RCT (61 people aged 18–75 years, mean age about 54 years, with recent onset atrial fibrillation of < 48 hours) found that quinidine plus digoxin significantly increased the proportion of people who converted to sinus rhythm within 12 hours compared with sotalol (24/28 [85.7%] with quinidine plus digoxin *v* 17/33 [51.5%] with sotalol; ARR 34%, 95% CI 16% to 58%; RR 1.66, 95% CI 1.16 to 2.39; NNT 3, 95% CI 2 to 6).[50] Quinidine was given as 200 mg orally up to three times with 2 hour intervals, and up to 0.75 mg of digoxin was given intravenously if the initial heart rate was greater than 100 beats/minute. Sotalol 80 mg was given orally, and the dose was repeated at 2, 6, and 10 hours after the initial dose if sinus rhythm was not achieved.[50] **Versus flecainide:** See benefits of flecainide, p 8.

Harms: **Versus placebo:** We found no RCTs that compared quinidine versus placebo. **Versus flecainide:** See harms of flecainide, p 10. **Quinidine plus digoxin versus sotalol:** One RCT reported broad complex tachycardia in 7/28 (27%) people with quinidine plus digoxin compared with 4/33 (13%) people with sotalol. Electrocardiogram R–R interval prolongation was also reported in both groups (total 3 people, longest R–R: 3.8 seconds with digoxin plus quinidine *v* 6.4 seconds with sotalol).[50]

Comment: None.

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OPTION SOTALOL

We found no RCTs comparing sotalol versus placebo. One small RCT in people with onset of atrial fibrillation of less than 48 hours found that quinidine plus digoxin increased the proportion of people who converted to sinus rhythm within 12 hours compared with sotalol.

Benefits: **Versus placebo:** We found no systematic review or RCTs that compared sotalol versus placebo in people with acute atrial fibrillation for conversion to sinus rhythm. **Versus quinidine plus digoxin:** See benefits of quinidine, p 14.

Harms: We found no RCTs that compared sotalol versus placebo.

Comment: We found one systematic review (search date 1996), which identified one open label RCT in people with acute atrial fibrillation.[51] The RCT compared oral sotalol 80 mg versus quinidine, but digoxin was also given to people with a heart rate of less than 100 beats a minute in the quinidine group. The RCT found insufficient evidence to draw any conclusions.[51] We also found another systematic review (search date 1998), which compared β blockers with placebo in people with acute or chronic atrial fibrillation⊖.[52] See comment on timolol, p 15.

OPTION VERAPAMIL

One RCT found that amiodarone increased rate of cardioversion compared with verapamil at 3 hours.

Benefits: **Versus placebo:** We found no systematic review or RCTs that compared verapamil versus placebo in people with acute atrial fibrillation for conversion to sinus rhythm. **Versus amiodarone:** See benefits of amiodarone, p 5.

Harms: **Versus placebo:** We found no RCTs that compared verapamil versus placebo. **Versus amiodarone:** See harms of amiodarone, p 6.

Comment: None.

QUESTION What are the effects of interventions to control heart rate in people with recent onset atrial fibrillation who are haemodynamically stable?

OPTION AMIODARONE

We found no systematic review or RCTs on the effects of amiodarone to control heart rate in people with acute atrial fibrillation who are haemodynamically stable.

Benefits: We found no systematic review or RCTs.

Harms: We found no RCTs.

Comment: None.

OPTION DIGOXIN

We found no placebo controlled RCTs limited to people with acute atrial fibrillation. Two RCTs found that intravenous digoxin reduced ventricular rate compared with placebo after 30 minutes and after 2 hours in people with atrial fibrillation of up to 7 days' duration. One RCT found that, compared with intravenous digoxin, intravenous diltiazem reduced heart rate within 5 minutes in people with acute atrial fibrillation and atrial flutter.

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Atrial fibrillation (recent onset)

Benefits: We found no systematic review. We found no RCTs limited to people with acute atrial fibrillation **Versus placebo:** We found two RCTs in people with atrial fibrillation of up to 7 days' duration.[30,31] The first RCT (239 people < 7 days of onset of atrial fibrillation, mean age 66 years, mean ventricular rate 122 beats/minute) found a rapid and clinically important reduction in ventricular rate at 2 hours (to 105 beats/minute with intravenous digoxin *v* 117 beats/minute with placebo; P = 0.0001).[30] The second RCT (40 people < 7 days of the onset of atrial fibrillation, mean age 64 years, 23 men) compared high dose intravenous digoxin 1.25 mg versus placebo.[31] The ventricular rate after 30 minutes was significantly lower with digoxin compared with placebo (P < 0.02). **Versus diltiazem:** See benefits of diltiazem, p 16.

Harms: **Versus placebo:** In the first RCT, some people developed asymptomatic bradycardia and one person with previously undiagnosed hypertrophic cardiomyopathy suffered circulatory distress.[30] In the second RCT, two people developed bradyarrhythmias.[31] **Versus diltiazem:** The RCT was not large enough to report adverse effects adequately.

Comment: We found one systematic review (search date 1998)[52] and RCTs of comparing digoxin versus placebo in people with chronic atrial fibrillationⒼ, which found that control of the ventricular rate during exercise was poor unless a β blocker or rate limiting calcium channel blocker (verapamil or diltiazem) was used in combination.[53,54]

OPTION DILTIAZEM

One RCT in people with atrial fibrillation (of unspecified duration) or atrial flutter found that intravenous diltiazem reduced heart rate in people within 15 minutes compared with placebo. One RCT found that in people with acute atrial fibrillation and atrial flutter, intravenous diltiazem reduced heart rate within 5 minutes compared with intravenous digoxin. One RCT found no significant difference between intravenous verapamil and intravenous diltiazem in rate control or measures of systolic function in people with acute atrial fibrillation or atrial flutter, but verapamil caused hypotension in some people.

Benefits: We found no systematic review but found three RCTs.[55–57] **Versus placebo:** One RCT (113 people; 89 with atrial fibrillation of unspecified duration and 24 with atrial flutterⒼ; ventricular rate > 120 beats/minute; systolic blood pressure ≥ 90 mm Hg without severe heart failure; 108 people with at least 1 underlying condition that may explain atrial arrhythmia; mean age 64 years) compared intravenous diltiazem versus placebo.[55] After randomisation, a dose of intravenous diltiazem (or equivalent placebo) 0.25 mg/kg every 2 minutes was given; if the first dose had no effect after 15 minutes, then the code was broken and diltiazem 0.35 mg/kg every 2 minutes was given regardless of randomisation. The RCT found that intravenous diltiazem significantly decreased heart rate during a 15 minute observation period compared with placebo (ventricular rate < 100 beats/minute: 42/56 [75%] with diltiazem *v* 4/57 [7%] with placebo; P < 0.001; average decrease in heart rate: 22% with diltiazem *v* 3% with placebo; median time from start of drug infusion to maximal decrease in heart rate: 4.3 minutes; mean rate decreased from 139 beats/minute to 114 beats/minute with diltiazem).[55] The RCT found no difference in response rate to diltiazem in people with atrial fibrillation compared with those with atrial flutter. **Versus digoxin:** One RCT (30 consecutive people, 10 men, mean age 72 years, 26 with acute atrial fibrillation, 4 with atrial flutter, unspecified duration) compared intravenous diltiazem versus intravenous digoxin versus both drugs given on admission to the emergency department.[56] Heart rate control was defined as a ventricular rate of less than 100

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beats a minute. Intravenous digoxin (25 mg as a bolus at 0 and 30 minutes) and intravenous diltiazem (initially 0.25 mg/kg over the first 2 minutes, followed by 0.35 mg/kg at 15 minutes and then a titratable infusion at a rate of 10–20 mg/hour) were given to maintain heart rate control. The dosing regimens were the same whether the drugs were given alone or in combination. The RCT found that diltiazem significantly decreased ventricular heart rate within 5 minutes compared with digoxin (P = 0.0006; mean rates: 111 beats/minute with diltiazem *v* 144 beats/minute with digoxin). The decrease in heart rate achieved with digoxin did not reach statistical significance until 180 minutes (P = 0.01; mean rates: 90 beats/minute with diltiazem *v* 117 beats/minute with digoxin). No additional benefit was found with the combination of digoxin and diltiazem. **Versus verapamil:** See benefits of verapamil, p 18.[57]

Harms: **Versus placebo:** In one RCT, in the diltiazem treated group, seven people developed asymptomatic hypotension (systolic blood pressure < 90 mm Hg), three developed flushing, three developed itching, and one developed nausea and vomiting; these were not significantly different from placebo.[55] **Versus digoxin:** The RCT was not large enough to adequately assess adverse effects, and none were apparent.[56] **Versus verapamil:** See harms of verapamil, p 18. Rate limiting calcium channel blockers may exacerbate heart failure and hypotension.

Comment: The evidence suggests that calcium channel blockers such as verapamil and diltiazem reduce ventricular rate in acute or recent onset atrial fibrillation, but they are probably no better than placebo for restoring sinus rhythm. We found no studies of the effect of rate limiting calcium channel blockers on exercise tolerance in people with acute or recent onset atrial fibrillation, but studies in people with chronic atrial fibrillation found improved exercise tolerance.

OPTION SOTALOL

We found no systematic review or RCTs on the effects of sotalol to control heart rate in people with acute atrial fibrillation who are haemodynamically stable.

Benefits: We found no systematic review or RCTs.

Harms: We found no RCTs.

Comment: None.

OPTION TIMOLOL

We found no RCTs limited to people with acute atrial fibrillation. One small RCT in people with atrial fibrillation of unspecified duration found that intravenous timolol (a β blocker) reduced ventricular rate within 20 minutes compared with placebo.

Benefits: We found no systematic review. **Versus placebo:** We found no RCTs limited to people with acute atrial fibrillation. We found one RCT (61 people with atrial fibrillation of unspecified duration, ventricular rate > 120 beats/minute) that compared intravenous timolol 1 mg (a β blocker) versus intravenous placebo given immediately and repeated twice at 20 minute intervals if sinus rhythm was not achieved.[58] It found that 20 minutes after the last injection, intravenous timolol significantly increased the proportion of people who had a ventricular rate below 100 beats a minute compared with placebo (41% with timolol *v* 3% with placebo; P < 0.01).

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Atrial fibrillation (recent onset)

Harms: In the RCT, the most common adverse effects were bradycardia (2%) and hypotension (9%).[58] β Blockers may exacerbate heart failure and hypotension in acute atrial fibrillation. β Blockers plus rate limiting calcium channel blockers (diltiazem and verapamil) may increase the risk of asystole and sinus arrest.[59–61] β Blockers can precipitate bronchospasm.[62]

Comment: We found one systematic review comparing β blockers versus placebo in people with acute or chronic atrial fibrillation G.[52] It found that in 7/12 (58%) comparisons at rest and in all during exercise, β blockers reduced ventricular rate compared with placebo.

OPTION VERAPAMIL

Two RCTs found that intravenous verapamil reduced heart rate at 10 or 30 minutes compared with placebo in people with atrial fibrillation or atrial flutter. One RCT in people with atrial fibrillation or acute atrial flutter found no significant difference between intravenous verapamil and intravenous diltiazem in rate control or measures of systolic function, but verapamil caused hypotension in some people.

Benefits: We found no systematic review in people with acute atrial fibrillation. **Versus placebo:** We found two RCTs.[63,64] Both found that that intravenous verapamil reduced heart rate at 10 or 30 minutes compared with placebo in people with atrial fibrillation or atrial flutter G. The first RCT (21 men with atrial fibrillation and a rapid ventricular rate, age 37–70 years) was a crossover comparison of intravenous verapamil versus placebo (saline).[63] It found that intravenous verapamil reduced ventricular rate within 10 minutes compared with placebo (reduction > 15% of the initial rate: 17/20 [85%] with verapamil *v* 2/14 [14%] with saline; $P < 0.001$). The second RCT (double blind, crossover study of 20 people with atrial fibrillation or atrial flutter for 2 hours to 2 years) compared intravenous low dose verapamil 0.075 mg/kg versus placebo.[64] A positive response was defined as conversion to sinus rhythm or a decrease of the ventricular response to less than 100 beats a minute or by more than 20% of the initial rate. If a positive response did not occur within 10 minutes, then a second bolus injection was given (placebo for people who initially received verapamil, and verapamil for people who initially received placebo). With the first bolus injection, verapamil significantly reduced ventricular rate compared with placebo (mean heart rate: 118 beats/minute with verapamil *v* 138 with placebo), and more people converted to sinus rhythm within 30 minutes but the difference was not significant (3/20 [15%] with verapamil *v* 0/15 [0%] with placebo; $P = 0.12$). **Versus diltiazem:** We found one small double blind, crossover RCT (17 men, 5 with acute atrial fibrillation, 10 with atrial flutter, and 2 with a combination of atrial fibrillation and atrial flutter; ventricular rate ≥ 120 beats/minute, systolic blood pressure > 100 mm Hg) compared intravenous verapamil versus intravenous diltiazem.[57] It found no significant differences in rate control or measures of systolic function.

Harms: **Versus placebo:** One RCT reported that intravenous verapamil caused a transient drop in systolic and diastolic blood pressure greater than with placebo (saline), which did not require treatment, but it did not state the number of people affected.[63] The second RCT reported development of 1 : 1 flutter in one person with previous Wolff Parkinson White syndrome G and 2 : 1 flutter.[64] **Versus diltiazem:** In the third RCT, which compared verapamil versus diltiazem, 3/17 (18%) people who received verapamil as the first drug developed symptomatic hypotension and were withdrawn from the study before crossover.[57] Two people

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recovered, but the episode in the third person was considered to be life threatening. In people with Wolff Parkinson White syndrome, verapamil may increase ventricular rate and can cause ventricular arrhythmias.[65] Rate limiting calcium channel blockers may exacerbate heart failure and hypotension.

Comment: See comment on diltiazem, p 17.

GLOSSARY

Atrial flutter A similar arrhythmia to atrial fibrillation but the atrial electrical activity is less chaotic and has a characteristic saw tooth appearance on an electrocardiogram.
Chronic atrial fibrillation Refers to more sustained or recurrent forms of atrial fibrillation, which can be subdivided into paroxysmal, persistent, or permanent atrial fibrillation.
Paroxysmal atrial fibrillation If the atrial fibrillation recurs intermittently with sinus rhythm, with spontaneous recurrences or termination, it is designated as "paroxysmal", and the objective of management is suppression of paroxysms and maintenance of sinus rhythm.
Permanent atrial fibrillation If cardioversion is inappropriate, and has not been indicated or attempted, atrial fibrillation is designated as "permanent", where the objective of management is rate control and antithrombotic treatment.
Persistent atrial fibrillation When atrial fibrillation is more sustained than paroxysmal, atrial fibrillation is designated "persistent" and needs termination with pharmacological treatment or electrical cardioversion.
Torsades de pointes A form of ventricular tachycardia with atypical QRS complexes electrocardiograph pattern.
Wolff Parkinson White syndrome Occurs when an additional electrical pathway exists between the atria and ventricles as a result of anomalous embryonic development. The extra pathway may cause rapid arrhythmias. Worldwide it affects about 0.2% of the general population. In people with Wolff Parkinson White syndrome, β blockers, calcium channel blockers, and digoxin can increase the ventricular rate and cause ventricular arrhythmias.

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Atrial fibrillation (recent onset)

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TABLE 1 **RCTs comparing propafenone versus placebo in conversion to sinus rhythm in people with acute atrial fibrillation (see text, p 10).**

RCT	Population	Intervention	Control	Outcome	Time	Result
40	75 people aged 18–75 years, onset of atrial fibrillation < 72 hours	Propafenone intravenous	Placebo	Conversion to sinus rhythm	3 hours	24/41 (58.5%) with propafenone *v* 10/34 (29.4%) with placebo (OR 3.2, 95% CI 1.3 to 7.9)
41	240 people, mean age 59 years, duration of atrial fibrillation < 7 days	Propafenone	Placebo	Conversion to sinus rhythm	3 hours	54/119 (45%) with propafenone *v* 22/121 (18%) with placebo (ARR 27%, 95% CI 17% to 39%)
					8 hours	91/119 (76%) with propafenone *v* 45/121 (37%) with placebo (ARR 39%, 95%, 29% to 52%)
42	55 people, mean age 59 years, duration of atrial fibrillation < 7 days	Propafenone	Placebo	Conversion to sinus rhythm	2 hours	12/29 (41%) with propafenone *v* 2/26 (8%) with placebo (P = 0.005)
					6 hours	65% with propafenone *v* 31% with placebo (P = 0.015)
					12 hours	69% with propafenone *v* 31% with placebo (P = 0.06)
					24 hours	79% with propafenone *v* 73% with placebo (P = 0.75)
43	156 people aged 18–80 years, onset of atrial fibrillation < 72 hours	Propafenone	Placebo	Conversion to sinus rhythm	2 hour	57/81 (70.3%) with propafenone *v* 13/75 (17.3%) with placebo (ARR 53% 95% CI 42% to 68%; RR 4.06, 95% CI 2.43 to 6.79)
44	123 people, onset of atrial fibrillation < 72 hours	Propafenone intravenous or oral	Placebo	Conversion to sinus rhythm	1 hour	25/81 (31%) with propafenone *v* 7/42 with placebo (17%) (RR 1.85, 95% CI 0.87 to 3.92)
					4 hours	49/81 (61%) with propafenone *v* 14/42 (33%) with placebo (RR 1.82, 95% CI 1.14 to 2.88)
					8 hours	53/81 (65%) with propafenone *v* 20/42 (48%) with placebo (RR 1.37, 95% CI 0.96 to 1.96)
		Propafenone intravenous	Propafenone oral		1 hour	19/40 (48%) with intravenous propafenone *v*6/41 (15%) with oral propafenone (RR 3.25, 95% CI 1.45 to 7.28)
					4 hours	20/40 (50%) with intravenous propafenone *v* 29/41 (71%) with oral propafenone (RR 0.71, 95% CI 0.49 to 1.02)
33	Three arm study, 123 people aged 18–75 years, onset of atrial fibrillation < 72 hours	Propafenone	Placebo	Conversion to sinus rhythm	1 hour	20/41 (49%) with propafenone *v* 6/42 (14%) with placebo (RR 3.42, 95% CI 1.53 to 7.63)

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TABLE 0 continued

RCT	Population	Intervention	Control	Outcome	Time	Result
45	Three arm study, 77 men, mean age, recent onset atrial fibrillation ≤ 48 hours	Propafenone	Placebo	Conversion to sinus rhythm	1 hour	36/46 (78.2%) with propafenone *v* 27/49 (55.1%) with placebo (RR 1.42, 95% CI 1.06 to 1.91)

Changing behaviour

Search date September 2003

Margaret Thorogood, Melvyn Hillsdon, and Carolyn Summerbell

QUESTIONS

INTERVENTIONS

See glossary, p 105

Key Messages

- **Advice from physicians and trained counsellors to quit smoking** Systematic reviews have found that simple, one off advice from a physician during a routine consultation increased the proportion of smokers quitting smoking and not relapsing for 1 year. One systematic review found that advice from trained counsellors also increased quit rates compared with minimal intervention.
- **Advice on cholesterol lowering diet** Systematic reviews have found that advice on cholesterol lowering diet (i.e. advice to lower total fat intake or increase the ratio of polyunsaturated : saturated fatty acid) leads to a small reduction in blood cholesterol concentrations in the long term (≥ 6 months).

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- **Advice on reducing sodium intake to reduce blood pressure** One systematic review found that, compared with usual care, intensive interventions to reduce sodium intake provided small reductions in blood pressure, however effects on deaths and cardiovascular events are unclear.
- **Antidepressants (bupropion or nortriptyline) as part of a smoking cessation programme (but no evidence of benefit for selective serotonin reuptake inhibitors or moclobemide)** Systematic reviews have found that quit rates are increased by bupropion and nortriptyline given as part of a smoking cessation programme, but not by moclobemide or selective serotonin reuptake inhibitors.
- **Antismoking interventions in people at high risk of disease** (evidence that counselling or bupropion are effective in this group) Systematic reviews and four subsequent RCTs have found that antismoking advice improves smoking cessation in people at high risk of smoking related disease. We found no evidence that high intensity advice is more effective than low intensity advice in high risk people. One RCT found that bupropion increased cessation rates in smokers with cardiovascular disease.
- **Antismoking interventions for pregnant women** Two systematic reviews have found that antismoking interventions in pregnant women increase abstinence rates during pregnancy. One RCT found that nicotine patches did not significantly increase quit rates in pregnant women compared with placebo.
- **Exercise advice to women over 80 years of age** One RCT found that exercise advice delivered in the home by physiotherapists increased physical activity and reduced the risk of falling in women over 80 years.
- **Lifestyle interventions for sustained weight loss** Two large RCTs found that weight loss advice resulted in greater weight loss than no advice. One RCT found that cognitive behavioural therapy was more effective than usual care in promoting weight loss. Systematic reviews have found that using behavioural therapy to support advice on diet and exercise is probably more effective in achieving weight loss than diet advice alone. One systematic review found limited evidence that partial meal replacement plans reduced weight loss at 1 year compared with reduced calorie diet in people who completed the treatment.
- **Nicotine replacement in smokers who smoke at least 10 cigarettes daily** One systematic review found that nicotine replacement is an effective additional component of cessation strategies in smokers who smoke at least 10 cigarettes daily. We found no evidence of any particular method of nicotine delivery having superior efficacy. We found limited evidence from five RCTs (follow up 2–8 years) that the benefit of nicotine replacement treatment on quit rates decreased with time.
- **Advice from nurses to quit smoking** One systematic review found limited evidence that advice from nurses to quit smoking increased quitting at 1 year compared with no advice.
- **Counselling sedentary people to increase physical activity** We found limited evidence from systematic reviews and subsequent RCTs that counselling sedentary people increased physical activity compared with no intervention. Limited evidence from RCTs suggests that consultation with an exercise specialist rather than or in addition to a physician may increase physical activity at 1 year. We found limited evidence that interventions delivered by new media can lead to short term changes in physical activity.

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- **Lifestyle interventions to maintain weight loss** One systematic review and additional RCTs have found that most types of maintenance strategy result in smaller weight gains or greater weight losses compared with no contact. Strategies that involve personal contact with a therapist, family support, walking training programmes, or multiple interventions, or are weight focused, seem most effective.
- **Self help materials for people who want to stop smoking** One systematic review found that self help materials slightly improved smoking cessation compared with no intervention. It found that individually tailored materials were more effective than standard or stage based materials. One subsequent RCT found no significant difference in abstinence rates at 6 months between self help materials based on the stages of change model and standard self help literature.
- **Telephone advice to quit smoking** One systematic review found limited evidence that telephone counselling improved quit rates compared with interventions with no personal contact.
- **Lifestyle advice to prevent weight gain** One small RCT found that low intensity education plus a financial incentive increased weight loss compared with no treatment. A second RCT found no significant effect on prevention of weight gain from a postal newsletter with or without a linked financial incentive compared with no contact. One RCT found that lifestyle advice prevented weight gain in perimenopausal women compared with assessment alone. One small RCT comparing a nutrition course for female students with no nutrition course found no significant increase in weight from baseline in either group at 1 year.
- **Physical exercise to aid smoking cessation** One systematic review found limited evidence that exercise may increase smoking cessation.
- **Training health professionals in promoting weight loss** One systematic review of poor quality RCTs provided insufficient evidence on the sustained effect of interventions to improve health professionals' management of obesity. One subsequent cluster RCT found limited evidence that training for primary care doctors in nutrition counselling plus a support programme reduced body weight of the people in their care over 1 year compared with usual care.
- **Training health professionals to give advice on smoking cessation (increases frequency of antismoking interventions, but may not improve effectiveness)** One systematic review found that training health professionals increased the frequency of antismoking interventions being offered. It found no good evidence that antismoking interventions are more effective if the health professionals delivering the interventions received training. One RCT found that a structured intervention delivered by trained community pharmacists increased smoking cessation rates compared with usual care delivered by untrained community pharmacists.
- **Acupuncture for smoking cessation** One systematic review found no significant difference between acupuncture and control in smoking cessation rates at 1 year.
- **Anxiolytics for smoking cessation** One systematic review found no significant difference in quit rates between anxiolytics and control.

DEFINITION Cigarette smoking, diet, and level of physical activity are important in the aetiology of many chronic diseases. Individual change in

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behaviour has the potential to decrease the burden of chronic disease, particularly cardiovascular disease. This chapter focuses on the evidence that specific interventions lead to changed behaviour.

INCIDENCE/ PREVALENCE In the developed world, the decline in smoking has slowed and the prevalence of regular smoking is increasing in young people. A sedentary lifestyle is becoming increasingly common and the prevalence of obesity is increasing rapidly.

AIMS OF INTERVENTION To encourage individuals to reduce or abandon unhealthy behaviours and to take up healthy behaviours; to support the maintenance of these changes in the long term.

OUTCOMES Ideal outcomes are clinical, and relate to the underlying conditions (longevity, quality of life, and rate of stroke or myocardial infarction). However, the focus of this chapter, and the outcomes reported by most studies, are proxy outcomes, such as the proportion of people changing behaviour (e.g. stopping smoking) in a specified period.

METHODS *Clinical Evidence* search and appraisal September 2003.

QUESTION What are the effects of interventions aimed at changing people's behaviour?

OPTION ADVICE TO QUIT SMOKING

Systematic reviews have found that simple, one off advice from a physician during a routine consultation increased the proportion of smokers quitting smoking and not relapsing for 1 year. One systematic review found that advice from trained counsellors also increases quit rates compared with minimal intervention. One systematic review found limited evidence that advice to quit smoking from nurses increased quitting at 1 year compared with no advice. One systematic review provided limited evidence that telephone counselling improved quit rates compared with interventions with no personal contact. One systematic review found that self help materials slightly improved smoking cessation compared with no intervention. It found that individually tailored materials were more effective than standard or stage based materials. One subsequent RCT found no significant difference in abstinence rates at 6 months between self help materials based on the stages of change model and standard self help literature.

Benefits: We found five systematic reviews[1–5] and two subsequent RCTs.[6,7] **Physicians:** The first review (search date 2000, 34 RCTs, 28 000 smokers) considered advice given by physicians, most often in the primary care setting, but also in hospitals and other clinics.[1] It found that brief advice improved quit rates compared with no advice (16 trials, 12 with follow up for at least 1 year; 451/7705 [5.9%] with brief advice *v* 241/5870 [4.1%] with no advice; meta-analysis OR 1.69, 95% CI 1.45 to 1.98). Intensive advice slightly improved quit rates compared with minimal advice among smokers not at high risk of disease (10 trials, 7 with follow up for at least 1 year; OR with intensive *v* minimal advice 1.23, 95% CI 1.02 to 1.49). The first subsequent RCT tested a brief (10 minute) intervention given by general practitioners who had received 2 hours of training.[6] The

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intervention increased the abstinence rate at 12 months (7.3% with control *v* 13.4% with intervention; $P < 0.05$). **Counsellors:** The second systematic review (search date 2002, 15 RCTs) examined individual counselling of at least 10 minutes by professionals trained in smoking cessation (social work, psychology, psychiatry, health education, and nursing).[2] Follow up was at 6–12 months. The review found that counselling increased the rate of quitting (340/2590 [13%] with counselling *v* 232/2592 [9%] with control; OR of quitting 1.64, 95% CI 1.33 to 2.01).[2] The authors did not find a greater effect of intensive counselling compared with brief counselling (3 RCTs; OR 0.98, 95% CI 0.61 to 1.56). **Nurses:** The third review (search date 2001, 22 RCTs, 5 with follow up for < 1 year) considered the effectiveness of smoking interventions delivered by a nurse. It found that advice from a nurse increased the rate of quitting by the end of follow up (meta-analysis of 18 studies: 646/4836 [13.4%] with advice *v* 405/3356 [12.1%] with control; OR 1.50, 95% CI 1.29 to 1.73).[3] However, this review did have methodological weaknesses (see comment below). **Telephone advice:** The fourth systematic review (search date 2000, 23 RCTs) considered counselling delivered by telephone.[4] Ten of the included trials (9 with follow up for at least 12 months) compared proactive telephone counselling versus minimum intervention (involving no person to person contact). Pooled analysis was not possible because of statistical heterogeneity among trials. However, three trials found that telephone counselling was significantly more effective than minimum intervention, four trials found a non-significant benefit, and none of the trials found significant harms of telephone counselling. **Self help materials:** We found one systematic review (search date 2002, 51 RCTs)[5] that examined effects of providing materials giving advice and information to smokers attempting to give up on their own and one subsequent RCT.[7] The review found that self help materials without face to face contact slightly improved smoking cessation compared with no intervention (11 RCTs, including 8 RCTs with at least 12 months' follow up; OR 1.24, 95% CI 1.07 to 1.49). Individually tailored materials were more effective than standard or stage based materials (10 RCTs; OR for cessation 1.36, 95% CI 1.13 to 1.64). The subsequent RCT (2471 smokers) found no significant difference in abstinence rates at 6 months between self help materials based on the stages of change model and standard self help literature (abstinence: OR for stage of change materials *v* standard self help material 1.53, 95% CI 0.76 to 3.10).[7]

Harms: We found no evidence of harm.

Comment: The effects of advice may seem small, but a year on year reduction of 2% in the proportion of smokers would represent a significant public health gain (see smoking cessation under primary prevention, p 159). In the systematic review of advice provided by nurses,[3] there was significant heterogeneity of the study results and many studies may not have been adequately randomised (7/18 [39%] studies did not specify the randomisation method and 3/18 [17%] used an inadequate form of randomisation).

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OPTION NICOTINE REPLACEMENT FOR SMOKING CESSATION

One systematic review found that nicotine replacement is an effective additional component of cessation strategies. We found no evidence of any particular method of nicotine delivery having superior efficacy. We found limited evidence from five RCTs (follow up 2–8 years) that the benefit of nicotine replacement treatment on quit rates decreased with time.

Benefits:

Abstinence at 12 months: We found one systematic review (search date 2002)[8] that identified 51 trials of nicotine chewing gum, 34 of nicotine transdermal patches, four of nicotine intranasal spray, four of inhaled nicotine, and three of sublingual tablets. All forms of nicotine replacement were more effective than placebo. When the abstinence rates for all trials were pooled according to the longest duration of follow up available, nicotine replacement increased the odds of abstinence compared with placebo (3335/19 783 [16.8%] with nicotine replacement *v* 1835/17 977 [10.2%] with placebo; OR 1.74, 95% CI 1.64 to 1.86). The review found no significant difference in abstinence with different forms of nicotine replacement in indirect comparisons (OR 1.66 for nicotine chewing gum *v* 2.27 for nicotine nasal spray) or direct comparisons (1 RCT, inhaler *v* patch; OR 0.57, 95% CI 0.19 to 1.65). In trials that directly compared 4 mg with 2 mg nicotine chewing gum, the higher dose improved abstinence in highly dependent smokers (OR 2.18, 95% CI 1.49 to 3.17). High dose patches slightly increased abstinence compared with standard dose patches (6 RCTs; OR 1.21, 95% CI 1.03 to 1.42). The review found no significant difference in effectiveness for 16 hour compared with 24 hour patches, and no difference in effect in trials where the dose was tapered compared with those where the patches were withdrawn abruptly. Use of the patch for 12 weeks was as effective as longer use and there was limited evidence that repeated use of nicotine replacement treatment in people who have relapsed after an initial course may produce further quitters, though the absolute effect was small. One included RCT (3585 people) found that abstinence at 1 week was a strong predictor of 12 month abstinence (25% of those abstinent at 1 week were abstinent at 12 months *v* 2.7% of those not abstinent at 1 week).[9] One meta-analysis of relapse rates in nicotine replacement trials found that nicotine replacement increased abstinence at 12 months, but that continued nicotine replacement did not significantly affect relapse rates between 6 weeks and 12 months.[10] **Longer term abstinence:** We found five RCTs[11–15] that found nicotine replacement did not affect long term abstinence. In one RCT that compared nicotine spray with placebo, 47 people abstinent at 1 year were followed for up to a further 2 years and 5 months, after which there was still a significant, although smaller, difference in abstinence (abstinence in the longer term 15.4% with nicotine spray *v* 9.3% with placebo; NNT [for 1 extra person to abstain] 7 at 1 year *v* 11 at 3.5 years).[11] The second RCT compared 5 months of nicotine patches plus nicotine spray versus the same patches plus a placebo spray. It found no significant difference between treatments after 6 years (16.2% abstinent with nicotine spray *v* 8.5% with placebo spray; P = 0.08).[12] The third RCT compared patches delivering different

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nicotine doses versus placebo patches. The trial followed everyone that quit at 6 weeks for a further 4–5 years and found no significant difference in relapse between the groups. Overall, 73% of people who quit at 6 weeks relapsed.[13] The fourth RCT followed up 840 of 1686 people, 8 years after they participated in a trial of nicotine replacement therapy.[14] It found similar rates of relapse in the active and placebo groups, with no significant difference between the groups in 8 year continuous abstinence rates (OR 1.39, 95% CI 0.89 to 2.17).[14] The fifth RCT followed 107 of 311 health care workers 5 years after they participated in a trial comparing nicotine replacement therapy versus placebo patch.[15] It found no significant difference in abstinence rates at 5 years (18% with nicotine *v* 14% with placebo; P = 0.797).

Harms: Nicotine chewing gum has been associated with hiccups, gastrointestinal disturbances, jaw pain, and orodental problems. Nicotine transdermal patches have been associated with skin sensitivity and irritation. Nicotine inhalers and nasal spray have been associated with local irritation at the site of administration. Nicotine sublingual tablets have been reported to cause hiccups, burning, smarting sensations in the mouth, sore throat, coughing, dry lips, and mouth ulcers.[16]

Comment: Nicotine replacement may not represent an "easy cure" for nicotine addiction, but it does improve the cessation rate. The evidence suggests that the most of smokers attempting cessation fail at any one attempt or relapse over the next 5 years. Multiple attempts may be needed.

OPTION ACUPUNCTURE FOR SMOKING CESSATION

One systematic review found no significant difference between acupuncture and control in smoking cessation rates at 1 year.

Benefits: We found one systematic review (search date 2002, 22 RCTs, 4158 adults, 330 young people aged 12–18 years) comparing acupuncture with sham acupuncture, other treatment, or no treatment.[17] Seven RCTs (2701 people) reported abstinence after at least 12 months. The review found no significant difference in smoking cessation with acupuncture compared with control at 12 months (OR 1.08, 95% CI 0.77 to 1.52).

Harms: None reported.

Comment: None.

OPTION PHYSICAL EXERCISE FOR SMOKING CESSATION

One systematic review found limited evidence that physical exercise may increase smoking cessation.

Benefits: We found one systematic review (search date 2002, 8 RCTs)[18] comparing exercise versus control interventions. Only one of the eight trials found evidence for exercise aiding smoking cessation. However, the trials which did not show a significant effect of exercise on smoking abstinence were too small to exclude reliably an effect of intervention and had numerous methodological limitations. One

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RCT (281 women) found that three exercise sessions a week for 12 weeks plus a cognitive behavioural programme (see glossary, p 105) improved continuous abstinence from smoking at 12 months compared with the cognitive behavioural programme alone (11.9% with programme plus exercise *v* 5.4% with programme alone; OR 2.36, 95% CI 0.97 to 5.70).[19]

Harms: None reported.

Comment: None.

OPTION ANTIDEPRESSANT AND ANXIOLYTIC TREATMENT FOR SMOKING CESSATION

Systematic reviews have found that quit rates are increased by bupropion and nortriptyline given as part of a smoking cessation programme, but not by moclobemide, selective serotonin reuptake inhibitors, or anxiolytics.

Benefits: **Antidepressants:** We found one systematic review of antidepressants given as part of a smoking cessation programme (search date 2002, 30 RCTs).[20] Sixteen of the RCTs (7397 people) reported 12 month cessation rates. The review found that bupropion significantly increased quit rates compared with placebo at 6–12 months (data from 10 RCTs with 12 months' follow up plus 6 RCTs with 6 months' follow up; OR of quitting 1.97, 95% CI 1.67 to 2.34).[20] Two RCTs identified by the review compared bupropion plus a nicotine patch versus patch alone and found different results. One RCT (893 people) found that combined treatment improved cessation compared with patch alone (OR 2.65, 95% CI 1.58 to 4.45). The second RCT (244 people) found no significant difference (OR 0.75, 95% CI 0.59 to 3.00). Five other included RCTs (3 with 6 months' and 2 with 12 months' follow up) found that nortriptyline improved long term (6–12 month) abstinence rates compared with placebo (OR 2.80, 95% CI 1.81 to 4.32). One RCT of moclobemide found no significant difference in abstinence at 12 months. Four included RCTs of selective serotonin reuptake inhibitors found no significant effect (OR 0.97, 95% CI 0.71 to 1.32). **Anxiolytics:** We found one systematic review of anxiolytics (search date 2000, 6 RCTs).[21] Four of the RCTs (626 people) reporting 12 month cessation rates found no significant increase in abstinence between anxiolytics and control treatment.[21]

Harms: **Antidepressants:** Headache, insomnia, and dry mouth were reported in people using bupropion.[21] Nortriptyline can cause sedation and urinary retention, and can be dangerous in overdose. One large RCT found that discontinuation rates caused by adverse events were 3.8% with placebo, 6.6% for nicotine replacement treatment, 11.9% for bupropion, and 11.4% for bupropion plus nicotine replacement treatment.[22] Allergic reactions to bupropion have been reported in about 1/1000 people. **Anxiolytics:** Anxiolytics may cause dependence and withdrawal problems, tolerance, paradoxical effects, and impair driving ability.

Comment: None.

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OPTION ANTISMOKING INTERVENTIONS FOR PREGNANT WOMEN

Two systematic reviews found that antismoking interventions in pregnant women increased abstinence rates during pregnancy. One RCT found that nicotine patches did not significantly increase quit rates in pregnant women compared with placebo.

Benefits: We found two systematic reviews[23,24] and three additional RCTs.[25–27] The most recent review (search date 1998, 44 RCTs) assessed smoking cessation interventions in pregnancy. It found that smoking cessation programmes improved abstinence (OR of continued smoking in late pregnancy with antismoking programmes *v* no programmes 0.53, 95% CI 0.47 to 0.60).[23] The findings were similar if the analysis was restricted to trials in which abstinence was confirmed by means other than self reporting. The review calculated that of 100 smokers attending a first antenatal visit, 10 stopped spontaneously and a further six or seven stopped as the result of a smoking cessation programme. Five included trials examined the effects of interventions to prevent relapse in 800 women who had quit smoking. Collectively, these trials found no evidence that the interventions reduced relapse rate.[23] One earlier systematic review (search date not reported, 10 RCTs, 4815 pregnant women)[24] of antismoking interventions included one trial of physician advice, one trial of advice by a health educator, one trial of group sessions, and seven trials of behavioural therapy based on self help manuals. Cessation rates among trials ranged from 1.9–16.7% in the control groups and from 7.1–36.1% in the intervention groups. The review found that antismoking interventions significantly increased the rate of quitting (ARI with intervention *v* no intervention 7.6%, 95% CI 4.3% to 10.8%).[24] One additional RCT found that nicotine patches did not significantly alter quit rates in pregnant women compared with placebo.[25] The second additional RCT (1120 pregnant women) compared a brief (10–15 minute) smoking intervention delivered by trained midwives at booking interviews versus usual care.[26] It found no significant difference in smoking behaviour between women receiving intervention compared with usual care (abstinence in final 12 weeks of pregnancy until birth 17% in each group; abstinence for 6 months after birth 7% with intervention *v* 8% with control). The intervention was difficult to implement (see comment below). The third additional RCT compared motivational interviewing (see glossary, p 105) with usual care in 269 women in their 28th week of pregnancy who had smoked in the past month.[27] It found no significant differences in cessation rate between intervention and control group at 34th week or at 6 months post partum.

Harms: None reported.

Comment: The recent review found that some women quit smoking before their first antenatal visit, and most of these will remain abstinent.[23] Recruitment to the RCT comparing midwife delivered intervention versus usual care was slow. Midwives reported that the intervention was difficult to implement because of a lack of time to deliver the intervention at the booking appointment.[26]

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OPTION ANTISMOKING INTERVENTIONS FOR PEOPLE AT HIGH RISK OF DISEASE

Systematic reviews and four subsequent RCTs have found that antismoking advice improves smoking cessation in people at high risk of smoking related disease. We found no evidence that high intensity advice is more effective than low intensity advice in high risk people. One RCT found that bupropion increased cessation rates in smokers with cardiovascular disease.

Benefits: We found no trials in which the same intervention was used in high and low risk people. We found one systematic review (search date not reported, 4 RCTs, 13 208 healthy men at high risk of heart disease),[24] one systematic review among people admitted to hospital (search date 2002, 17 RCTs),[28] one systematic review among people with chronic obstructive pulmonary disease (search date 2002, 5 RCTs),[29] and five subsequent RCTs.[30–34] The first review found that antismoking advice improved smoking cessation rates compared with control interventions among healthy men at high risk of heart disease (ARI of smoking cessation 21%, 95% CI 10% to 31%; NNT 5, 95% CI 4 to 10).[24] One early trial (223 men) that was included in the review used non-random allocation after myocardial infarction. The intervention group was given intensive advice by the therapeutic team while in the coronary care unit. The trial found that the self reported cessation rate at 1 year or more was higher in the intervention group than the control group (63% quit in the intervention group *v* 28% in the control group; ARI of quitting 36%, 95% CI 23% to 48%).[35] The second review included seven trials (6 of them with at least 12 months' duration) of high intensity behavioural interventions (defined as contact in hospital plus active follow up for at least 1 month) among smokers admitted to hospital. The review found that active intervention increased quit rates compared with usual care (OR 1.82, 95% CI 1.49 to 2.22).[28] The third review (search date 2002, 2 RCTs reporting cessation rate at ≥ 12 months) concentrated on smoking cessation among people with chronic obstructive pulmonary disease.[29] It found that psychosocial interventions plus nicotine replacement therapy plus a bronchodilator significantly increased cessation rates at 5 years compared with no treatment (RR 4.00, 95% CI 3.25 to 4.93). The first subsequent RCT compared postal advice on smoking cessation versus no intervention in men aged 30–45 years with either a history of asbestos exposure, or forced expiratory volume in 1 second in the lowest quartile for their age. Postal advice increased the self reported sustained cessation rate at 1 year compared with no intervention (5.6% with postal advice *v* 3.5% with no intervention; $P < 0.05$).[30] The second subsequent RCT (254 smokers admitted to hospital with coronary artery disease) compared a stepped care approach where people who did not quit by the end of each stage received successively more intense interventions (consisting of counselling plus nicotine patch) versus a brief cessation intervention.[31] It found no significant difference in cessation rates at 1 year (39% with more intensive intervention *v* 36% with brief intervention; $P = 0.36$). The third subsequent RCT (223 smokers admitted to hospital) compared intensive counselling plus outpatient follow up plus nicotine patches versus minimal counselling plus nicotine

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patches.[32] It found no significant difference in cessation rate between intensive and minimal intervention at 12 months (16% with intensive counselling *v* 9% with minimal counselling; P = 0.21). The fourth subsequent RCT (432 people with cancer) compared a brief structured intervention from a physician versus usual care.[33] It found no significant difference between interventions in cessation rates at 1 year (13.3% with intervention *v* 13.6% with usual care; P = 0.52). The fifth subsequent RCT (629 people with cardiovascular disease) compared sustained release bupropion (150 mg/day increasing to 150 mg twice daily) therapy versus placebo for 7 weeks.[34] It found that bupropion significantly increased cessation rates at 12 months compared with placebo (22% with bupropion *v* 9% with placebo; P < 0.001).

Harms: The fifth subsequent RCT found that bupropion increased insomnia, dry mouth, and cardiovascular events compared with placebo (insomnia: 24% with bupropion *v* 12% with placebo; dry mouth: 18% with bupropion *v* 10% with placebo; cardiovascular events: 7.7% with bupropion *v* 4.5% with placebo; P value not reported).[34] The systematic reviews and other RCTs did not report harms.

Comment: There was heterogeneity in the four trials included in the review among healthy men at high risk of heart disease, partly because of a less intense intervention in one trial and the recording of a change from cigarettes to other forms of tobacco as success in another.[24] One of the included trials was weakened by use of self reported smoking cessation as an outcome and non-random allocation to the intervention.[35]

OPTION TRAINING HEALTH PROFESSIONALS TO ENCOURAGE SMOKING CESSATION

One systematic review found that training health professionals increases the frequency of antismoking interventions being offered. It found no good evidence that antismoking interventions are more effective if the health professionals delivering the interventions received training. One RCT found that a structured intervention delivered by trained community pharmacists increased smoking cessation rates compared with usual care delivered by untrained community pharmacists.

Benefits: We found one systematic review[36] and one subsequent RCT.[37] The review (search date 2000, 9 RCTs) included eight RCTs of training medical practitioners and one RCT of training dental practitioners to give antismoking advice.[36] All the trials took place in the USA. The training was provided on a group basis, and variously included lectures, videotapes, role play, and discussion. The importance of setting quit dates and offering follow up was emphasised in most of the training programmes. The review found no good evidence that training health professionals leads to higher quit rates in people receiving antismoking interventions from those professionals, although training increased the frequency with which such interventions were offered. Three of the trials used prompts and reminders to practitioners to deploy smoking cessation techniques, and found that prompts increased the frequency of health professional interventions.[36] The subsequent RCT compared a structured smoking cessation intervention delivered by community pharmacists, who

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had received 3 hours of training versus no specific training or antismoking intervention.[37] Intervention delivered by trained pharmacists improved abstinence compared with usual care (AR of abstinence at 12 months: 14.3% with intervention *v* 2.7% with usual care; RR 5.3; NNT 9; CI values not reported; $P < 0.001$).

Harms: None reported.

Comment: The results of the systematic review should be interpreted with caution because there were variations in the way the analysis allowed for the unit of randomisation.

OPTION COUNSELLING FOR INCREASING PHYSICAL ACTIVITY IN SEDENTARY PEOPLE

We found limited evidence from systematic reviews and subsequent RCTs that counselling sedentary people increased physical activity compared with no intervention. Limited evidence from RCTs suggests that consultation with an exercise specialist rather than or in addition to a physician may increase physical activity at 1 year. We found limited evidence that interventions delivered by new media can lead to short term changes in physical activity.

Benefits: We found three systematic reviews that focused on different types of interventions[38–40] and nine subsequent RCTs.[41–49] The first review (search date 1996, 11 RCTs based in the USA, 1699 people) assessed the effect of single factor physical activity promotion on exercise behaviour.[38] Seven trials evaluated advice to undertake exercise from home (mainly walking, but including jogging and swimming), and six evaluated advice to undertake facility based exercise (including jogging and walking on sports tracks, endurance exercise, games, swimming, and exercise to music classes). An increase in activity in the intervention groups was seen in trials in which home based moderate exercise was encouraged and regular brief follow up of participants was provided. In most of the trials, participants were self selected volunteers, so the effects of the interventions may have been exaggerated. The second systematic review (search date not reported, 3 RCTs, 420 people) compared "lifestyle" physical activity interventions with either standard exercise treatment or a control group.[39] Lifestyle interventions were defined as those concerned with the daily accumulation of moderate or vigorous exercise as part of everyday life. The first RCT in the review (60 adults, 65–85 years old) found significantly more self reported physical activity in the lifestyle group than a standard exercise group. The second RCT in the review (235 people, 35–60 years old) found no significant difference in physical activity between the groups. The third RCT in the review (125 women, 23–54 years old) of encouraging walking found no significant difference in walking levels at 30 months' follow up between people receiving an 8 week behavioural intervention and those receiving a 5 minute telephone call and written information about the benefits of exercise, although both groups increased walking. The third review (search date 2002, 7 RCTs and 1 quasi-randomised trial, 9054 people) examined the efficacy of exercise counselling from a primary care clinician compared with a control or comparison group.[40] Counselling was delivered using advice only, the promotion

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of self efficacy, posted educational materials, referral to community resources, and written exercise prescriptions. The review found equivocal results and at least one methodological limitation in most studies. There was limited evidence that the interventions in these studies led to short term (< 3 months) improvements in physical activity. There were insufficient studies to consider the relationship between the components of the interventions and the reported efficacy. Only two RCTs identified by the review[40] were rated as good quality.[50,51] The first good quality RCT identified by the review (874 people) compared 3 minutes of physician advice plus educational materials, all the above plus behavioural counselling plus interactive mail, and all the above plus telephone counselling plus classes.[50] It found no significant difference in self reported activity between interventions at 24 months. The second good quality RCT identified by the review (355 sedentary people) compared a brief 5 minute message, a prescription for exercise, and a follow up visit with usual care.[51] It found no significant difference in the proportion of people meeting the Healthy People 2010 goal after 8 months (28% with advice or prescription *v* 23% with usual care; difference +5%, 95% CI −6% to +14%). All but two of the subsequent trials[47,49] involved primary care delivered interventions, although they were not restricted to clinician led interventions.[41–46] Two of the three trials in which advice was delivered by an exercise specialist rather than a physician found significant improvement in self reported physical activity at long term (> 6 months) follow up compared with controls.[43,44] A third RCT (1658 people in a primary care setting), which compared a client centred, negotiating style to direct advice and a no intervention control group, did not find any significant difference in changes in physical activity.[46] One cluster RCT (878 people from 42 rural and urban general practices) compared clinician advice plus a written "green" exercise prescription and up to three 10–20 minute telephone calls from an exercise specialist over 3 months versus usual care.[48] Clinicians in the intervention practices were offered training in motivational interviewing (see glossary, p 105) and interviews averaged 7 minutes of general practitioner time or 13 minutes of nurse time. The physical activity goals in the "green" exercise prescription were tailored to the individual but typically involved home based physical activity or walking. It found that the intervention significantly increased physical activity at 12 months compared with usual care (leisure exercise per week: 55 minutes with intervention *v* 17 minutes with usual care; difference: 33.6 minutes, 95% CI 2.4 minutes to 64.2 minutes). Short term improvement was found in two further trials, but not maintained at 9 months or 1 year.[41,42] One RCT (298 people) compared physical activity counselling with nutrition counselling, both delivered with automated telephone conversations using digitised human speech.[47] The system used information about current behaviour and some known determinants to counsel people on either physical activity or nutrition. The percentage of individuals meeting current physical activity recommendations at 3 months' follow up was significantly greater in the physical activity group compared with the nutrition group at 3 months. However, there was no significant difference at 6 months (3 months: 26% with activity counselling *v* 19.6% with dietary counselling; P = 0.04). One RCT

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(229 women) of encouraging women to increase walking found significantly increased walking in the intervention group at 10 years' follow up (86% of women available for follow up, median estimated calorie expenditure from self reported amount of walking 1344 kcal/week with encouragement *v* 924 kcal/week with no encouragement; P = 0.01).[52] A further RCT (260 people in a primary care setting) compared the additional offer of community walks (led by lay people) versus advice alone.[45] It found no significant difference in physical activity at 12 months' follow up (ARR for achieving at least 120 minutes of moderate intensity activity a week +6%, 95% CI −5% to +16.4%). One RCT (299 office based civil servants) in a workplace setting compared individual counselling tailored according to the workers' stage of change (7 sessions of 20 minutes each) versus written information on lifestyle.[49] It found that the intervention significantly increased energy expenditure and cardiorespiratory fitness at 9 months compared with information only (difference in energy expenditure: 176.2 kcal/day, 95% CI 60.6 kcal/day to 291.8 kcal/day; difference in submaximal heart rate: −4.7 beats/minute, 95% CI −7.4 beats/minute to −2.05 beats/minute).[14] It found no significant difference in the proportion of people meeting criteria for moderate intensity physical activity (OR 1.46, 95% CI 0.76 to 2.79).

Harms: Insufficient detail is available from these studies to judge the potential harm of exercise counselling. In the RCT comparing behavioural counselling with brief advice identified by the third systematic review,[40] 60% of participants experienced a musculoskeletal event during the 2 years of the study.[50] About half of these required a visit to the physician. About 5% of all participants were admitted to hospital for a suspected cardiovascular event. The trial lacked a non-intervention control group. We found no evidence that counselling people to increase activity levels increased adverse events compared with no counselling.

Comment: Self reporting of effects by people in a trial, especially where blinding to interventions is not possible (as is the case with advice or encouragement), is a potential source of bias. Few studies conduct intention to treat analyses, which may lead to an exaggeration of the true effect of interventions. Methodological problems in RCTs included in the third review included only moderate follow up rates, highly motivated providers, differences in physical activity levels at baseline between intervention groups, uncertain or low provided adherence, inclusion of some counselling advice in usual care control groups, and inadequate power to detect a clinically important difference.[40]

OPTION EXERCISE ADVICE IN WOMEN AGED OVER 80 YEARS

One RCT found that exercise advice increased physical activity in women aged over 80 years and decreased the risk of falling.

Benefits: We found no systematic review. One RCT (233 women > 80 years old, conducted in New Zealand) compared four visits from a physiotherapist who advised a course of 30 minutes of home based exercises three times a week that was appropriate for the individual

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versus a similar number of social visits.[53] After 1 year, women who had received physiotherapist visits were significantly more active than women in the control group, and 42% were still completing the recommended exercise programme at least three times a week. The mean annual rate of falls in the intervention group was 0.87 compared with 1.34 in the control group, a difference of 0.47 falls a year (95% CI 0.04 falls/year to 0.90 falls/year).

Harms: No additional harms in the intervention group were reported.

Comment: None.

OPTION ADVICE ON A CHOLESTEROL LOWERING DIET

Systematic reviews have found that advice on eating a cholesterol lowering diet (i.e. advice to reduce fat intake or increase the polyunsaturated : saturated fatty acid ratio in the diet) leads to a small reduction in blood cholesterol concentrations in the long term (≥ 6 months).

Benefits: **Effects on blood cholesterol:** We found three systematic reviews[16,54,55] and two subsequent RCTs[56,57] that reported biochemical rather than clinical end points. None of the reviews included evidence after 1996. One review (search date 1993) identified five trials of cholesterol lowering dietary advice (principally advice from nutritionists or specially trained counsellors) with follow up for 9–18 months.[54] It found a mean reduction in blood cholesterol concentration in the intervention group of 0.22 mmol/L (95% CI 0.05 mmol/L to 0.39 mmol/L) compared with the control group. There was significant heterogeneity ($P < 0.02$), with two outlying studies — one showing no effect and one showing a larger effect. This review excluded trials in people at high risk of heart disease. Another systematic review (search date 1994) identified 13 trials of more than 6 months' duration and included people at high risk of heart disease.[16] It found that dietary advice reduced blood cholesterol (mean reduction in blood cholesterol concentration with advice 4.5%, 95% CI 3.9% to 5.1%; given a mean baseline cholesterol of 6.3 mmol/L, mean AR about 0.3 mmol/L). The third systematic review (search date 1996, 1 trial,[58] 76 people) found no significant difference between brief versus intensive advice from a general practitioner and dietician on blood cholesterol at 1 year.[55] The first subsequent RCT (186 men and women at high risk of coronary heart disease) compared advice on healthy eating versus no intervention. At 1 year it found no significant differences between groups in total and low density lipoprotein cholesterol concentrations for either sex, even though the reported percentage of energy from fat consumed by both women and men in the advice group decreased significantly compared with that reported by the women and men in the control group.[56] These results may reflect bias caused by self reporting of dietary intake. The second RCT, in 531 men with hypercholesterolaemia (with and without other hyperlipidaemias) and fat intake of about 35%, compared dietary advice aimed at reducing fat intake to 30% versus 26% versus 22%. All interventions were similarly effective for reducing fat intake (total fat intake after intervention about 26% in all groups).[57] **Effects on**

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clinical outcomes: We found two systematic reviews that reported on morbidity and mortality.[16,59] The first review (search date 1994) compared 13 separate and single dietary interventions.[16] It found no significant effect of dietary interventions on total mortality or coronary heart disease mortality (total mortality: OR 0.93, 95% CI 0.84 to 1.03; coronary heart disease mortality: OR 0.93, 95% CI 0.82 to 1.06). However, it found a reduction in non-fatal myocardial infarction (OR 0.77, 95% CI 0.67 to 0.90). The second review (search date 1999, 27 studies including 40 intervention arms, 30 901 person years) found dietary advice to reduce or modify dietary fat had no significant effect on total mortality or cardiovascular disease mortality compared with no dietary advice (total mortality: HR 0.98, 95% CI 0.86 to 1.12; cardiovascular disease mortality: HR 0.98, 95% CI 0.77 to 1.07). However, dietary advice significantly reduced cardiovascular disease events (HR 0.84, 95% CI 0.72 to 0.99).[59] RCTs in which people were followed for more than 2 years showed significant reductions in the rate of cardiovascular disease events. The relative protection from cardiovascular disease events was similar in both high and low risk groups, but was significant only in high risk groups.

Harms: We found no evidence about harms.

Comment: The finding of a 0.2–0.3 mmol/L reduction in blood cholesterol in the two systematic reviews accords with the findings of a meta-analysis of the plasma lipid response to changes in dietary fat and cholesterol.[60] The analysis included data from 244 published studies (trial duration 1 day to 6 years), and concluded that adherence to dietary recommendations (30% energy from fat, < 10% saturated fat, and < 300 mg cholesterol/day) compared with average US dietary intake would reduce blood cholesterol by about 5%.

OPTION ADVICE ON REDUCING SODIUM INTAKE

One systematic review found that, compared with usual care, intensive interventions to reduce sodium intake provided small reductions in blood pressure, however effects on deaths and cardiovascular events are unclear.

Benefits: We found one systematic review (search date not reported).[61] The review identified three RCTs in 2326 normotensive people, five RCTs in 387 people with untreated hypertension, and three RCTs in 801 people with treated hypertension.[61] Follow up ranged from 6 months to 7 years. The large, high quality RCTs compared intensive behavioural interventions aimed at reducing salt intake (including comprehensive dietary and behaviour change programmes, group counselling sessions, newsletters, self assessment, goal setting, food tasting, and recipes) versus control interventions that did not promote salt reduction. In the included RCTs, outcomes were inconsistently defined and reported. Overall, the RCTs reported no significant difference in mortality between low salt and usual diet (4 RCTs; AR 8/1151 [0.69%] with low sodium *v* 9/1242 [0.72%] with control; P = 0.8). The review found no significant difference in cardiovascular events between low sodium diet and usual diet (2 RCTs; AR 42/374 [11.2%] with low sodium *v* 51/374 [13.6%] with

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usual diet; P = 0.3). It found that advice to reduce salt intake significantly reduced systolic blood pressure and reduced diastolic blood pressure at 13–60 months compared with control, although the reduction in diastolic pressure was not statistically significant (4 RCTs, 2347 people; reduction in systolic blood pressure: 1.1 mm Hg, 95% CI 1.8 mm Hg to 0.4 mm Hg; reduction in diastolic blood pressure: +0.6 mm Hg, 95% CI +1.5 mm Hg to –0.3 mm Hg). The degree of reduction in sodium intake was not related to change in blood pressure. The review found no significant difference between treatments for systolic or diastolic blood pressure at 7 years but may have lacked power to detect a clinically important difference (1 RCT, 128 normotensive people, change in systolic blood pressure: –1.6 mm Hg with low salt diet *v* +2.20 mm Hg with usual diet; P = 0.07; change in diastolic blood pressure: –7.5 mm Hg with low salt diet *v* –5.3 mm Hg with usual diet; P = 0.1). One large RCT identified by the review found that low salt diet advice significantly improved maintenance of blood pressure control after antihypertensive treatment medications were stopped compared with usual diet (1 RCT, 975 people, combined outcome of high blood pressure or restarting treatment or clinical cardiovascular event: RR 0.83, 95% CI 0.75 to 0.92).

Harms: None reported.

Comment: None.

OPTION LIFESTYLE INTERVENTIONS FOR SUSTAINED WEIGHT LOSS

Two large RCTs found that weight loss advice resulted in greater weight loss than no advice. One RCT found that cognitive behavioural therapy was more effective than usual care in promoting weight loss. Systematic reviews found that using behavioural therapy to support advice on diet and exercise is probably more effective in achieving weight loss than diet advice alone. One systematic review found limited evidence that partial meal replacement plans reduced weight loss at 1 year compared with reduced calorie diet in people who completed the treatment.

Benefits: We found four systematic reviews[62–65] and 21 additional RCTs (see table 1, p 110).[66–86] The first systematic review (search date 1995) identified one relevant RCT that found that the combination of diet and exercise in conjunction with behavioural therapy produced significantly greater weight loss than diet alone at 1 year (mean weight loss: 7.9 kg with diet plus exercise plus behavioural therapy *v* 3.8 kg with diet alone; significance result not reported).[62] The second systematic review (search date 1997, 3 RCTs) found that diet supported by behavioural therapy was more effective than diet alone at 1 year.[63] The third systematic review of the detection, prevention, and treatment of obesity (search date 1999) included eight RCTs comparing dietary prescriptions versus exercise, counselling, or behavioural therapy for the treatment of obesity, and three RCTs comparing dietary counselling alone versus no intervention. In both comparisons, initial weight loss was followed by gradual weight regain once treatment had stopped (mean difference in weight change at least 2 years after baseline, 2–6 kg with dietary

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prescription *v* 2–4 kg with dietary counselling).[64] The fourth systematic review (search date 2001, 6 RCTs, 487 people, 75% women, 24% with diabetes) found that partial meal replacement plans (see glossary, p 105) significantly increased weight loss at 1 year compared with a reduced calorie diet (weight loss for 219 completers, fixed effects model: 7.31 kg with partial meal *v* 2.61 kg with reduced calorie; P = 0.001).[66] However, results should be interpreted with caution, because of the high rate of withdrawal (47% with partial meal *v* 64 % with reduced calorie; P for difference = 0.001) and significant heterogeneity among RCTs (P ≤ 0.005). The additional RCTs are summarised in table 1, p 110. Two large RCTs found that weight loss advice resulted in greater weight loss than no advice.[66,79] One RCT found that cognitive behavioural therapy significantly increased weight loss compared with usual care at 1 year.[85] The heterogeneity of interventions used in the additional RCTs makes comparison of trials difficult, but no major differences were found among the various weight loss programmes.

Harms: The systematic reviews and RCTs provided no evidence about harms.

Comment: In one RCT (78 obese women), the withdrawal rate for a diet programme was 41% compared with 8% in a non-diet control.[73]

OPTION LIFESTYLE INTERVENTIONS FOR MAINTAINING WEIGHT LOSS

One systematic review and additional RCTs found that most types of maintenance strategy result in smaller weight gains or greater weight losses compared with no contact. Strategies that involve personal contact with a therapist, family support, walking training programmes, or multiple interventions, or are weight focused, seem most effective.

Benefits: We found one systematic review[63] and nine additional RCTs.[87–95] The systematic review (search date 1995, 21 studies) compared different types and combinations of interventions. It found that increased contact with a therapist in the long term produced smaller weight gain or greater weight loss, and that additional self help peer groups, self management techniques, or involvement of the family or spouse may increase weight loss. The largest weight loss was seen in programmes using multiple strategies. Two additional small RCTs (102 people[87] and 100 people in two trials[91]) assessed simple strategies without face to face contact with a therapist. Frequent telephone contacts, optional food provision, continued self monitoring, urge control, or relapse prevention did not reduce the rate of weight regain. One small RCT (117 people) found that telephone contacts plus house visits did reduce the rate of weight regain compared with no intervention (3.65 kg with telephone contacts plus house visits *v* 6.42 kg with no intervention; P = 0.048).[88] One further small RCT (80 obese women) found no difference in weight change at 1 year between participants offered relapse prevention training or problem solving compared with no further contact.[93] One RCT (82 women) compared two walking programmes (4.2 or 8.4 MJ/week) plus diet counselling versus diet counselling alone after a 12 week intensive weight reduction

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programme.[92] Both walking programmes reduced weight regain at 1 year (reduction in weight gain compared with dietary counselling alone 2.7 kg, 95% CI 0.2 kg to 5.2 kg with low intensity programme and 2.6 kg, 95% CI 0 kg to 5.1 kg with high intensity programme). At 2 years, weight regain was not significantly different between high intensity programme and control, but was reduced in the low intensity group (reduction in weight gain 3.5 kg, 95% CI 0.2 kg to 6.8 kg with low intensity programme and +0.2 kg, 95% CI –3.1 kg to +3.6 kg with high intensity programme). One additional small RCT (67 people) found that people on a weight focused programme maintained weight loss better than those on an exercise focused programme (weight gain 0.8 kg with weight focused programme *v* 4.4 kg with exercise focused programme; $P < 0.01$).[89] One 5 year RCT (489 menopausal women) compared behavioural intervention in two phases aimed at lifestyle changes in diet and physical activity with lifestyle assessment. People in the intervention group were encouraged to lose weight during the first 6 months (phase I), and thereafter maintain this weight loss for a further 12 months (phase II). The intervention resulted in weight loss compared with control during the first 6 months (–8.9 lb [–4.0 kg] with intervention *v* –0.8 lb [–0.4 kg] with control; $P < 0.05$), most of which was sustained over phase II (–6.7 lb [–3.0 kg] with intervention *v* –0.6 lb [–0.3 kg] with control; $P < 0.05$).[90] One RCT (90 obese men) compared the effects of walking, resistance training of moderate dose at 6 months, and no increase in exercise control after a 2 month weight loss programme with a very low energy diet.[95] It found no significant difference in long term weight maintenance between walking and resistance training programmes and control at 23 months (adjusted mean difference in weight compared with control: +0.8 kg with walking, 95% CI –4.0 kg to +5.6 kg *v* –0.5 kg with resistance, 95% CI –5.0 kg to +4.0 kg; P between interventions = 0.8). There was poor adherence to prescribed exercise (82% with walking *v* 66% with resistance).[95] One RCT (122 overweight men and women, 101 analyzed) compared the effects of a weight maintenance programme conducted in person (frequent support or minimal support) or over the Internet for 1 year, after a 6 month weight loss programme.[94] It found significantly less weight loss with Internet support compared with in person support (weight loss: –5.7 kg with Internet support *v* –10.4 kg with minimal in person support *v* –10.4 kg with frequent in person support; $P < 0.05$).[94]

Harms: We found no direct evidence that interventions designed to maintain weight loss are harmful.

Comment: Weight regain is common. The resource implication of providing long term maintenance of any weight loss may be a barrier to the routine implementation of maintenance programmes. One RCT (122 obese people) comparing in person and Internet support for weight maintenance, found attrition rates of 18% after 6 months and 24% after 18 months.[94]

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OPTION LIFESTYLE ADVICE TO PREVENT WEIGHT GAIN

One small RCT found that low intensity education plus a financial incentive increased weight loss compared with no treatment. A second RCT found no significant effect on prevention of weight gain from a postal newsletter with or without a linked financial incentive compared with no contact. One RCT found that lifestyle advice prevented weight gain in perimenopausal women compared with assessment alone. One small RCT comparing a nutrition course for female students with no nutrition course found no significant increase in weight from baseline in either group at 1 year.

Benefits: We found three systematic reviews (search dates 1995,[62] 1999,[63] and not reported[96]) that included the same two RCTs[97,98] and two subsequent RCTs.[99,100] The first RCT (219 people) compared low intensity education with a financial incentive to maintain weight versus an untreated control group. It found significantly greater average weight loss in the intervention group than in the control group (–0.95 kg with intervention *v* –0.14 kg with control; P = 0.03).[97] The second RCT (228 men and 998 women) compared a monthly newsletter versus the newsletter plus a lottery incentive versus no contact. There was no significant difference in weight gain after 3 years between the groups (1.6 kg with newsletter *v* 1.5 kg with newsletter plus lottery incentive *v* 1.8 kg with no contact).[98] The first subsequent RCT (535 perimenopausal women) found that lifestyle advice reduced weight gain over 2 years compared with assessment alone (weight gain 0.5 kg with advice *v* 11.5 kg with assessment alone).[99] The second small subsequent RCT (40 female students, 33 analyzed) compared the effects of a one semester nutrition course (4 months) with no such course.[100] It found no significant change from mean baseline weight in either group 1 year after the end of intervention (66.7 kg at baseline to 67.7 kg at 1 year with course *v* 65.7 kg at baseline to 68.9 kg at 1 year with no course).

Harms: None reported.

Comment: None.

OPTION TRAINING HEALTH PROFESSIONALS IN PROMOTING WEIGHT LOSS

One systematic review of poor quality RCTs provided insufficient evidence on the sustained effect of interventions to improve health professionals' management of obesity. One subsequent cluster RCT found limited evidence that training for primary care doctors in nutrition counselling plus a support programme reduced body weight of the people in their care over 1 year compared with usual care.

Benefits: We found one systematic review (search date 2000, 18 RCTs, 8 with follow up > 1 year)[101] and one subsequent cluster RCT.[102] The studies in the review were heterogeneous and poor quality.[101] The subsequent cluster RCT (1162 people registered with 45 primary

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care doctors) compared nutrition counselling training plus a support programme for primary care doctors versus usual care (see comment below).[102] The nutrition supported intervention compared with usual care increased weight loss at 1 year (additional weight loss 2.3 kg; $P < 0.001$).

Harms: None reported.

Comment: In the subsequent RCT, the doctors were randomly allocated to training but the analysis of results was based on the people in the care of those doctors.[102] No allowance was made for cluster bias. This increases the likelihood that the additional weight loss could have occurred by chance.

GLOSSARY

Behavioural choice therapy A cognitive behavioural intervention based on a decision making model of women's food choice. This relates situation specific eating behaviour to outcomes and goals using decision theory. The outcomes and goals governing food choice extend beyond food related factors to include self esteem and social acceptance.

Cognitive behavioural programme Traditional cognitive behavioural topics (e.g. self monitoring, stimulus control, coping with cravings and high risk situations, stress management, and relaxation techniques) along with topics of particular importance to women (e.g. healthy eating, weight management, mood management, and managing work and family).

Motivational interviewing A goal directed counselling style that helps participants to understand and resolve areas of ambivalence that impede behavioural change.

Partial meal replacement plan A programme that prescribes a low energy (between 800–1600 kcal/day) diet, where one or two daily meals are replaced by commercially available, energy reduced products that are fortified with vitamins and minerals, and remaining meals consist of normal food.

Standard behavioural therapy A behavioural weight management programme that incorporates moderate calorie restriction to promote weight loss.

Substantive changes

Advice to quit smoking One RCT added;[7] categorisation unchanged.

Nicotine replacement Two RCTs added;[14,15] categorisation unchanged but benefits data enhanced.

High risk people One systematic review and two RCTs added;[29,31–34] categorisation unchanged but benefits and harms data enhanced.

Counselling Two RCTs added;[48,49] categorisation unchanged.

Lifestyle interventions for sustained weight loss One systematic review[65] and four additional RCTs added;[83–86] categorisation unchanged but benefits data enhanced.

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TABLE 1 **RCTs examining lifestyle interventions to achieve sustained weight loss.**

Reference	Participants	Interventions	Results
66	585 overweight and hypertensive elderly people (subgroup analysis)	Weight loss advice *v* no weight loss advice	Weight loss advice reduced body weight more than no weight loss advice, but significance not reported (weight change at 30 months: –4.7 kg with weight loss programme *v* –0.9 kg with no weight loss programme)
67	154 non-diabetic people who were 30–100% overweight, with family history of diabetes	Compared 4 treatments for 2 years: diet (reduced calories and fat), exercise, diet + exercise, and no treatment	No significant difference between treatments at 2 years for weight change (–2.1 kg with diet *v* +1.0 kg with exercise *v* –2.5 kg with diet + exercise *v* –0.3 kg with no treatment; P value not reported)
68	40 obese women aged 21–60 years, BMI 32.9 kg/m2	16 week treatment programme: diet + lifestyle advice (advice to increase activity) *v* diet + aerobics (3 classes/week)	83% completed; no significant difference in weight regain 1 year after treatment (1.6 kg with aerobic *v* 0.08 kg with lifestyle; P = 0.06)
69	148 sedentary overweight women	Compared 3 behavioural weight control programmes: LB exercise, SB exercise, and SBEQ programme	78% completed 18 month programme; SBEQ significantly increased weight loss compared with SB (7.4 kg with SBEQ *v* 3.7 kg with SB; P < 0.05). No significant difference between weight loss with LB (5.8 kg) and either SB or SBEQ
70	24 obese women	Behavioural choice therapy *v* SBT	Behavioural choice therapy increased weight loss at 12 months compared with OFF (10.1 kg with behavioural choice therapy *v* 4.3 kg with SBT; P < 0.01)

TABLE 1 continued

Reference	Participants	Interventions	Results
71	80 obese non-smoking people aged 25–45 years, 120–140% ideal body weight	Energy restricted diet *v* fat restricted diet	Energy restricted diet significantly increased weight loss compared with fat restricted diet at 6 and 18 months (at 6 months: 11.2 kg with energy restricted diet *v* 6.1 kg with fat restricted diet; $P < 0.001$; at 18 months: 7.5 kg with energy restricted diet *v* 1.8 kg with fat restricted diet; $P < 0.001$)
72	166 people	SBT + support from friends *v* SBT without support	No additional weight loss at 16 months with social support from friends (4.7 kg with behavioural therapy + support *v* 3.0 kg with behavioural therapy without support; $P > 0.05$)
73	193 obese men and women	5 treatments compared: SBT, SW, SBT + SW, SBT + SW + PT, SBT + SW + PT + I	No significant difference between treatments in weight loss at 18 months (7.6 kg with SBT *v* 3.8 kg with SW *v* 2.9 kg with SBT + SW *v* 4.5 kg with SBT + SW + PT *v* 5.1 kg with SBT + SW + PT + I)
74	42 moderately obese young women, age 18–30 years, 6.8–20.5 kg overweight	3 12 week treatments compared: standard behaviour intervention (weekly meetings + exercise contracting), intensive intervention (weekly meetings + supervised exercise sessions 3 times/week), minimal contact intervention (written lessons with feedback)	38 completers analyzed. Intensive intervention significantly increased weight loss at 1 year compared with standard behaviour intervention or minimal contact (4.6 kg with supervised exercise *v* 4.3 kg with contracted exercise *v* 4.2 kg with minimal contact; $P < 0.05$)
75	22 sedentary moderately obese women	Continuous exercise (supervised exercise 30 minutes 3 times/week) *v* intermittent exercise (advice to walk briskly, twice daily for 15 minutes/session)	Continuous exercise reduced weight at 16 months but the reduction was not significant (from 81.4 kg to 79.7 kg with continuous *v* from 85.6 kg to 85 kg with intermittent; P value not reported)

TABLE 1 continued

Reference	Participants	Interventions	Results
76	76 women, 58 analyzed	Cognitive behavioural programme (10 weeks) *v* modified cognitive behavioural programme (10 weeks)	No significant difference between programmes after 1 year follow up (weight loss: 2.1 kg with modified programme *v* 3.8 kg with standard programme; P value not reported)
77 (Study 1)	25 people with type 2 diabetes	Diet + moderate exercise for 10 weeks *v* diet alone	19 people analyzed. No significant difference in weight loss at year (7.8 kg with diet + exercise *v* 4.0 kg with diet alone; $P > 0.10$)
77 (Study 2)	30 people with type 2 diabetes	Diet + more intensive exercise for 10 weeks *v* diet alone	Diet + intensive exercise significantly increased weight loss compared with diet alone at 1 year (from 104 kg to 96.2 kg with intensive exercise *v* from 102 kg to 98.2 kg with diet alone; $P = 0.01$)
78	65 obese men and women	Body image treatment + dietician led treatment *v* dietician led treatment alone	No significant difference in weight loss between treatments at 1 year (4.96% with body image + dietician led *v* 5.90% with dietician led alone; P value not reported)

TABLE 1 continued

Reference	Participants	Interventions	Results
79	1191 overweight and hypertensive people	Weight loss advice *v* no weight loss advice	Weight loss advice significantly reduced weight and hypertension more than no weight loss advice at 3 years (weight change at 3 years: –0.2 kg with advice *v* +1.8 kg with control; RR for hypertension with advice *v* control 0.81, 95% CI 0.70 to 0.95)
79	588 overweight people	Compared 3 different cognitive behavioural approaches for tailoring lifestyle modification goals to the individual: workbook alone (no tailoring), workbook + computerised tailoring (using computer kiosks with touch screen monitors), workbook + computerised tailoring + personal tailoring (staff consultation)	After 12 months, mean weight loss from baseline was significant in all groups. Combined computerised + personal tailoring significantly improved weight loss compared with workbook alone (mean weight loss: 1 kg with workbook *v* 2.1 kg with computerised tailoring *v* 3.3 kg with personal + computerised tailoring; P = 0.02 for workbook *v* combined group)
81	78 obese women, described as 'chronic dieters'	24 week 'non-diet' wellness programme *v* traditional 'weight loss' programme	Weight loss programme significantly increased weight loss compared with non-diet programme at 1 year (from 101.1 kg to 95.2 kg with diet *v* from 99.6 kg to 99.9 kg with non-diet; P < 0.001)
82	101 obese men and women	Moderate fat (based on the Mediterranean diet), low energy diet *v* low fat, low energy diet	Moderate fat diet increased weight loss compared with low fat diet after 18 months (mean weight change: –4.1 kg with moderate fat/low energy diet *v* +2.9 kg with low energy/low fat diet; difference in weight change 7.0 kg, 95% CI 5.3 kg to 8.7 kg)
83	120 premenopausal obese women	Advice to eat a low energy Mediterranean style diet *v* advice on healthy food choices. Both groups advised to increase their levels of physical activity	Low energy Mediterranean style diet advice increased weight loss compared with healthy food choice advice at 2 years (difference –11 kg, 95% CI –14 kg to –8 kg, intention to treat analysis)

TABLE 1 continued

Reference	Participants	Interventions	Results
84	423 moderately overweight people	Commercial weight loss programme *v* self help group	Commercial weight loss programme significantly reduced weight compared with self help at 2 years (weight change: –2.9 kg with commercial programme *v* + 0.2 kg with self help; $P < 0.001$, intention to treat analysis). Withdrawal rate was similar between groups (29% with commercial programme *v* 25% with self help)
85	122 people treated in general practice	CBT (16 sessions of about 90 minutes each) *v* usual care	CBT group significantly increased weight loss compared with usual care at 1 year (1.8 kg with CBT *v* 0.2 kg with usual care; $P < 0.001$). Withdrawal rate was similar with both treatments (23% with CBT *v* 29% with usual care)
86	92 obese people	Internet based weight loss programme + email based behavioural counselling *v* Internet-based weight loss programme alone	Combined intervention significantly increased weight loss compared with Internet-based programme alone at 1 year (4.4 kg with combined *v* 2.0 kg with Internet programme alone; $P = 0.04$, intention to treat analysis)

BMI, body mass index; CBT, cognitive behavioural therapy; I, monetary incentives; LB, long bout; PT, personal trainer; SB, short bout; SBEQ, short bout exercise plus home exercise equipment; SBT, standard behavioural therapy; SW, supervised walks

Heart failure

Search date February 2005

Robert McKelvie

QUESTIONS

INTERVENTIONS

Key Messages

Non-drug treatments

- **Multidisciplinary interventions** One systematic review and subsequent RCTs found that multidisciplinary programmes reduced all cause mortality, all cause hospitalisations, and heart failure hospitalisations compared with conventional care.
- **Exercise** Two systematic reviews found that exercise training reduced death rates compared with usual care but the reduction was not statistically significant in one review. Two systematic reviews found that exercise training improved exercise performance compared with usual care.

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Heart failure

Drug treatments

- **Angiotensin converting enzyme inhibitors** Systematic reviews and RCTs found that angiotensin converting enzyme inhibitors reduced ischaemic events, mortality, and hospital admission for heart failure compared with placebo. Relative benefits were similar in different groups of people, but absolute benefits were greater in people with severe heart failure. For a report on studies comparing angiotensin converting (ACE) inhibitors versus angiotensin II receptor blockers (ARB) and the effects of combined ACE inhibitors and ARBs see the section on angiotensin II receptor blockers, p 7.
- **Angiotensin II receptor blockers** One systematic review found that angiotensin II receptor blockers reduced mortality and admission for heart failure compared with placebo in people with New York Heart Association functional class II–IV heart failure, and were an effective alternative in people who were intolerant to angiotensin converting enzyme inhibitors. One systematic review found no significant difference between angiotensin II receptor blockers and angiotensin converting enzyme inhibitors in all cause mortality or hospital admission. One systematic review found that angiotensin II receptor blockers plus angiotensin converting enzyme inhibitors reduced cardiovascular mortality and admission for heart failure compared with angiotensin converting enzyme inhibitors alone. Effects on all cause mortality remained uncertain.
- **Beta Blockers** Systematic reviews found strong evidence that adding a beta blocker to an angiotensin converting enzyme inhibitor decreased mortality and hospital admission in symptomatic people with heart failure of any severity. Limited evidence from a subgroup analysis of one RCT found no significant effect on mortality in black people.
- **Cardiac resynchronisation therapy** One systematic review and one subsequent RCT found that cardiac resynchronisation therapy improved functional capacity, reduced heart failure hospitalisation, and reduced all cause mortality compared with standard care.
- **Digoxin (improves morbidity in people already receiving diuretics and angiotensin converting enzyme inhibitors)** One systematic review found that digoxin reduced hospitalisations and clinical deterioration compared with placebo in people in sinus rhythm but found no significant difference between digoxin and placebo for mortality.
- **Eplerenone (in people with myocardial infarction complicated by left ventricular dysfunction and heart failure already on medical treatment)** One large RCT in people with recent myocardial infarction complicated by left ventricular dysfunction and clinical heart failure already on medical treatment (which could include angiotensin converting enzyme inhibitors, angiotensin receptor blockers, diuretics, beta blockers, or coronary reperfusion therapy) found that adding eplerenone (an aldosterone receptor antagonist) reduced mortality compared with adding placebo.
- **Implantable cardiac defibrillators in people at high risk of arrhythmia** One systematic review found that implantable cardiac defibrillators reduced mortality in people with heart failure who have experienced a near fatal ventricular arrythmia or are at high risk of sudden death. A second systematic review found that implantable cardiac defibrillators reduced mortality in people with heart failure due to non-ischaemic cardiomyopathy.
- **Spironolactone in people with severe heart failure** One large RCT in people with severe heart failure taking diuretics, angiotensin converting enzyme inhibitors, and digoxin found that adding spironolactone reduced mortality after 2 years compared with adding placebo.
- **Amiodarone** Systematic reviews found weak evidence that amiodarone may reduce mortality compared with placebo. However, we were unable to draw firm conclusions about the effects of amiodarone in people with heart failure.
- **Anticoagulation** A preliminary report from one RCT found no significant difference between warfarin and no antithrombotic treatment or between warfarin and aspirin in the combined outcome of death, myocardial infarction, and stroke after 27 months. However, the RCT may have lacked power to detect a clinically important difference. The effects of antiplatelet treatment in combination with angiotensin converting enzymes requires further research.
- **Antiplatelet agents** A preliminary report from one RCT found no significant difference between aspirin and no antithrombotic treatment or between aspirin and warfarin in the combined outcome of death, myocardial infarction, and stroke after 27 months. However, the RCT may have lacked power to detect a clinically important difference. The effects of antiplatelet treatment in combination with angiotensin converting enzymes requires further research.

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- **Calcium channel blockers** One systematic review found no significant difference in mortality between second generation dihydropyridine calcium channel blockers and placebo. RCTs comparing other calcium channel blockers versus placebo also found no evidence of benefit. Calcium channel blockers have been found to exacerbate symptoms of heart failure or increase mortality after myocardial infarction in people who also have pulmonary congestion or left ventricular dysfunction.
- **Non-amiodarone antiarrhythmic drugs** Evidence extrapolated from one systematic review in people treated after a myocardial infarction suggested that other antiarrhythmic drugs (apart from β blockers) may have increased mortality in people with heart failure.
- **Positive inotropes (other than digoxin)** RCTs in people with heart failure found that positive inotropic drugs other than digoxin (ibopamine, milrinone, and vesnarinone) increased mortality over 6–11 months compared with placebo. One systematic review in people with heart failure found that intravenous adrenergic inotropes non-significantly increased mortality compared with placebo or control, and found insufficient evidence about effects on symptoms. It suggested that their use may not be safe.

High risk people: ACE inhibitors

- **Angiotensin converting enzyme inhibitors in people with asymptomatic left ventricular dysfunction or other risk factors** RCTs in people with asymptomatic left ventricular systolic dysfunction found that angiotensin converting enzyme inhibitors delayed the onset of symptomatic heart failure, reduced cardiovascular events, and improved long term survival compared with placebo.

Diastolic heart failure

- **Angiotensin II receptor blockers** One RCT found that candesartan, an angiotensin II receptor blocker, reduced the combined outcome of cardiovascular death or hospital admission for heart failure compared with placebo, although the difference was not significant. It found no significant difference in cardiovascular death between the two groups, but found that candesartan reduced hospital admission compared with placebo.
- **Other treatments** We found no RCTs examining effects of other treatments in people with diastolic heart failure.

DEFINITION

Heart failure occurs when abnormality of cardiac function causes failure of the heart to pump blood at a rate sufficient for metabolic requirements under normal filling pressure. It is characterised clinically by breathlessness, effort intolerance, fluid retention, and poor survival. Fluid retention and the congestion related to this can often be relieved with diuretic therapy. However, generally diuretic therapy should not be used alone and, if required, it should be combined with the pharmacological therapies outlined in this chapter. Heart failure can be caused by systolic or diastolic dysfunction and is associated with neurohormonal changes.[1] Left ventricular systolic dysfunction (LVSD) is defined as a left ventricular ejection fraction below 0.40. It may be symptomatic or asymptomatic. Defining and diagnosing diastolic heart failure can be difficult. Recently proposed criteria include: (1) clinical evidence of heart failure; (2) normal or mildly abnormal left ventricular systolic function; and (3) evidence of abnormal left ventricular relaxation, filling, diastolic distensibility, or diastolic stiffness.[2] However, assessment of some of these criteria is not standardised.

INCIDENCE/ PREVALENCE

Both the incidence and prevalence of heart failure increase with age. Studies of heart failure in the USA and Europe found that under 65 years of age the annual incidence is 1/1000 for men and 0.4/1000 for women. Over 65 years of age, the annual incidence is 11/1000 for men and 5/1000 for women. Under age 65 years the prevalence of heart failure is 1/1000 for men and 1/1000 for women; over age 65 years the prevalence is 40/1000 for men and 30/1000 for women.[3] The prevalence of asymptomatic LVSD is 3% in the general population.[4–6] The mean age of people with asymptomatic LVSD is lower than that for symptomatic individuals. Both heart failure and asymptomatic LVSD are more common in men.[4–6] The prevalence of diastolic heart failure in the community is unknown. The prevalence of heart failure with preserved systolic function in people in hospital with clinical heart failure varies from 13–74%.[7,8] Fewer than 15% of people with heart failure under 65 years have normal systolic function, whereas the prevalence is about 40% in people over 65 years.[7]

AETIOLOGY/ RISK FACTORS

Coronary artery disease is the most common cause of heart failure.[3] Other common causes include hypertension and idiopathic dilated congestive cardiomyopathy. After adjustment for hypertension, the presence of left ventricular hypertrophy remains a risk factor for the development of heart failure. Other risk factors include cigarette smoking, hyperlipidaemia, and diabetes mellitus.[4] The common causes of left ventricular diastolic dysfunction are coronary artery disease and systemic hypertension. Other causes are hypertrophic cardiomyopathy, restrictive or infiltrative cardiomyopathies, and valvular heart disease.[8]

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Heart failure

PROGNOSIS

The prognosis of heart failure is poor, with 5 year mortality ranging from 26–75%.[3] Up to 16% of people are readmitted with heart failure within 6 months of first admission. In the USA, heart failure is the leading cause of hospital admission among people over 65 years of age.[3] In people with heart failure, a new myocardial infarction increases the risk of death (RR 7.8, 95% CI 6.9 to 8.8). About a third of all deaths in people with heart failure are preceded by a major ischaemic event.[9] Sudden death, mainly caused by ventricular arrhythmia, is responsible for 25–50% of all deaths, and is the most common cause of death in people with heart failure.[10] The presence of asymptomatic LVSD increases an individual's risk of having a cardiovascular event. One large prevention trial found that the risk of heart failure, admission for heart failure, and death increased linearly as ejection fraction fell (for each 5% reduction in ejection fraction: RR for mortality 1.20, 95% CI 1.13 to 1.29; RR for hospital admission 1.28, 95% CI 1.18 to 1.38; RR for heart failure 1.20, 95% CI 1.13 to 1.26).[4] The annual mortality for people with diastolic heart failure varies in observational studies (1.3–17.5%).[7] Reasons for this variation include age, the presence of coronary artery disease, and variation in the partition value used to define abnormal ventricular systolic function. The annual mortality for left ventricular diastolic dysfunction is lower than that found in people with systolic dysfunction.[11]

AIMS OF INTERVENTION

To relieve symptoms; to improve quality of life; to reduce morbidity and mortality; with minimum adverse effects.

OUTCOMES

Functional capacity (assessed by the New York Heart Association functional classification or more objectively by using standardised exercise testing or the 6 minute walk test);[12] quality of life (assessed with questionnaires);[13] mortality; adverse effects of treatment. Proxy measures of clinical outcome (e.g. left ventricular ejection fraction and hospital readmission rates) are used only when clinical outcomes are unavailable.

METHODS

Clinical Evidence search and appraisal February 2005. Generally, RCTs with fewer than 500 people have been excluded because of the number of large RCTs available. If for any comparison very large RCTs exist then much smaller RCTs have been excluded, even if they have more than 500 people.

QUESTION What are the effects of non-drug treatments?

OPTION MULTIDISCIPLINARY INTERVENTIONS

One systematic review and subsequent RCTs found that multidisciplinary programmes reduced all cause mortality, all cause hospitalisations, and heart failure hospitalisations compared with conventional care.

Benefits:

We found two systematic reviews (search date 2003, 29 RCTs, 5039 people;[14] and search date 2003, 27 RCTs[15]) and one subsequent RCT.[16] The first systematic review analysed all types of interventions combined and also analysed interventions according to type: multidisciplinary heart failure clinic; multidisciplinary team providing specialised follow up in non-clinic setting; telephone follow up and attendance with primary care physician if there is deterioration; and enhanced patient self care activities.[14] It found that all types of intervention combined significantly reduced all cause mortality, all cause hospitalisations, and heart failure hospitalisations compared with control (all cause mortality: RR 0.83, 95% CI 0.70 to 0.99; all cause hospitalisations: RR 0.84, 95% CI 0.75 to 0.93; heart failure hospitalisations: RR 0.73, 95% CI 0.66 to 0.82). It found that a multidisciplinary team in either a clinic or non-clinic setting significantly reduced all cause mortality, all cause hospitalisation, and heart failure hospitalisation (all cause mortality: 12 RCTs, 2129 people; RR 0.75, 95% CI 0.59 to 0.96; all cause hospitalisation: 14 RCTs; RR 0.81, 95% CI 0.71 to 0.92; heart failure hospitalisation: 9 RCTs; RR 0.74, 95% CI 0.63 to 0.87). Statistically significant heterogeneity was found for all cause hospitalisations ($P < 0.01$) but not for all cause mortality ($P = 0.15$) or heart failure hospitalisation ($P = 0.36$). It found that strategies employing telephone follow up significantly reduced heart failure hospitalisations but not all cause mortality or all cause hospitalisations (heart failure hospitalisations: 6 RCTs; RR 0.75, 95% CI 0.57 to 0.99; all cause mortality: 7 RCTs, 1193 people; RR 0.91, 95% CI 0.67 to 1.29; all cause hospitalisations: 6 RCTs; RR 0.98, 95% CI 0.80 to 1.20). The second systematic review identified one RCT that was not included in the first review (see comment below).[15] The RCT (1518 people) found that frequent telephone follow up providing education, counselling and monitoring to enhance self care, timely medical visits, diet, and compliance with drug treatment significantly reduced a combined outcome of heart failure hospitalisation or death, heart failure hospitalisation alone, and all cause hospital

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admission compared with control (heart failure hospitalisation or death: 26.3% with intervention *v* 31% with control; P = 0.02; heart failure hospitalisation: 16.8% with intervention *v* 22.3% with control; P = 0.005; all cause hospital admission: 34.3% with intervention *v* 39.1% with control; P = 0.05).[15] The duration of follow up was 1.2 years. The subsequent RCT (a non-selected group of 338 people hospitalised for heart failure) found that a discharge and outpatient management programme conducted at three tertiary referral centres significantly reduced readmission or death and increased the time to these events compared with control after a median follow up of 509 days (AR of readmission or death per 100 person years of observation: 70 with intervention *v* 117 with control; ARR 47%, 95% CI 29% to 65%; time to event; P < 0.001).[16] It found that the intervention significantly reduced all cause readmission, heart failure admission, and death compared with control (events per 100 person years; AR for all cause readmission: 31 with intervention *v* 47 with control; ARR 16%, 95% CI 4% to 28%; heart failure admission: 18 per year with intervention *v* 37 with control; ARR 19%, 95% CI 0.09% to 29%; death: 14 per year with intervention *v* 24 per year with control; ARR 10%, 95% CI 0.02% to 0.18%). It found that the intervention significantly improved quality of life at 1 year compared with control (Minnesota living with heart failure questionnaire G, range 0 to 105, higher scores indicate worse quality of life, 220 people analysed, baseline score 51.6 and 51.9 for treatment groups: 28.9 with intervention *v* 35.5 with control; P = 0.01).

Harms: The reviews and subsequent RCT did not report on harms (see comment below).[14–16]

Comment: The second systematic review (search date 2003) appeared to count follow up reports of included RCTs and studies reporting combinations of included RCTs as separate studies, and so results from meta-analyses were not reported for this review.[15] The RCTs of multidisciplinary treatment were generally small, involving highly selected patient populations. Many lasted less than 6 months and were usually carried out in academic centres, and so the results may not generalise to longer term outcomes based in smaller community centres. The reviews have suggested that disease management programmes may reduce mortality, all cause hospitalisations, and heart failure hospitalisations. Larger, multicentre studies are required to confirm the benefits of heart failure management programmes.

OPTION EXERCISE

Two systematic reviews found that exercise training reduced death rates compared with usual care but the reduction was not statistically significant in one review. Two systematic reviews found that exercise training improved exercise performance compared with usual care.

Benefits: **Exercise versus usual care:** We found three systematic reviews (search date not reported, 9 RCTs, 801 people;[17] search date 2001, 29 parallel group or crossover RCTs;[18] and search date 2003, 30 parallel group RCTs plus one crossover RCT[19]). The reviews reported different outcomes. The first review found that exercise training (to 60–80% of peak heart rate or peak oxygen consumption) significantly reduced death rate and the combined outcome of death or hospital admission compared with usual care G (death: HR 0.65, 95% CI 0.46 to 0.92; death or admission: HR 0.72, 95% CI 0.56 to 0.93).[17] The second review included all but one of the RCTs in the first review.[18] It found that exercise significantly increased exercise duration and distance on the 6 minute walk compared with no exercise (WMD for increase in exercise duration: 15 RCTs, 510 people; 2.38 minutes, 95% CI 2.85 minutes to 1.92 minutes; WMD for increase in distance: 8 RCTs, 282 people; 40.9 metres, 95% CI 64.7 metres to 17.1 metres). Most RCTs in the second review[18] were also included in the third review.[19] In the third systematic review follow up among RCTs ranged from 4 to 192 weeks; about half of the RCTs included follow up for 3 months or less. It found no significant difference in events (including hospitalisation causing temporary or permanent withdrawal from exercise) or deaths during exercise training or during the mean 5.9 months of follow up compared with control (events: 14 parallel group RCTs, 1197 people; 30/622 [4.8%] with exercise *v* 34/575 [5.9%] with control; OR 0.83, 95% CI 0.50 to 1.39; deaths: 26/622 [5.8%] with exercise *v* 41/575 [7.1%] with control; OR 0.71, 95% CI 0.37 to 1.02).

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Heart failure

Harms: The first and second systematic reviews did not report on adverse effects of exercise training.[17,18] The third review found no reports of deaths that were directly related to exercise during more than 60 000 people hours of exercise training.[19]

Comment: Individual studies were small, involved highly selected patient populations, and were carried out in well resourced academic centres. The results may not generalise to smaller community centres. The specific form of exercise training varied among studies, and the relative merits of each strategy are unknown. The studies generally lasted less than 1 year, and long term effects are unknown. A large RCT over a longer period of time is required to assess further the clinical benefits of exercise training.

QUESTION **What are the effects of drug and invasive treatments?**

OPTION **ANGIOTENSIN CONVERTING ENZYME INHIBITORS**

Systematic reviews and RCTs found that angiotensin converting enzyme inhibitors reduced ischaemic events, mortality, and hospital admission for heart failure compared with placebo. Relative benefits were similar in different groups of people, but absolute benefits were greater in people with severe heart failure. For a report on studies comparing angiotensin converting (ACE) inhibitors versus angiotensin II receptor blockers (ARB) and the effects of combined ACE inhibitors and ARBs see the section on angiotensin II receptor blockers, p 7.

Benefits: **Angiotensin converting enzyme (ACE) inhibitors versus placebo:** We found two systematic reviews (search dates 1994[20] and not reported[21]) of ACE inhibitors versus placebo in heart failure. The first review (32 RCTs, duration 3–42 months, 7105 people, New York Heart Association functional class III or IV G) found that ACE inhibitors significantly reduced mortality compared with placebo (611/3870 [16%] with ACE inhibitors *v* 709/3235 [22%] with placebo; ARR 6%, 95% CI 4% to 8%; OR 0.77, 95% CI 0.67 to 0.88).[20] Relative reductions in mortality were similar in different subgroups (stratified by age, sex, cause of heart failure, and New York Heart Association functional class). The second review (5 RCTs, 12 763 people with left ventricular dysfunction or heart failure of mean duration 35 months) analysed long term results from large RCTs that compared ACE inhibitors versus placebo.[21] Three RCTs examined effects of ACE inhibitors in people for 1 year after myocardial infarction. In these three postinfarction trials (5966 people), ACE inhibitors compared with placebo significantly reduced mortality (702/2995 [23.4%] with ACE inhibitors *v* 866/2971 [29.1%] with placebo; OR 0.74, 95% CI 0.66 to 0.83), readmission for heart failure (355/2995 [11.9%] with ACE inhibitors *v* 460/2971 [15.5%] with placebo; OR 0.73, 95% CI 0.63 to 0.85), and reinfarction (324/2995 [10.8%] with ACE inhibitors *v* 391/2971 [13.2%] with placebo; OR 0.80, 95% CI 0.69 to 0.94). For all five trials, ACE inhibitors compared with placebo significantly reduced mortality (1467/6391 [23.0%] with ACE inhibitors *v* 1710/6372 [26.8%] with placebo; OR 0.80, 95% CI 0.74 to 0.87), reinfarction (571/6391 [8.9%] with ACE inhibitors *v* 703/6372 [11.0%] with placebo; OR 0.79, 95% CI 0.70 to 0.89), and readmission for heart failure (876/6391 [13.7%] with ACE inhibitors *v* 1202/6372 [18.9%] with placebo; OR 0.67, 95% CI 0.61 to 0.74). The relative benefits began soon after the start of treatment, persisted in the long term, and were independent of age, sex, and baseline use of diuretics, aspirin, and beta blockers. Although there was a trend toward greater relative reduction in mortality or readmission for heart failure in people with lower ejection fraction, benefit was apparent over the range examined. **Dose:** We found one large RCT (3164 people with New York Heart Association functional class II–IV heart failure), which compared low dose lisinopril (2.5 or 5.0 mg/day) versus high dose lisinopril (32.5 or 35.0 mg/day).[22] It found no significant difference in mortality (717/1596 [44.9%] with low dose *v* 666/1568 [42.5%] with high dose; ARR 2.4%, CI not reported; HR 0.92, 95% CI 0.80 to 1.03; P = 0.128), but found that high dose lisinopril reduced the combined outcome of death or hospital admission for any reason (events: 1338/1596 [83.8%] with low dose *v* 1250/1568 [79.7%] with high dose; ARR 4.1%, CI not reported; HR 0.88, 95% CI 0.82 to 0.96) and reduced admissions for heart failure (admissions: 1576/1596 [98.7%] with low dose *v* 1199/1568 [76.5%] with high dose; ARR 22.2%, CI not reported; P = 0.002). **Comparison of different ACE inhibitors:** The first systematic review found similar benefits with different ACE inhibitors.[20]

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Harms: The main adverse effects in large RCTs were cough, hypotension, hyperkalaemia, and renal dysfunction. Compared with placebo, ACE inhibitors increased cough (37% with ACE inhibitor *v* 31% with placebo; ARI 7%, 95% CI 3% to 11%; RR 1.23, 95% CI 1.11 to 1.35) and dizziness or fainting (57% with ACE inhibitor *v* 50% with placebo; ARI 7%, 95% CI 3% to 11%; RR 1.14, 95% CI 1.06 to 1.21), and increased creatinine concentrations above 177 μmol/L (10.7% with ACE inhibitor *v* 7.7% with placebo; ARI 3.0%, 95% CI 0.6% to 6.0%; RR 1.38, 95% CI 1.09 to 1.67) and increased potassium concentrations above 5.5 mmol/L (AR 6.4% with ACE inhibitor *v* 2.5% with placebo; ARI 4%, 95% CI 2% to 7%; RR 2.56, 95% CI 1.92 to 3.20).[23] Risk of angio-oedema was similar with ACE inhibitors and placebo (3.8% with enalapril *v* 4.1% with placebo; ARI +0.3%, 95% CI −1.4% to +1.5%).[23] The trial comparing low versus high doses of lisinopril found that most adverse effects were more common with high dose (dizziness: 12% with low dose *v* 19% with high dose; hypotension: 7% with low dose *v* 11% with high dose; worsening renal function: 7% with low dose *v* 10% with high dose; significant change in serum potassium concentration: 7% with low dose *v* 7% with high dose; P values not reported), although there was no difference in withdrawal rates between groups (18% discontinued with low dose *v* 17% with high dose).[22] The trial found that cough was less commonly experienced with high dose than with low dose lisinopril (cough: 13% with low dose *v* 11% with high dose). We found one systematic review (search date 1999), which specifically examined adverse effects of ACE inhibitors in people with heart failure.[24] It found that ACE inhibitors significantly increased withdrawal because of adverse effects compared with control (placebo or non-ACE inhibitor treatments) after about 2 years (22 RCTs, 9668 people; AR 13.8% with ACE inhibitor *v* 9.4% with control; RR 1.54, 95% CI 1.30 to 1.83). ACE inhibitors significantly increased cough, hypotension, renal dysfunction, dizziness, and impotence compared with control treatments (cough: RR 3.19, 95% CI 2.22 to 4.57; hypotension: RR 1.95, 95% CI 1.39 to 2.74; renal dysfunction: RR 1.84, 95% CI 1.20 to 2.81; dizziness: RR 1.60, 95% CI 1.15 to 2.23; impotence: RR 6.46, 95% CI 1.14 to 36.58).

Comment: The relative benefits of ACE inhibitors were similar in different subgroups of people with heart failure. Most RCTs evaluated left ventricular function by assessing left ventricular ejection fraction, but some studies defined heart failure clinically, without measurement of left ventricular function in people at high risk of developing heart failure (soon after myocardial infarction). It is unclear whether there are additional benefits from adding ACE inhibitor to antiplatelet treatment in people with heart failure (see antiplatelet agents, p 17).

OPTION ANGIOTENSIN II RECEPTOR BLOCKERS

One systematic review found that angiotensin II receptor blockers reduced mortality and admission for heart failure compared with placebo in people with New York Heart Association functional class II–IV heart failure, and were an effective alternative in people who were intolerant to angiotensin converting enzyme inhibitors. One systematic review found no significant difference between angiotensin II receptor blockers and angiotensin converting enzyme inhibitors in all cause mortality or hospital admission. One systematic review found that angiotensin II receptor blockers plus angiotensin converting enzyme inhibitors reduced cardiovascular mortality and admission for heart failure compared with angiotensin converting enzyme inhibitors alone. Effects on all cause mortality remained uncertain.

Benefits: **Angiotensin II receptor blockers versus placebo:** We found one systematic review (search date 2003, 24 RCTs, 38 080 people with New York Heart Association functional class II–IV, follow up 4 weeks to 2.7 years).[25] It found that that angiotensin receptor antagonists significantly reduced all cause mortality and heart failure hospitalisations compared with placebo (all cause mortality: 9 RCTs, 4623 people; OR 0.83, 95% CI 0.69 to 1.00; heart failure hospitalisations: 3 RCTs, 2590 people; OR 0.64, 95% CI 0.53 to 0.78). **Angiotensin II receptor blockers versus angiotensin converting enzyme inhibitors:** We found one systematic review (search date 2003, 8 RCTs, 5201 people with New York Heart Association functional class II–IV, follow up 4 weeks to 2.7 years).[25] It found no significant difference between angiotensin II receptor blockers and

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Heart failure

angiotensin converting enzyme inhibitors for all cause mortality or heart failure hospitalisations (all cause mortality: OR 1.06, 95% CI 0.90 to 1.26; heart failure hospitalisations: 3 RCTs, 4310 people; OR 0.95, 95% CI 0.80 to 1.13). **Angiotensin II receptor blockers plus angiotensin converting enzyme inhibitors versus angiotensin converting enzyme inhibitors alone:** We found two systematic reviews (search date 2003, 7 RCTs, 8260 people with New York Heart Association functional class II–IV heart failure;[25] search date 2003, 4 RCTs[26]). The first systematic review found that angiotensin II receptor blockers plus angiotensin converting enzyme inhibitors significantly reduced heart failure hospitalisations compared with angiotensin converting enzyme inhibitors alone, but found no significant difference between treatments for all cause mortality (heart failure hospitalisations: 4 RCTs, 8108 people; OR 0.77, 95% CI 0.69 to 0.87; all cause mortality: 7 RCTs, 8206 people; OR 0.97, 95% CI 0.87 to 1.08).[25] The second systematic review[26] (4 RCTs included in the first systematic review,[25] 7666 people) compared angiotensin II receptor blockers plus angiotensin converting enzyme inhibitors versus angiotensin converting enzyme inhibitors alone for people taking and not taking beta blockers. Significant heterogeneity was found in the meta-analysis of people taking beta blockers (see comment below).

Harms: **Angiotensin II receptor blockers versus placebo:** The systematic review did not report on harms.[25] **Angiotensin II receptor blockers versus angiotensin converting enzyme inhibitors:** The systematic review did not report on harms.[25] **Angiotensin II receptor blockers plus angiotensin converting enzyme inhibitors versus angiotensin converting enzyme inhibitors alone:** The systematic reviews did not report on harms.[25,26]

Comment: **Angiotensin II receptor blockers plus angiotensin converting enzyme inhibitors versus angiotensin converting enzyme inhibitors alone:** The second systematic review[26] (4 RCTs included in the first systematic review,[25] 7666 people) compared angiotensin II receptor blockers plus angiotensin converting enzyme inhibitors versus angiotensin converting enzyme inhibitors alone for people taking and not taking beta blockers. Meta-analysis found no significant difference between treatments for the combined outcome of morbidity and mortality or mortality alone in people taking beta blockers, however, studies were statistically heterogeneous with different directions of effect (morbidity or mortality: 2 RCTs; OR 0.94, 95% CI 0.82 to 1.10; mortality: 2 RCTs; OR 1.08, 95% CI 0.90 to 1.29). The review found that angiotensin II receptor blockers plus angiotensin converting enzyme inhibitors significantly reduced the combined outcome of morbidity and mortality compared with angiotensin converting enzyme inhibitors alone in people not taking beta blockers but found no significant difference between treatments for mortality (morbidity or mortality: 2 RCTs; OR 0.83, 95% CI 0.73 to 0.94; mortality: 2 RCTs; OR 0.93, 95% CI 0.81 to 1.06; no significant heterogeneity in either analysis). The evidence suggests that in people who are intolerant of angiotensin converting enzyme inhibitors, an angiotensin receptor antagonist would be as useful in reducing mortality and morbidity. Furthermore, the evidence suggests that, for patients with New York Heart Association functional class II–IV, an angiotensin receptor antagonist should be added to therapy after angiotensin converting enzyme inhibition and beta blocker therapy have been optimised to reduce further both mortality and morbidity.

OPTION POSITIVE INOTROPIC AGENTS

One systematic review found that, in people in sinus rhythm with heart failure, digoxin reduced clinical worsening of heart failure compared with placebo. RCTs in people with heart failure found that positive inotropic drugs other than digoxin (ibopamine, milrinone, and vesnarinone) increased mortality over 6–11 months compared with placebo. One systematic review in people with heart failure found that intravenous adrenergic inotropes non-significantly increased mortality compared with placebo or control, and found insufficient evidence about effects on symptoms. It suggested that their use may not be safe.

Benefits: **Digoxin:** We found one systematic review (search date 2003, 13 RCTs with more than 7 weeks follow up, 7896 people in sinus rhythm).[27] It found that digoxin significantly reduced hospitalisations and reduced the deterioration in clinical status compared with

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placebo but found no significant difference between treatments for mortality (hospitalisations: 4 RCTs, 7262 people; OR 0.68, 95% CI 0.61 to 0.75; clinical deterioration: 12 RCTs, 1096 people; OR 0.31, 95% CI 0.21 to 0.43; mortality: 8 RCTs, 7756 people; OR 0.98, 95% CI 0.89 to 1.09). All but one of the RCTs included in the review followed up people for 6 months or less. The largest RCT in the review, which dominated the meta-analysis (6800 people, 88% male, mean age 64 years, New York Heart Association functional class I–III, 94% already taking angiotensin converting enzyme inhibitors, 82% taking diuretics) compared blinded additional treatment with either digoxin or placebo for a mean of 37 months.[28] It found no significant difference between digoxin and placebo in all cause mortality (1181/3397 [34.8%] with digoxin *v* 1194/3403 [35.1%] with placebo; ARR +0.3%, 95% CI −2.0% to +2.6%; RR 0.99, 95% CI 0.93 to 1.06). It found that digoxin significantly reduced admission rates for heart failure over 37 months compared with placebo and reduced the combined outcome of death or hospital admission caused by worsening heart failure (heart failure admissions: 910/3397 [27%] with digoxin *v* 1180/3403 [35%] with placebo; ARR 8%, 95% CI 6% to 10%; RR 0.77, 95% CI 0.72 to 0.83; NNT 13, 95% CI 10 to 17; death or hospital admission: 1041/3397 [31%] with digoxin *v* 1291/3403 [38%] for placebo; ARR 7.3%, 95% CI 5.1% to 9.4%; RR 0.81, 95% CI 0.75 to 0.87). **Other inotropic agents:** One non-systematic review (6 RCTs, 8006 people) of RCTs found that non-digitalis inotropes increased mortality compared with placebo.[10] The largest RCT in the review (3833 people with heart failure) found significantly increased mortality with vesnarinone 60 mg daily compared with placebo over 9 months (292/1275 [23%] with vesnarinone *v* 242/1280 [19%] with placebo; ARI 4%, 95% CI 1% to 8%; RR 1.21, 95% CI 1.04 to 1.40).[29] Another large RCT (1088 people with heart failure) found that milrinone significantly increased mortality over 6 months compared with placebo (168/561 [30%] with milrinone *v* 127/527 [24%] with placebo; ARI 6.0%, 95% CI 0.5% to 12.0%; RR 1.24, 95% CI 1.02 to 1.49).[30] A third large RCT (1906 people with heart failure) compared ibopamine versus placebo over 11 months.[31] It found that ibopamine significantly increased mortality compared with placebo (232/953 [25%] with ibopamine *v* 193/953 [20%] with placebo; RR 1.26, 95% CI 1.04 to 1.53). The review found that some RCTs reported improved functional capacity and quality of life, but this was not consistent across all RCTs. One systematic review (search date 2000, 21 RCTs, 632 people) examined the use of intravenous inotropic agents that act through the adrenergic pathway in people with heart failure.[32] Sixteen RCTs (474 people) contributed data from acute invasive haemodynamic studies of symptomatically severe heart failure, and five RCTs (158 people) were based on intermittent inotropic treatment in an outpatient setting. Included RCTs were often small. It found 11 RCTs comparing inotropic agents (including dobutamine, dopexamine, toborinone, and milrinone) versus placebo or control. The review found that, compared with placebo or control, intravenous inotropes that act through the adrenergic pathway tended to increase mortality, although this did not reach significance (11 RCTs; OR 1.50, 95% CI 0.51 to 3.92; absolute numbers not reported). It reported that there were insufficient data to determine whether symptoms improved (see comment below).

Harms:

Digoxin: The systematic review did not report on harms.[27] The largest RCT in the systematic review (6800 people) found that significantly more people had suspected digoxin toxicity in the digoxin group compared with placebo (11.9% with digoxin *v* 7.9% with placebo; ARI 4.0%, 95% CI 2.4% to 5.8%; RR 1.50, 95% CI 1.30 to 1.73).[28] The RCT found no significant difference between digoxin and placebo in the risk of ventricular fibrillation or tachycardia (37/3397 [1.1%] with digoxin *v* 27/3403 [0.8%] with placebo; ARI +0.3%, 95% CI −0.1% to +1.0%; RR 1.37, 95% CI 0.84 to 2.24). It found that, compared with placebo, digoxin significantly increased rates of supraventricular arrhythmia (2.5% with digoxin *v* 1.2% with placebo; ARI 1.3%, 95% CI 0.5% to 2.4%; RR 2.08, 95% CI 1.44 to 2.99) and second or third degree atrioventricular block (1.2% with digoxin *v* 0.4% with placebo; ARI 0.8%, 95% CI 0.2% to 1.8%; RR 2.93, 95% CI 1.61 to 5.34). **Other inotropic agents:** Most RCTs found that inotropic agents other than digoxin increased risk of death (see benefits above).

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Heart failure

Comment: The systematic review on intravenous inotropic agents in people with heart failure concluded that "intravenous inotropic agents acting through the adrenergic pathway are often used in patients with worsening heart failure to achieve arbitrary haemodynamic targets. Our analyses show that there is very little evidence that such treatment improves symptoms or patient outcomes and may not be safe."[32]

OPTION BETA BLOCKERS

Systematic reviews found strong evidence that adding a beta blocker to an angiotensin converting enzyme inhibitor decreased mortality and hospital admission in symptomatic people with heart failure of any severity. Limited evidence from a subgroup analysis of one RCT found no significant effect on mortality in black people.

Benefits: We found two systematic reviews (search dates 2000[33] and not reported[34]) and two subsequent RCTs[35,36] of the effects of beta blockers in heart failure. **In people with any severity of heart failure:** The first systematic review (22 RCTs, 10 315 people with heart failure, most people receiving triple therapy, in particular angiotensin converting enzyme inhibitors) found that beta blockers significantly reduced the risk of death and hospital admission compared with placebo (death: 444/5273 [8.4%] with beta blockers *v* 624/4862 [12.8%] with placebo; OR 0.65, 95% CI 0.53 to 0.80; hospital admissions: 540/5244 [10.3%] with beta blockers *v* 754/4832 [15.6%] with placebo; OR 0.64, 95% CI 0.53 to 0.79).[33] This is equivalent to three fewer deaths and four fewer hospital admissions per 100 people treated for 1 year. The results were consistent for selective and non-selective beta blockers. Sensitivity analysis and funnel plots found that publication bias was unlikely. **In people with severe heart failure:** The second systematic review (4 RCTs, 635 people with class IV heart failure, on angiotensin converting enzyme inhibitors and diuretic with or without digitalis) found that beta blockers significantly reduced the risk of death compared with placebo (56/313 [17.9%] with beta blockers *v* 81/322 [25.1%] with placebo; RR 0.71, 95% CI 0.52 to 0.96).[34] The two subsequent RCTs compared beta blockers versus placebo in people with New York Heart Association functional class III or IV heart failure.[35,36] The first RCT (2289 people with class IV heart failure, who were euvolaemic [defined as the absence of rales and ascites and the presence of no more than minimal peripheral oedema] and who had an ejection fraction of < 25%, but were not receiving intensive care, iv vasodilators, or positive inotropic drugs) compared carvedilol versus placebo over 10.4 months.[35] It was stopped early because of a significant beneficial effect on survival that exceeded the pre-specified interim monitoring boundaries. It found that beta blockers significantly reduced mortality compared with placebo (130/1156 [11.2%] with beta blockers *v* 190/1133 [16.8%] with placebo; RR 0.65, 95% CI 0.52 to 0.81) and the combined outcome of death or hospital admission (425/1156 [36.8%] with beta blockers *v* 507/1133 [44.7%] with placebo; RR 0.76, 95% CI 0.67 to 0.87). One subsequent report from this RCT found that, compared with placebo, carvedilol significantly reduced days in hospital for any reason or for heart failure compared with placebo (mean days in hospital for any reason: 6.2 per person with carvedilol *v* 8.5 per person with placebo; P = 0.0005; mean days in hospital for heart failure: 2.9 per person with carvedilol *v* 4.9 per person with placebo; P < 0.0001).[37] Another report from this RCT examined the short term risks of initiating carvedilol in severe heart failure.[38] During the first 8 weeks of treatment it found that, compared with placebo, carvedilol non-significantly reduced mortality and the combined outcome of death or hospitalisation compared with placebo (mortality: HR 0.75, 95% CI 0.41 to 1.35; death or hospitalisation for any reason: HR 0.85, 95% CI 0.67 to 1.07). The second RCT compared bucindolol versus placebo in people with severe heart failure (2708 people with class III or IV heart failure and ejection fraction ≤ 35%; about 70% of the people were white and 24% were black).[36] The RCT was stopped early because of accumulated evidence from other studies. It found that death was more common with placebo, but the difference did not reach significance (411/1354 [30.4%] with bucindolol *v* 449/1354 [33.1%] with placebo; HR 0.90, 95% CI 0.78 to 1.02). The RCT found a significant interaction of treatment effect with race (black *v* non-black people). There was no evidence of benefit in black people (HR 1.17, 95% CI 0.89 to 1.53), although there was a significant effect for non-black people (HR 0.82, 95% CI 0.70 to 0.96).

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Heart failure

Harms: One systematic review (search date 2002, 9 RCTs, 14 594 people followed up for 6–24 months) assessed harms of beta blockers in people with heart failure.[39] It found that beta blockers reduced the risk of withdrawal from treatment, death, and worsening heart failure compared with placebo (withdrawal: 16% with beta blocker *v* 18% with placebo; RR 0.89, 95% CI 0.81 to 0.98; death: 13% with beta blockers *v* 17% with placebo; RR 0.73, 95% CI 0.62 to 0.85; worsening heart failure: 4 RCTs; RR 0.83, 95% CI 0.71 to 0.98). It found that beta blockers significantly increased dizziness and bradycardia and non-significantly increased hypotension compared with placebo, but it found no significant difference between treatments for fatigue (dizziness: 4 RCTs; RR 1.37, 95% CI 1.09 to 1.71; bradycardia: 7 RCTs; RR 3.62, 95% CI 2.48 to 5.28; hypotension: 7 RCTs; RR 1.41, 95% CI 0.96 to 2.06; fatigue: 3 RCTs; RR 1.04, 95% CI 0.97 to 1.11).

Comment: Fears that beta blockers may cause excessive problems with worsening heart failure, bradyarrhythmia, or hypotension have not been confirmed. Good evidence was found for beta blockers in people with moderate symptoms (New York Heart Association functional class II or III) receiving standard treatment, including angiotensin converting enzyme inhibitors. The value of beta blockers is uncertain in heart failure with preserved ejection fraction and in asymptomatic left ventricular systolic dysfunction. One recent RCT (1959 people) found that carvedilol reduced all cause mortality compared with placebo (AR for death: 12% with carvedilol *v* 15% with placebo; HR 0.77, 95% CI 0.60 to 0.98) in people with acute myocardial infarction and left ventricular ejection fraction 40% or less.[40] The RCTs of beta blockers have consistently found a mortality benefit, but it is not clear whether this is a class effect. One recent small RCT (150 people) comparing metoprolol versus carvedilol found some differences in surrogate outcomes, but both drugs produced similar improvements in symptoms, submaximal exercise tolerance, and quality of life.[41] Another recent RCT (3029 people) compared carvedilol versus metoprolol tartrate in people with heart failure.[42] It found that carvedilol significantly reduced all cause mortality compared with metoprolol (512/1511 [34%] with carvedilol *v* 600/1518 [40%] with metoprolol; HR 0.83, 95% CI 0.74 to 0.93). It found no significant difference between groups for the composite outcome of mortality or all cause admission (P = 0.122). The results of this RCT suggest that carvedilol extends survival compared with metoprolol. However, potential limitations to this RCT were that the target dose of metoprolol was less than usually suggested, and metoprolol was not the long acting formulation used in a previous RCT[33] that had shown significant clinical benefit. The results for non-black people were consistent between bucindolol and carvedilol. The lack of observed benefit for black people in one RCT[36] raises the possibility that there may be race specific responses to pharmacological treatment for cardiovascular disease. A recent meta-analysis (6 RCTs, 13 129 people) examined whether beta blockers are as efficacious in people with heart failure with diabetes mellitus as in those without.[43] It found that overall mortality was significantly increased in people with diabetes mellitus compared with people without diabetes mellitus, regardless of treatment (RR 1.25, 95% CI 1.15 to 1.36). Although beta blockers significantly reduced mortality compared with placebo in people with diabetes (RR 0.84, 95% CI 0.73 to 0.96), the magnitude of benefit was significantly less than that in people who did not have diabetes mellitus (P = 0.023). A recent RCT (2128 elderly people with heart failure, mean age 76 years, mean left ventricular ejection fraction 36%, 35% of people had ejection fraction >35%) examined the effects of nebivolol in the elderly.[44] It found that nebivolol significantly reduced the composite end point of all cause mortality or cardiovascular hospital admission compared with placebo (31.1% with nebivolol *v* 35.3% with placebo; HR 0.86, 95% CI 0.74 to 0.99). It found no significant difference between treatment in all cause mortality (15.8% with nebivolol *v* 18.1% with placebo; HR 0.88, 95% CI 0.71 to 1.08). The absence of a statistically significant effect of nebivolol on death may have been due to the inclusion of many people with a left ventricular ejection fraction above 35%.

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Heart failure

OPTION CALCIUM CHANNEL BLOCKERS

One systematic review found no significant difference in mortality between second generation dihydropyridine calcium channel blockers and placebo. RCTs comparing other calcium channel blockers versus placebo also found no evidence of benefit. Calcium channel blockers have been found to exacerbate symptoms of heart failure or increase mortality after myocardial infarction in people who also have pulmonary congestion or left ventricular dysfunction.

Benefits: **Calcium channel blockers after myocardial infarction:** See calcium channel blockers under acute myocardial infarction, p 01. **Calcium channel blockers for other heart failure:** We found one systematic review (search date not reported, 18 RCTs, 3128 people with moderate to advanced heart failure for > 2 months) of second generation dihydropyridine calcium channel blockers,[45] one non-systematic review of all calcium channel blockers (3 RCTs, 1790 people with heart failure),[10] and one subsequent RCT.[46] The systematic review found no significant difference in mortality (2 RCTs, 1603 people; OR 0.94, 95% CI 0.79 to 1.12; significant heterogeneity was found; P = 0.48).[45] The largest RCT in the non-systematic review[10] (1153 people with New York Heart Association functional class III or IV, left ventricular ejection fraction < 0.30, using diuretics, digoxin, and angiotensin converting enzyme inhibitors) found no significant difference between amlodipine and placebo on the primary combined end point of all cause mortality and hospital admission for cardiovascular events over 14 months (222/571 [39%] with amlodipine *v* 246/582 [42%] with placebo; ARR +3.4%, 95% CI −2.3% to +8.8%; RR 0.92, 95% CI 0.79 to 1.06).[47] Subgroup analysis of people with primary cardiomyopathy found a significant reduction in mortality with amlodipine (45/209 [22%] with amlodipine *v* 74/212 [35%] with placebo; ARR 13%, 95% CI 5% to 20%; RR 0.62, 95% CI 0.43 to 0.85). There was no significant difference in the group with heart failure caused by coronary artery disease. The second RCT (186 people, idiopathic dilated cardiomyopathy, New York Heart Association functional class I–III) compared diltiazem versus placebo.[10] It found no evidence of a difference in survival between diltiazem and placebo in people who did not have a heart transplant, although people on diltiazem had improved cardiac function, exercise capacity, and subjective quality of life. The third RCT (451 people with mild heart failure, New York Heart Association functional class II or III) compared felodipine versus placebo.[10] It found no significant effect. The subsequent RCT (2590 people with New York Heart Association functional class II–IV heart failure, mean follow up of 1.5 years with mibefradil and 1.6 years with placebo) found no significant difference in death rates between mibefradil and placebo (350/1295 [27.0%] with mibefradil *v* 319/1295 [24.6%] with placebo; RR 1.10, 95% CI 0.96 to 1.25).[46]

Harms: Calcium channel blockers have been found to exacerbate symptoms of heart failure or increase mortality after myocardial infarction in people who also have pulmonary congestion or left ventricular dysfunction (see calcium channel blockers under acute myocardial infarction, p 01).[10] The subsequent RCT found that mibefradil increased risk of death in people taking digoxin, class I or II antiarrhythmics, amiodarone, or drugs associated with torsade de pointes compared with placebo.[46] The review found that second generation dihydropyridine calcium channel blockers did not cause significant adverse effects.[45]

Comment: Many of the RCTs were underpowered and had wide confidence intervals. One RCT of amlodipine in people with primary dilated cardiomyopathy is in progress.

OPTION ALDOSTERONE RECEPTOR ANTAGONISTS

One large RCT in people with severe heart failure taking diuretics, angiotensin converting enzyme inhibitors, and digoxin found that adding spironolactone reduced mortality after 2 years compared with adding placebo. One large RCT in people with recent myocardial infarction complicated by left ventricular dysfunction and clinical heart failure already on medical treatment (which could include angiotensin converting enzyme inhibitors, angiotensin receptor blockers, diuretics, beta blockers, or coronary reperfusion therapy) found that adding eplerenone reduced mortality compared with adding placebo.

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Benefits: **Aldosterone receptor antagonists versus placebo:** We found no systematic review but found two RCTs.[48,49] The first RCT (1663 people with heart failure, New York Heart Association functional class III or IV, left ventricular ejection fraction < 0.35, all taking angiotensin converting enzyme inhibitors and loop diuretics, and most taking digoxin) compared spironolactone 25 mg daily versus placebo.[48] The trial was stopped early because spironolactone significantly reduced all cause mortality compared with placebo after 2 years (mortality: 284/822 [35%] with spironolactone *v* 386/841 [46%] with placebo; ARR 11%, 95% CI 7% to 16%; RR 0.75, 95% CI 0.66 to 0.85; NNT 9, 95% CI 6 to 15). The second RCT compared eplerenone (a selective aldosterone receptor antagonist) versus placebo in people found to have left ventricular dysfunction (ejection fraction of ≤ 40%) and clinical symptoms of heart failure after an acute myocardial infarction within the previous 3–14 days.[49] People were already receiving "optimal" medical treatment, which could include angiotensin converting enzyme inhibitors, angiotensin receptor blockers, diuretics, beta blockers, or coronary reperfusion therapy, but excluded potassium sparing diuretics. The RCT found that eplerenone significantly reduced death from any cause after 16 months compared with placebo (478/3319 [14%] with eplerenone *v* 554/3313 [17%] with placebo; RR 0.85, 95% CI 0.75 to 0.96). It found that, compared with placebo, eplerenone significantly reduced death from cardiovascular causes (407/3319 [12%] with eplerenone *v* 483/3313 [15%] with placebo; RR 0.83, 95% CI 0.72 to 0.94) and significantly reduced the composite end point of death from cardiovascular causes or hospitalisation for cardiovascular events (885/3319 [27%] with eplerenone *v* 993/3313 [30%] with placebo; RR 0.87, 95% CI 0.79 to 0.95).

Harms: **Aldosterone receptor antagonists versus placebo:** The first RCT found no evidence that adding spironolactone to an angiotensin converting enzyme inhibitor increased risk of clinically important hyperkalaemia.[48] Gynaecomastia or breast pain were reported in 10% of men given spironolactone and 1% of men given placebo (P < 0.001). In the RCT comparing eplerenone versus placebo, the rate of serious hyperkalaemia was significantly higher in the eplerenone group (180/3307 [5.5%] with eplerenone *v* 126/3301 [3.9%] with placebo; P = 0.002).[49]

Comment: The first RCT was large and well designed. Because only people with New York Heart Association functional class III or IV were included, these results cannot necessarily be generalised to people with milder heart failure. A recent population based time series analysis[50] examined the trends in the rate of spironolactone prescriptions and the rate of hospitalisations for hyperkalaemia in ambulatory patients before and after the publication of an RCT that demonstrated the benefits of spironolactone.[48] The spironolactone prescription rate significantly increased after publication (34/1000 people to 149/1000 people; P < 0.001). The rate of hospitalisation for hyperkalaemia also increased from 2.4/1000 patients to 11.0/1000 patients (P < 0.001) and the associated mortality rate increased from 0.3/1000 people to 2.0/1000 people (P < 0.001). The results of the study are very important because it emphasises the need for appropriate monitoring of people treated with spironolactone.

OPTION ANTIARRHYTHMIC DRUG TREATMENT

Systematic reviews found weak evidence that amiodarone may reduce mortality compared with placebo. However, we were unable to draw firm conclusions about the effects of amiodarone in people with heart failure. Evidence extrapolated from one systematic review in people treated after a myocardial infarction suggested that other antiarrhythmic agents (apart from β blockers) may have increased mortality in people with heart failure.

Benefits: **Amiodarone:** We found two systematic reviews comparing amiodarone versus placebo in heart failure.[51,52] The most recent review (search date 1997, 10 RCTs, 4766 people) included people with a wide range of conditions (symptomatic and asymptomatic heart failure, ventricular arrhythmia, recent myocardial infarction, and recent cardiac arrest).[51] Eight of these RCTs reported the number of deaths. The review found that treatment with amiodarone over 3–24 months significantly reduced the risk of death from any cause compared with placebo or conventional treatment (436/2262 [19%] with amiodarone *v* 507/2263 [22%] with control; ARR 3.0%, 95% CI 0.8% to 5.3%; RR 0.86, 95% CI 0.76

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Heart failure

to 0.96). This review did not perform any subgroup analyses in people with heart failure. The earlier systematic review (search date not reported) found eight RCTs (5101 people after myocardial infarction) comparing prophylactic amiodarone versus placebo or usual care, and five RCTs (1452 people) in people with heart failure.[52] Mean follow up was 16 months. Analysis of results from all 13 RCTs found a lower total mortality with amiodarone than with control (annual mortality: 10.9% with amiodarone *v* 12.3% with control). The effect was significant with some methods of calculation (fixed effects model: OR 0.87, 95% CI 0.78 to 0.99) but not with others (random effects model: OR 0.85, 95% CI 0.71 to 1.02). The effect of amiodarone was significantly greater in RCTs that compared amiodarone versus usual care than in placebo controlled RCTs. It found that amiodarone significantly reduced arrhythmic death or sudden death compared with placebo (OR 0.71, 95% CI 0.59 to 0.85). Subgroup analysis found that amiodarone significantly reduced mortality in the five heart failure RCTs compared with placebo (annual mortality: 19.9% with amiodarone *v* 24.3% with placebo; OR 0.83, 95% CI 0.70 to 0.99). **Other antiarrhythmics:** Apart from beta blockers, other antiarrhythmic drugs increase mortality in people at high risk (see class I antiarrhythmic agents under secondary prevention of ischaemic cardiac events, p 00).

Harms:

Amiodarone: Amiodarone did not significantly increase non-arrhythmic death rate (OR 1.02, 95% CI 0.87 to 1.19).[52] In placebo controlled RCTs, after 2 years 41% of people in the amiodarone group and 27% in the placebo group had permanently discontinued study medication.[52] In 10 RCTs comparing amiodarone versus placebo, amiodarone increased the odds of reporting adverse drug reactions compared with placebo (OR 2.22, 95% CI 1.83 to 2.68). Nausea was the most common adverse effect. Hypothyroidism was the most common serious adverse effect (7.0% with amiodarone *v* 1.1% with placebo). Hyperthyroidism (1.4% with amiodarone *v* 0.5% with placebo), peripheral neuropathy (0.5% with amiodarone *v* 0.2% with placebo), lung infiltrates (1.6% with amiodarone *v* 0.5% with placebo), bradycardia (2.4% with amiodarone *v* 0.8% with placebo), and liver dysfunction (1.0% with amiodarone *v* 0.4% with placebo) were all more common in the amiodarone group.[52] **Other antiarrhythmics:** These agents (particularly class I antiarrhythmics) may increase mortality (see class I antiarrhythmic agents under secondary prevention of ischaemic cardiac events, p 00).

Comment:

Amiodarone: RCTs of amiodarone versus usual treatment found larger effects than placebo controlled trials.[52] These findings suggest bias; unblinded follow up may be associated with reduced usual care or improved adherence with amiodarone. Further studies are required to assess the effects of amiodarone treatment on mortality and morbidity in people with heart failure.

OPTION IMPLANTABLE CARDIAC DEFIBRILLATORS

One systematic review found that implantable cardiac defibrillators reduced mortality in people with heart failure who have experienced a near fatal ventricular arrythmia or are at high risk of sudden death. A second systematic review found that implantable cardiac defibrillators reduced mortality in people with heart failure due to non-ischaemic cardiomyopathy.

Benefits:

Implantable cardiac defibrillators: We found two systematic reviews.[53,54] The first systematic review (search date 2002, 8 RCTs, 4909 people) compared implantable cardiac defibrillator versus usual care in the primary or secondary prevention of life-threatening arrhythmias and sudden cardiac death.[53] Over all studies (for primary and secondary prevention combined), it found that implantable cardiac defibrillator significantly reduced sudden cardiac death and all cause mortality compared with usual care (cardiac death: RR 0.43, 95% CI 0.35 to 0.53; all cause mortality: RR 0.74, 95% CI 0.67 to 0.82). For secondary prevention, it found that implantable cardiac defibrillator significantly reduced sudden cardiac death and all cause death (3 RCTs, 1963 people; cardiac death: RR 0.50, 95% CI 0.38 to 0.66; all cause mortality: RR 0.76, 95% CI 0.65 to 0.89). For primary prevention, it found that implantable cardiac defibrillator significantly reduced sudden cardiac death and all cause death (5 RCTs, 2946 people; cardiac death: RR 0.37, 95% CI 0.27 to 0.50; all cause mortality: RR 0.72, 95% CI 0.63 to 0.84). In primary prevention trials, the magnitude of absolute mortality

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benefit increased with increasing baseline risk of sudden cardiac death. The second systematic review (search date 2004, 7 RCTs, 2110 people) compared implantable cardiac defibrillator treatment versus usual care in people with heart failure due to non-ischaemic cardiomyopathy and analysed results separately for primary and secondary prevention RCTs.[54] For primary prevention, it found that implantable cardiac defibrillator treatment significantly reduced all cause mortality compared with usual care (4 RCTs, 1457 people; RR 0.74, 95% CI 0.58 to 0.96). For secondary prevention, it found that implantable cardiac defibrillator treatment reduced all cause mortality compared with usual care but the difference was not statistically significant (2 RCTs, 256 people; RR 0.69, 95% CI 0.39 to 1.24). The number analysed may have been too small to detect a significant difference. For all studies, it found that implantable cardiac defibrillator treatment significantly reduced mortality compared with usual care (RR 0.69, 95% CI 0.56 to 0.86).

Harms: **Implantable cardiac defibrillators:** The first systematic review found that complications associated with implantable cardiac defibrillator treatment included perioperative infection (0.7–12.3%), lead fracture or device malfunction (range 0.8–14%), serious bleeding (range 1–6%), and pneumothorax (<1%).[53] The second systematic review did not report harms.[54]

Comment: The systematic reviews suggest that implantable cardiac defibrillators are more beneficial than drug therapy for secondary prevention of sudden cardiac death and for primary prevention in certain high risk groups.[53,54] However, the therapy is expensive and must be used appropriately in those for whom the indications for therapy clearly exist. Further research is required to develop accurate risk stratification tools, to determine the impact of implantable cardiac defibrillators therapy in different subgroups of patients, and to evaluate quality of life issues.

OPTION CARDIAC RESYNCHRONISATION THERAPY New

One systematic review and one subsequent RCT found that cardiac resynchronisation therapy improved functional capacity, reduced heart failure hospitalisation, and reduced all cause mortality compared with standard care.

Benefits: **Cardiac resynchronisation therapy:** We found one systematic review (search date 2003, 9 RCTs, 3216 people, 85% with New York Heart Association (NYHA) functional class III or IV G symptoms[55]) and one subsequent RCT.[56] The systematic review found that cardiac resynchronisation therapy significantly improved quality of life and function compared with usual care (weighted mean reduction in quality of life score on the Minnesota Living with Heart Failure Questionnaire G score: 7.6 points, 95% CI 3.8 points to 11.5 points; function improved by at least one NYHA functional class: 4 RCTs; 58% *v* 37% with usual care G; RR 1.6, 95% CI 1.3 to 1.9).[55] It found that cardiac resynchronisation therapy reduced heart failure hospitalisations compared with usual care and significantly reduced heart failure hospitalisations in people with NYHA class III or IV symptoms at baseline (all heart failure hospitalisations: RR 0.68, 95% CI 0.41 to 1.12; NYHA class III or IV symptoms at baseline: RR 0.65, 95% CI 0.48 to 0.88). It found that cardiac resynchronisation therapy significantly reduced all cause mortality and reduced death from progressive heart failure (all cause mortality: RR 0.79, 95% CI 0.66 to 0.96; death from progressive heart failure: RR 0.60, 95% CI 0.36 to 1.01). The subsequent RCT (813 people with NYHA class III–IV heart failure) found that standard care plus cardiac resynchronisation therapy significantly reduced the combined outcome (death from any cause or an unplanned hospitalisation for a major cardiovascular event) and death compared with standard care alone after mean follow up of 29.4 months (combined outcome: 39% with resynchronisation therapy *v* 55% with standard care alone; HR 0.63, 95% CI 0.51 to 0.77; death: 20% with resynchronisation *v* 30% with standard care alone; HR 0.64, 95% CI 0.48 to 0.85). It found that cardiac resynchronisation therapy significantly improved symptoms and the quality of life compared with standard care (NYHA class: 2.7 with resynchronisation therapy *v* 2.1 with standard care; $P < 0.001$; Minnesota Living with Heart Failure score: 40 with resynchronisation therapy *v* 31 with standard care; $P < 0.001$; European Quality of Life–5 Dimensions score G: 0.63 with resynchronisation therapy *v* 0.70 with standard care; $P < 0.001$).

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Heart failure

Harms: **Cardiac resynchronisation therapy:** The systematic review (the search date 2003) found that the cardiac resynchronisation implant success rate was 90% (95% CI 89% to 91%) and 0.4% of patients died during implantation (95% CI 0.2% to 0.7%).[55] It found that over a median 6 months of follow up, leads dislodged in 9% of recipients (95% CI 7% to 10%) and mechanical malfunctions occurred in 7% (95% CI 5% to 8%). The subsequent RCT (409 people with cardiac resynchronisation implant) found that lead displacement occurred in 24/409 [5.9%], coronary sinus dissection in 10/409 [2.4%], pocket erosion in 8/409 [2%], pneumothorax in 6/409 [1.5%], and device related infection in 3/409 [0.7%]).[56]

Comment: The subsequent RCT also found that resynchronisation reduced the interventricular mechanical delay, the end systolic volume index, and the area of the mitral regurgitant jet ($P < 0.01$ for all comparisons).[56] The results presented in the systematic review and the subsequent RCT indicate that there are beneficial effects with cardiac resynchronisation therapy.[55,56] The group with the most benefit appears to be those with the more severe symptoms of heart failure. For the most part, people included in the studies were well selected, the procedure was performed in centres with a great deal of experience, and, because in almost all of the trials the people were randomly assigned to different modes of operation after placement of the pacemaker, the results may overestimate the potential benefits of cardiac resynchronisation therapy.

OPTION ANTICOAGULATION

A preliminary report from one RCT found no significant difference between warfarin and no antithrombotic treatment or between warfarin and aspirin in the combined outcome of death, myocardial infarction, and stroke after 27 months. However, the RCT may have lacked power to detect a clinically important difference. The effects of antiplatelet treatment in combination with angiotensin converting enzymes requires further research.

Benefits: **Anticoagulation versus placebo:** We found one systematic review (search date 2001, 1 RCT, 279 people, 70% with New York Heart Association functional class III⊖).[57] The RCT identified by the review was a pilot study comparing warfarin (international normalised ratio 2.5), aspirin (300 mg/day), and no antithrombotic treatment.[58] The RCT found no significant difference between warfarin and no antithrombotic treatment in the combined outcome of death, myocardial infarction, and stroke after a mean follow up of 27 months (combined outcome: 26% with warfarin *v* 27% with no antithrombotic treatment; P value not reported).[58] **Anticoagulation versus antiplatelet agents:** See benefits of antiplatelet agents, p 17.

Harms: **Anticoagulation versus placebo:** The RCT found four haemorrhagic events with warfarin and none with no antithrombotic treatment (total number of people in each group not reported).[58]

Comment: The systematic review (search date 2001)[57] found three additional non-randomised trials. Meta-analysis of these trials and the RCT[58] found that anticoagulant significantly reduced death from all causes and cardiovascular event rates compared with control (death from all causes: 1087 people; OR 0.64, 95% CI 0.45 to 0.90; cardiovascular event rates: 1130 people; OR 0.26, 95% CI 0.16 to 0.43).[57] Meta-analysis of two non-randomised trials (645 people) found no significant difference in bleeding complications between warfarin and no warfarin (OR 1.52, 95% CI 0.56 to 4.10). The non-randomised controlled studies were performed in the early 1950s in hospitalised people with a high prevalence of rheumatic heart disease and atrial fibrillation, and the methods used may be considered unreliable today. One retrospective analysis assessed the effect of anticoagulants used at the discretion of individual investigators in RCTs on the incidence of stroke, peripheral arterial embolism, and pulmonary embolism.[59] The first cohort was from one RCT (642 men with chronic heart failure) comparing hydralazine plus isosorbide dinitrate versus prazosin versus placebo. The second cohort was from another RCT (804 men with chronic heart failure) comparing enalapril versus hydralazine plus isosorbide dinitrate. All people were given digoxin and diuretics. The retrospective analysis found that, without treatment, the incidence of all thromboembolic events was low (2.7/100 patient years in the first RCT; 2.1/100 patient years in the

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second RCT) and that anticoagulation did not reduce the incidence of thromboembolic events (2.9/100 patient years in the first RCT; 4.8/100 patient years in the second RCT). In this group of people, atrial fibrillation was not found to be associated with a higher risk of thromboembolic events. A second retrospective analysis was from two large RCTs (2569 people with symptomatic and asymptomatic left ventricular dysfunction), which compared enalapril versus placebo.[60] The analysis found that people treated with warfarin at baseline had significantly lower risk of death during follow up (HR adjusted for baseline differences 0.76, 95% CI 0.65 to 0.89). Warfarin use was associated with a reduction in the combined outcome of death plus hospital admission for heart failure (adjusted HR 0.82, 95% CI 0.72 to 0.93). The benefit with warfarin use was not significantly influenced by the presence of symptoms, randomisation to enalapril or placebo, sex, presence of atrial fibrillation, age, ejection fraction, New York Heart Association functional class G, or cause of heart failure. Warfarin reduced cardiac mortality, specifically deaths that were sudden or associated with either heart failure or myocardial infarction. Neither of the retrospective studies was designed to determine the incidence of thromboembolic events in heart failure or the effects of treatment. Neither study included information about the intensity of anticoagulation or warfarin use. We found several additional cohort studies that showed a reduction in thromboembolic events with anticoagulation, but they all reported on too few people to provide useful results. An RCT is needed to compare anticoagulation versus no anticoagulation in people with heart failure.

OPTION ANTIPLATELET AGENTS

A preliminary report from one RCT found no significant difference between aspirin and no antithrombotic treatment or between aspirin and warfarin in the combined outcome of death, myocardial infarction, and stroke after 27 months. However, the RCT may have lacked power to detect a clinically important difference. The effects of antiplatelet treatment in combination with angiotensin converting enzymes requires further research.

Benefits: **Antiplatelet agents versus no treatment:** We found one systematic review (search date 2001, 1 RCT, 279 people, 70% with New York Heart Association functional class III G).[57] The RCT identified by the review was a pilot study comparing aspirin (300 mg/day) versus warfarin (international normalised ratio 2.5) versus no antithrombotic treatment.[58] The RCT found no significant difference between aspirin and no antithrombotic treatment for the combined outcome of death, myocardial infarction, and stroke after a mean follow up of 27 months (combined outcome: 32% with aspirin *v* 27% with no antithrombotic treatment; P value reported as not significant). It found that aspirin significantly increased all cause hospital admission compared with placebo ($P < 0.05$; no data reported). **Antiplatelet agents versus warfarin:** The RCT found no significant difference between aspirin and warfarin for the combined outcome of death, myocardial infarction, and stroke after a mean follow up of 27 months (combined outcome: 32% with aspirin *v* 26% with warfarin; P value reported as not significant).[58] It found that all cause hospital admissions were significantly higher for aspirin compared with warfarin ($P = 0.05$; no data reported).

Harms: **Antiplatelet agents:** Preliminary information on one RCT reported five haemorrhagic events with aspirin compared with four with warfarin (total number of people in each group not reported).[58] The total number of serious adverse reactions were similar in all groups (198 with aspirin *v* 163 with warfarin *v* 178 with no antithrombotic treatment; $P = 0.08$).[61]

Comment: **In people not taking angiotensin converting enzyme inhibitors:** We found no systematic review and no RCTs. We found one retrospective cohort analysis within one RCT in 642 men with heart failure.[59] The RCT compared hydralazine plus isosorbide dinitrate versus prazosin versus placebo in men receiving digoxin and diuretics. Aspirin or dipyridamole, or both, were used at the discretion of the investigators. The number of thromboembolic events was low in both groups (1 stroke, 0 peripheral and 0 pulmonary emboli in 184 people years of treatment with antiplatelet agents *v* 21 strokes, 4 peripheral and 4 pulmonary emboli in 1068 people years of treatment without antiplatelet agents; 0.5 events/100 people years with antiplatelet agents *v* 2.0 events/100

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Heart failure

patient years without antiplatelet agents; P = 0.07). **In people taking angiotensin converting enzyme inhibitors:** We found no RCTs. We found two large retrospective cohort studies.[59,62] The first retrospective analysis assessed the effect of antiplatelet agents used at the discretion of individual investigators on the incidence of stroke, peripheral arterial embolism, and pulmonary embolism within one RCT.[59] The RCT (804 men with chronic heart failure) compared enalapril versus hydralazine plus isosorbide dinitrate. It found that the incidence of all thromboembolic events was low without antiplatelet treatment and found no significant difference between groups (1.6 events/100 patient years with antiplatelet treatment *v* 2.1 events/100 people years with no antiplatelet treatment; P = 0.48). The second cohort analysis was from two large RCTs, which compared enalapril versus placebo (2569 people with symptomatic and asymptomatic left ventricular dysfunction). It found that people treated with antiplatelet agents at baseline had a significantly lower risk of death (HR adjusted for baseline differences 0.82, 95% CI 0.73 to 0.92).[62] Subgroup analysis suggested that antiplatelet agents might have an effect in people randomised to placebo (mortality HR for antiplatelet treatment at baseline *v* no antiplatelet treatment at baseline 0.68, 95% CI 0.58 to 0.80), but not in people randomised to enalapril (mortality HR for antiplatelet treatment *v* no antiplatelet treatment 1.00, 95% CI 0.85 to 1.17). Both retrospective studies have important limitations common to studies with a retrospective cohort design. One study did not report on the proportions of people taking aspirin and other antiplatelet agents.[59] The other study noted that more than 95% of people took aspirin, but the dosage and consistency of antiplatelet use was not recorded.[62] One retrospective non-systematic review (4 RCTs, 96 712 people) provided additional evidence about the effect of aspirin on the benefits of early angiotensin converting enzyme inhibitors in heart failure.[63] It found a similar reduction in 30 day mortality with angiotensin converting enzyme inhibitor versus control for those people not taking aspirin compared with those taking aspirin (aspirin: OR 0.94, 95% CI 0.89 to 0.99; no aspirin: OR 0.90, 95% CI 0.81 to 1.01). However, the analysis may not be valid because the people who did not receive aspirin were older and had a worse baseline prognosis than those taking aspirin. The effects of antiplatelet treatment in combination with angiotensin converting enzyme inhibitors in people with heart failure requires further research.

QUESTION **What are the effects of angiotensin converting enzyme inhibitors in people at high risk of heart failure?**

OPTION **ANGIOTENSIN CONVERTING ENZYME INHIBITORS IN PEOPLE AT HIGH RISK OF HEART FAILURE**

RCTs in people with asymptomatic left ventricular systolic dysfunction found that angiotensin converting enzyme inhibitors delayed the onset of symptomatic heart failure, reduced cardiovascular events, and improved long term survival compared with placebo.

Benefits: **Angiotensin converting enzyme inhibitors in people with asymptomatic left ventricular systolic dysfunction:** We found no systematic review but found three RCTs, one of which reported 12 year follow up of the first RCT.[64–66] The first large RCT (4228 people) compared an angiotensin converting enzyme (ACE) inhibitor (enalapril) versus placebo over 40 months in people with asymptomatic left ventricular systolic dysfunction (ejection fraction < 0.35).[64] It found no significant difference between enalapril and placebo in total mortality and cardiovascular mortality (all cause mortality: 313/2111 [14.8%] with ACE inhibitor *v* 334/2117 [15.8%] with placebo; ARR +0.9%, 95% CI −1.3% to +2.9%; RR 0.94, 95% CI 0.81 to 1.08; cardiovascular mortality: 265/2111 [12.6%] with ACE inhibitor *v* 298/2117 [14.1%] with placebo; ARR +1.5%, 95% CI −0.6% to +3.3%; RR 0.89, 95% CI 0.76 to 1.04). During the study, more people assigned to the placebo received digoxin, diuretics, or ACE inhibitors that were not part of the study protocol, which may have contributed to the lack of significant difference in mortality between the two groups. The RCT found that, compared with placebo, enalapril significantly reduced symptomatic heart failure, hospital admission for heart failure, and fatal or non-fatal myocardial infarction (symptomatic heart failure: 438/2111 [21%] with ACE inhibitor *v* 640/2117 [30%] with placebo; ARR 9.5%, 95% CI 7.0% to 12.0%; RR 0.69, 95% CI 0.61 to 0.77; admission for heart failure: 306/2111 [15%] with ACE

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inhibitor *v* 454/2117 [21%] with placebo; ARR 7%, 95% CI 5% to 9%; RR 0.68, 95% CI 0.59 to 0.77; fatal or non-fatal myocardial infarction: 7.6% with ACE inhibitor *v* 9.6% with placebo; ARR 2%, 95% CI 0.4% to 3.4%; RR 0.79, 95% CI 0.65 to 0.96).[9,64] Twelve year follow up of this RCT found that enalapril given for 3–4 years significantly reduced death from all causes and cardiac deaths compared with placebo (all cause mortality: HR 0.86, 95% CI 0.79 to 0.93; cardiac death: HR 0.85, 95% CI 0.77 to 0.94).[66] The second RCT in asymptomatic people after myocardial infarction with documented left ventricular systolic dysfunction found that an ACE inhibitor (captopril) reduced the risk of all ischaemic events, all myocardial infarctions, and fatal myocardial infarctions compared with placebo (all ischaemic events: 29% with captopril *v* 33% with placebo; RR 0.86, 95% CI 0.74 to 1.0; total myocardial infarctions: 12% with captopril *v* 15% with placebo; RR 0.75, 95% CI 0.60 to 0.95; fatal myocardial infarctions: 5% with captopril *v* 7% with placebo; RR 0.68, 95% CI 0.49 to 0.96).[65]

Harms: **Angiotensin converting enzyme inhibitors in people with asymptomatic left ventricular systolic dysfunction:** The first RCT over 40 months found that a high proportion of people in both groups reported adverse effects (76% with enalapril *v* 72% with placebo).[64] Dizziness or fainting (46% with enalapril *v* 33% with placebo) and cough (34% with enalapril *v* 27% with placebo) were reported more often in the enalapril group (P value not reported). The incidence of angio-oedema was the same in both groups (1.4%). Study medication was permanently discontinued by 8% of the people in the enalapril group compared 5% in the placebo group (P value not reported). The 12 year follow up of this RCT did not report on adverse effects.

Comment: Asymptomatic left ventricular systolic dysfunction is prognostically important, but we found no prospective studies that evaluated screening to detect its presence.

QUESTION What are the effects of treatments for diastolic heart failure?

OPTION TREATMENTS FOR DIASTOLIC HEART FAILURE

One RCT found that candesartan, an angiotensin II receptor blocker, reduced the combined outcome of cardiovascular death or hospital admission for heart failure compared with placebo, although the difference was not significant. It found no significant difference in cardiovascular death between the two groups, but found that candesartan reduced hospital admission compared with placebo. We found no RCTs examining effects of other treatments in people with diastolic heart failure.

Benefits: **Angiotensin II receptor blockers:** We found one RCT (3023 patients with New York Heart Association functional class II–IV  heart failure and left ventricular ejection fraction > 40%), which compared candesartan (started at 4 or 8 mg daily with target dose 32 mg once daily from 6 weeks onward) versus placebo.[67] It found that, during a median follow up of 36.6 months, candesartan reduced the combined outcome of cardiovascular death or hospital admission for chronic heart failure compared with placebo (22% with candesartan *v* 24.3% with placebo; adjusted HR 0.86, 95% CI 0.74 to 1.00). It found no significant difference in cardiovascular death between the two groups, but found that candesartan significantly reduced hospital admission for heart failure compared with the placebo group (cardiovascular death: 11.2% with candesartan *v* 11.3% with placebo; adjusted HR 0.95, 95% CI 0.76 to 1.18; hospital admission for congestive heart failure: 15.9% with candesartan *v* 18.3% with placebo; adjusted HR 0.84, 95% CI 0.70 to 1.00). **Other treatments:** We found no RCTs.

Harms: **Angiotensin II receptor blockers:** The RCT found that candesartan significantly increased permanent discontinuation of therapy because of an adverse event or an abnormal laboratory value compared with placebo (adverse events were hypotension, hyperkalaemia, and increase in plasma creatinine; 17.8% with candesartan *v* 13.5% with placebo; P = 0.001).[67]

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Heart failure

Comment: The causes of diastolic dysfunction vary among people with diastolic heart failure. Current treatment is largely based on the results of small clinical studies and consists of treating the underlying cause and coexistent conditions with interventions optimised for individuals.[6,68,69] Further RCTs with clinically relevant outcome measures are needed to determine the benefits and harms of treatments other than angiotensin II receptor blockers in diastolic heart failure.

GLOSSARY

European Quality of Life–5 Dimensions (EuroQol EQ–5D) scores range from –0.594 to 1.000, with lower numerical scores reflecting a poorer quality of life and negative scores associated with a quality of life that is considered worse than death.

Minnesota Living with Heart Failure Questionnaire scores range from 1 to 105, with higher scores reflecting a lower quality of life.

New York Heart Association functional classification Classification of severity by symptoms. Class I: no limitation of physical activity; ordinary physical activity does not cause undue fatigue or dyspnoea. Class II: slight limitation of physical activity; comfortable at rest, but ordinary physical activity results in fatigue or dyspnoea. Class III: limitation of physical activity; comfortable at rest, but less than ordinary activity causes fatigue or dyspnoea. Class IV: unable to carry out any physical activity without symptoms; symptoms are present even at rest; if any physical activity is undertaken, symptoms are increased.

Usual or conventional care describes the comparator arm of some controlled trials. It refers to appropriate drug and non-drug treatment, in the absence of the intervention being examined in the active treatment arm of the trial.

Substantive changes

Multidisciplinary interventions Two systematic reviews and one RCT added;[14–16] categorisation changed from Likely to be beneficial to Beneficial.

Exercise Two systematic reviews added;[18,19] categorisation unchanged (likely to be beneficial).

Angiotensin II receptor blockers Two systematic reviews added;[25,26] categorisation unchanged (beneficial).

Digoxin One systematic review added;[27] categorisation unchanged (beneficial).

Beta Blockers One systematic review added;[39] categorisation unchanged (beneficial).

Calcium channel blockers Categorisation changed from Unlikely to be beneficial to Likely to be ineffective or harmful based on re-evaluation of the evidence.

Implantable cardiac defibrillators in people at high risk of arrhythmia Two systematic reviews added;[53,54] categorisation unchanged (likely to be beneficial).

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Heart failure

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Peripheral arterial disease

Search date December 2005

Kevin Cassar and Paul Bachoo

QUESTIONS

INTERVENTIONS

*Based on observational evidence and consensus

See glossary

Key Messages

Treatments

- **Antiplatelet agents** Systematic reviews found that antiplatelet agents (aspirin, clopidogrel, aspirin plus dipyridamole, or ticlopidine) reduced major cardiovascular events over an average of about 2 years compared with control treatment. Systematic reviews also found that antiplatelet agents (aspirin and ticlopidine) reduced the risk of arterial occlusion and revascularisation procedures compared with placebo or no treatment. The balance of benefits and harms is in favour of treatment for most people with symptomatic peripheral arterial disease, because as a group they are at much greater risk of cardiovascular events. One systematic review in people undergoing peripheral endovascular intervention found no significant difference between low dose aspirin plus dipyridamole and placebo in restenosis or reocclusion at 6 months.
- **Exercise** Systematic reviews and subsequent RCTs in people with chronic stable claudication found that regular exercise at least three times weekly for between 3 and 6 months improved total walking distance and maximal exercise time after 3–12 months compared with no exercise. One RCT found that vitamin E plus regular exercise increased walking duration compared with placebo at 6 months. One RCT found that a "stop smoking and keep walking" intervention increased the maximal walking distance compared with usual care at 12 months.
- **HMG-CoA reductase inhibitors (statins)** Three RCTs including people with peripheral arterial disease found that statins (simvastatin, atorvastatin, and pravastatin) reduced cardiovascular events (including non-fatal myocardial infarction, coronary death, total coronary events, and fatal and non-fatal stroke) compared with placebo. However, people with peripheral arterial disease formed only a small proportion (5–13%) of all people included in these RCTs. One RCT found that simvastatin increased time to onset of claudication compared with placebo at 12 months. One RCT found that simvastatin increased pain free walking distance and total walking distance compared with placebo at 6 months. One RCT found that atorvastatin increased pain free walking time compared with placebo at 12 months.
- **Percutaneous transluminal angioplasty (transient benefit only)** Two small RCTs identified by a systematic review, in people with mild to moderate intermittent claudication, found limited evidence that percutaneous angioplasty improved walking distance after 6 months compared with no angioplasty but found no significant difference after 2 or 6 years. Two small RCTs identified by a systematic review and four additional RCTs in people with stenosis between the femoral and popliteal arteries or between the aorta and iliac arteries found no significant difference between angioplasty

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Peripheral arterial disease

alone and angioplasty plus stent placement in patency rates, occlusion rates, or clinical improvement. The RCTs may have lacked power to detect a clinically important effect. One RCT found no significant difference between percutaneous transluminal angioplasty plus lovastatin and percutaneous transluminal angioplasty alone in restenosis rates at 12 months. One systematic review found, in people with chronic progressive peripheral arterial disease, that percutaneous transluminal angioplasty was less effective in improving patency compared with surgery after 12–24 months but found no significant difference after 4 years. The review found no difference in mortality after 12–24 months.

- **Smoking cessation*** RCTs of advice to stop smoking would be considered unethical. The consensus view is that smoking cessation improves symptoms in people with intermittent claudication. One systematic review of observational studies found inconclusive results of stopping smoking, both in terms of increasing absolute claudication distance and reducing the risk of symptom progression, compared with people who continue to smoke.
- **Cilostazol** One non-systematic meta-analysis and one additional RCT found that cilostazol improved claudication distance at 12–24 weeks compared with placebo. However, adverse effects of cilostazol were common in the RCTs, and included headache, diarrhoea, and palpitations. One RCT found limited evidence that cilostazol increased initial and absolute claudication distance compared with pentoxifylline.
- **Bypass surgery (compared with percutaneous transluminal angioplasty)** One systematic review found that surgery in people with chronic progressive peripheral arterial disease improved primary patency after 12–24 months compared with percutaneous transluminal angioplasty, but it found no significant difference after 4 years. The review found no significant difference in mortality after 12–24 months. Although the consensus view is that bypass surgery is the most effective treatment for people with debilitating symptomatic peripheral arterial disease, we found inadequate evidence from RCTs reporting long term clinical outcomes to confirm this view.
- **Pentoxifylline** One systematic review and one subsequent RCT found insufficient evidence to compare pentoxifylline versus placebo. One RCT found limited evidence that pentoxifylline was less effective at improving initial and absolute claudication distance compared with cilostazol after 24 weeks.

*Based on observational evidence and consensus

DEFINITION	Peripheral arterial disease arises when there is significant narrowing of arteries distal to the arch of the aorta. Narrowing can arise from atheroma, arteritis, local thrombus formation, or embolisation from the heart or more central arteries. This topic includes treatment options for people with symptoms of reduced blood flow to the leg that are likely to arise from atheroma. These symptoms range from calf pain on exercise (intermittent claudication G) to rest pain, skin ulceration, or symptoms of ischaemic necrosis (gangrene) in people with critical limb ischaemia G.
INCIDENCE/ PREVALENCE	Peripheral arterial disease is more common in people aged over 50 years than in younger people, and it is more common in men than in women. The prevalence of peripheral arterial disease of the legs (assessed by non-invasive tests) is about 13.9–16.9% in men and 11.4–20.5% in women over 55 years of age.[1,2] The overall annual incidence of intermittent claudication is 4.1–12.9/1000 in men and 3.3–8.2/1000 in women.[3]
AETIOLOGY/ RISK FACTORS	Factors associated with the development of peripheral arterial disease include age, gender, cigarette smoking, diabetes mellitus, hypertension, hyperlipidaemia, obesity, and physical inactivity. The strongest associations are with smoking (RR 2.0–4.0) and diabetes (RR 2.0–3.0).[4] Acute limb ischaemia G may result from thrombosis arising within a peripheral artery or from embolic occlusion.
PROGNOSIS	The symptoms of intermittent claudication G can resolve spontaneously, remain stable over many years, or progress rapidly to critical limb ischaemia. About 15% of people with intermittent claudication eventually develop critical limb ischaemia, which endangers the viability of the limb. The annual incidence of critical limb ischaemia in Denmark and Italy in 1990 was 0.25–0.45/1000 people.[5,6] Coronary heart disease is the major cause of death in people with peripheral arterial disease of the legs. Over 5 years, about 20% of people with intermittent claudication have a non-fatal cardiovascular event (myocardial infarction or stroke).[7] The mortality rate of people with peripheral arterial disease is two to three times higher than that of age and sex matched controls. Overall mortality after the diagnosis of peripheral arterial disease is about 30% after 5 years and 70% after 15 years.[7]
AIMS OF INTERVENTION	To reduce symptoms (intermittent claudication), local complications (arterial leg ulcers, critical limb ischaemia), and general complications (myocardial infarction and stroke).

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OUTCOMES **Primary outcome:** Initial claudication distance. **Secondary outcomes:** Absolute claudication distance, generic/disease specific quality of life, clinical end points (intervention rates, postintervention morbidity/mortality), physiological measures (ankle brachial pressure index), and all cause cardiovascular morbidity/mortality.

METHODS *Clinical Evidence* search and appraisal December 2005.

QUESTION What are the effects of treatments for people with chronic peripheral arterial disease?

OPTION ANTIPLATELET AGENTS

Systematic reviews found that antiplatelet agents (aspirin, clopidogrel, aspirin plus dipyridamole, or ticlopidine) reduced major cardiovascular events over an average of about 2 years compared with control treatment. Systematic reviews also found that antiplatelet agents (aspirin and ticlopidine) reduced the risk of arterial occlusion and revascularisation procedures compared with placebo or no treatment. The balance of benefits and harms is in favour of treatment for most people with symptomatic peripheral arterial disease, because as a group they are at much greater risk of cardiovascular events. One systematic review in people undergoing peripheral endovascular intervention found no significant difference between low dose aspirin plus dipyridamole and placebo in restenosis or reocclusion at 6 months.

Benefits:

Antiplatelet agents versus control to prevent cardiovascular events: We found two systematic reviews.[8,9] The first systematic review (search date 1999) found that antiplatelet treatment significantly reduced vascular events (non-fatal myocardial infarction, non-fatal stroke, or vascular death) compared with placebo (24 RCTs, 6036 people with intermittent claudication; vascular events: 202/3100 [6.5%] with antiplatelet treatment *v* 238/2936 [8.1%] with placebo; OR 0.78, 95% CI 0.63 to 0.96).[8] The review also found that antiplatelet treatments (ticlopidine, clopidogrel, or aspirin plus dipyridamole) significantly reduced vascular events compared with aspirin (5 RCTs, 6928 people with peripheral arterial disease; vascular events: 292/3467 [8.4%] with aspirin *v* 227/3461 [6.6%] with other antiplatelet treatments; OR 0.76, 95% CI 0.64 to 0.91). The second systematic review (search date 2004) found that antiplatelet treatment (aspirin, ticlopidine, dipyridamole, aspirin plus dipyridamole) significantly reduced serious vascular events compared with control treatment (42 RCTs, 9214 people with peripheral arterial disease; 280/4844 [5.8%] with antiplatelet agent *v* 347/4862 [7.1%] with control; $P < 0.004$).[9] **Antiplatelet agents versus control to prevent peripheral arterial disease complications:** We found three systematic reviews.[10–12] The first systematic review (search date 1990, 14 RCTs; 3226 people with either intermittent claudication, bypass surgery of the leg, or peripheral artery angioplasty) found that antiplatelet treatment significantly reduced the risk of arterial occlusion over 19 months compared with no additional treatment (arterial occlusion: 3226 people; RRR 36.9%; $P < 0.00001$).[10] The second systematic review (search date 1998) found that aspirin significantly reduced arterial occlusion or revascularisation procedures compared with placebo at 3 months (1 RCT, 2810 people; arterial occlusion or revascularisation procedures: OR 0.46, 95% CI 0.27 to 0.77).[11] It also found that ticlopidine significantly reduced arterial occlusion or revascularisation procedures compared with placebo at up to 7 years (2 RCTs, 1302 people; OR 0.62, 95% CI 0.41 to 0.93). The third systematic review (search date 2004) found that the administration of low dose aspirin plus dipyridamole in people undergoing peripheral endovascular intervention did not significantly reduce the risk of restenosis or reocclusion at 6 months compared with placebo (2 RCTs, 356 people, OR 0.69, 95% CI 0.44 to 1.10).[12]

Harms:

Antiplatelet agents versus control to prevent cardiovascular events: The first systematic review found no significant difference between antiplatelet treatment and placebo in major bleeding (36 RCTs, 8449 people with claudication undergoing surgery or percutaneous transluminal angioplasty; major bleeds: 47/4349 [1%] with antiplatelet treatment *v* 33/4100 [< 1%] with placebo; OR 1.40, 95% CI 0.90 to 2.20).[8] The review also found no significant difference between aspirin and other antiplatelet agents

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Peripheral arterial disease

(ticlopidine, clopidogrel, or dipyridamole plus aspirin) in major bleeding (5 RCTs, 7028 people with peripheral arterial disease; major bleeds: 68/3467 [2.0%] with aspirin *v* 50/3561 [1.4%] with other antiplatelet agents; OR 0.73, 95% CI 0.51 to 1.06). The number of events was likely to have been too low to detect a clinically important increase in major bleeding. Across a wide range of people, antiplatelet agents have been found to increase significantly the risk of major haemorrhage. The second systematic review found that adverse events associated with ticlopidine included rash (25%), neutropenia (1–2%), and thrombotic thrombocytopenic purpura (0.025–0.05%; significance not reported for any outcome).[9] Results for the control group were not reported. **Antiplatelet agents versus control to prevent peripheral arterial disease complications:** The first systematic review reported pooled harms for all included RCTs using antiplatelet regimens (also including coronary and other conditions) rather than for people with peripheral arterial disease alone. It found that the risk of non-fatal "major" bleed and reoperation, haematoma, or infection due to bleed was significantly increased with antiplatelet agents compared with control (non-fatal "major" bleed: 70/3214 [2.18%] with antiplatelet therapy *v* 29/3201 [0.91%] with control, P = 0.002; reoperation, haematoma, or infection due to bleed: 109/1997 [5.46%] with antiplatelet therapy *v* 72/2002 [3.6%] with control, P = 0.02).[10] It found no significant difference between groups in fatal bleeding although the result was of borderline significance (5/3267 [0.15%] with antiplatelet therapy *v* 1/3262 [0.03%] with control; P = 0.06).[10] One other systematic review also pooled results for all included RCTs (also including coronary and other conditions) rather than for people with peripheral arterial disease alone. It found that antiplatelet therapy significantly increased the risk of a major extracranial bleed compared with control therapy (535/47 158 [1.13%] with antiplatelet therapy *v* 333/47 168 [0.71%] with control; OR 1.6, 95% CI 1.4 to 1.8).[13] The second systematic review did not report on harms.[11] The third systematic review reported that one included RCT found no significant difference between antiplatelet and placebo in bleeding at the puncture site after endovascular treatment (OR 1.52, 95% CI 0.47 to 4.96).[12]

Comment: We found no evidence about the effects of combined clopidogrel and aspirin compared with a single antiplatelet agent in people with peripheral arterial disease. Peripheral arterial disease increases the risk of cardiovascular events, so for most people the risk of bleeding is outweighed by the benefits of regular antiplatelet use.

OPTION EXERCISE

Systematic reviews and subsequent RCTs in people with chronic stable claudication found that regular exercise at least three times weekly for between 3 and 6 months improved total walking distance and maximal exercise time after 3–12 months compared with no exercise. One RCT found that vitamin E plus regular exercise increased walking duration compared with placebo at 6 months. One RCT found that a "stop smoking and keep walking" intervention increased the maximal walking distance compared with usual care at 12 months.

Benefits: **Walking exercise versus no exercise:** We found two systematic reviews,[14,15] which compared exercise versus control treatments (placebo tablets or instructions "to continue with normal lifestyle"), and four subsequent RCTs.[16–19] The first review (search date 1996) found that exercise programmes (at least 30 minutes of walking as far as claudication permits, at least 3 times weekly, for 3–6 months in people also being treated with surgery, aspirin, or dipyridamole) significantly increased both the initial claudication distance G and the absolute claudication distance G compared with no exercise after 3–12 months (mean increase in initial claudication distance between exercise and no exercise; 4 RCTs, 94 people with chronic stable intermittent claudication G [see comment below]: 139 m, 95% CI 31 m to 247 m; mean increase in absolute claudication distance between exercise and no exercise; 5 RCTs, 115 people: 179 m, 95% CI 60 m to 298 m).[14] The second review (search date not reported) found that exercise increased maximal exercise time compared with no exercise after 12 weeks to 15 months' follow up (3 RCTs, 53 people; WMD 6.5 minutes, 95% CI 4.4 minutes to 8.7 minutes).[15] The first subsequent RCT compared a 24 week programme of initially supervised, regular polestriding (walking at 1.8 miles an hour with a 12% gradient using modified ski poles) versus a no exercise programme.[16] All participants received standard medical treatment. At 24 weeks, it found that regular

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exercise significantly increased exercise tolerance compared with no exercise on a controlled work treadmill test (52 people; mean increase in exercise duration: about 28 minutes with exercise programme *v* 11 minutes without exercise programme; $P < 0.0001$). The second subsequent RCT compared treadmill exercise three times weekly versus no exercise.[17] People in the exercise group were encouraged to exercise for up to 30 minutes with mild to moderate claudication pain. The RCT found that exercise significantly increased time to onset of claudication compared with no exercise after 12 weeks (64 people, excluding people with rest pain or exertional angina; 3.3 minutes at baseline to 6.2 minutes with exercise *v* 2.9 minutes at baseline to 3.2 minutes with no exercise; $P = 0.01$). The third RCT compared four treatments: polestriding exercise (45–60 minutes, 3 times weekly for 24 weeks) plus vitamin E; polestriding exercise plus placebo; vitamin E alone; and placebo alone.[18] It found that exercise improved walking duration on a constant work rate treadmill test compared with placebo alone at 6 months (52 people with intermittent claudication; walking duration: 804 seconds at baseline to 2020 seconds at 6 months with exercise *v* 612 seconds to 623 seconds with placebo; P value not reported). The fourth RCT found that a 24 week polestriding training programme (3 times weekly) significantly increased exercise time compared with no exercise (49 people with intermittent claudication; symptom limited treadmill test, baseline to 24 weeks: 10.3 minutes to 15.1 minutes with exercise *v* 11.2 minutes to 10.3 minutes with no exercise; $P < 0.001$).[19] **Exercise as part of a multicomponent intervention versus usual care or placebo:** We found two RCTs.[18,20] The first RCT compared four treatments: polestriding exercise (45–60 minutes 3 times weekly for 24 weeks) plus vitamin E; polestriding exercise plus placebo; vitamin E alone; and placebo alone.[18] It found that exercise plus vitamin E improved walking duration on a constant work rate treadmill test compared with placebo alone at 6 months (52 people with intermittent claudication; walking duration: 486 seconds at baseline to 1886 seconds at 6 months with exercise plus vitamin E *v* 612 seconds to 623 seconds with placebo; P value not reported). The second RCT compared a "stop smoking and keep walking" intervention package versus usual care (see comment below).[20] All participants completed the Edinburgh Claudication Questionnaire at randomisation and at follow up (2 months and 12 months). The questionnaires were used to compare self-reported maximum walking distance at baseline and at follow up. It found that the intervention significantly increased self-reported maximal walking distance compared with usual care at 12 months (882 men with early peripheral vascular disease identified by population screening; 23% with intervention *v* 15% with control; $P = 0.008$). It found no significant difference between intervention and usual care in intermittent claudication grade (Edinburgh Claudication Questionnaire: $P = 0.26$). **Different types of exercise:** We found one RCT, which compared arm exercise versus leg exercise of similar intensity.[21] A third group of 15 people was non-randomly allocated to no exercise. The RCT found no significant difference between arm and leg exercises in improvement in initial claudication distance or absolute claudication distance, although both groups improved after 6 weeks (67 people with moderate to severe intermittent claudication; improvement in initial claudication distance: 122% with arm exercise *v* 93% with leg exercise; P value not reported; improvement in absolute claudication distance: 147% with arm exercise *v* 150% with leg exercise; P value not reported).

Harms: The reviews and subsequent RCTs did not report on the harms of the exercise programmes.[14,16–21]

Comment: The RCTs in the systematic reviews had low withdrawal rates, but it is unclear whether those assessing the outcomes were blind to the group allocation. Concealment of the allocation to participants was not possible.[14,15] Most (5/6) exercise programmes in the second review occurred under supervision.[15] In the second RCT examining exercise as a part of a multicomponent intervention, participants in the intervention group received an educational package, a brochure about community physiotherapy services, and information on the benefits of smoking cessation.[20] The general practitioners of these participants received a letter plus educational material (including information about the effects of smoking cessation, about nicotine replacement products, and about peripheral arterial disease) and a recommendation to refer the person to community physiotherapy. The community physiotherapist received details about likely referrals. Physiotherapists provided a community based mobility programme for senior citizens,

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Peripheral arterial disease

consisting of supervised or home based exercise sessions and advice to walk for at least 30 minutes per day. We found one further systematic review (search date 1993, 21 observational studies or RCTs of exercise, 564 people with peripheral arterial disease).[22] It calculated effects based on the differences in claudication distance before and after exercise treatment, but it made no allowance for any spontaneous improvement that might have occurred in the participants. It reported large increases with exercise in the initial claudication distance (126–351 m) and in the absolute claudication distance (325–723 m), but these estimates were based on observational data. The benefit from arm exercise remains unconfirmed, but suggests that improved walking may be caused by generally improved cardiovascular function rather than local changes in the peripheral circulation.

OPTION HMG-COA REDUCTASE INHIBITORS (STATINS)

Three RCTs including people with peripheral arterial disease found that statins (simvastatin, atorvastatin, and pravastatin) reduced cardiovascular events (including non-fatal myocardial infarction, coronary death, total coronary events, and fatal and non-fatal stroke) compared with placebo. However, people with peripheral arterial disease formed only a small proportion (5–13%) of all people included in these RCTs. One RCT found that simvastatin increased time to onset of claudication compared with placebo at 12 months. One RCT found that simvastatin increased pain free walking distance and total walking distance compared with placebo at 6 months. One RCT found that atorvastatin increased pain free walking time compared with placebo at 12 months.

Benefits: We found no systematic reviews. **Vascular events:** We found three RCTs, which compared statins versus placebo.[23–25] The first RCT found that simvastatin 40 mg daily significantly reduced all cause mortality, coronary death, non-fatal or fatal stroke, and coronary or non-coronary revascularisation compared with placebo at 5 years (20 536 people, 2701 with peripheral arterial disease; all cause mortality: 1328/10 269 [12.9%] with simvastatin *v* 1507/10 267 [14.7%] with placebo, P = 0.0003; coronary death: 587/10 269 [5.7%] with simvastatin *v* 707/10 267 [6.9%] with placebo, P = 0.0005; non-fatal or fatal stroke: 444/10 269 [4.3%] with simvastatin *v* 585/10 267 [5.7%] with placebo, P < 0.0001; coronary or non-coronary revascularisation: 939/10 269 [9.1%] with simvastatin *v* 1205/10 267 [11.7%] with placebo, P < 0.0001; see comment below).[23] The second RCT found that atorvastatin 10 mg daily significantly reduced total cardiovascular events (non-fatal myocardial infarction and fatal coronary heart disease), total coronary events, and fatal and non-fatal stroke compared with placebo at follow up (10 305 hypertensive patients, 514 with peripheral arterial disease, median follow up 3.3 years; total cardiovascular events: 389/5168 [7.5%] with atorvastatin *v* 486/5137 [9.5%] with placebo; HR 0.79, 95% CI 0.69 to 0.90; total coronary events: 178/5168 [3.4%] with atorvastatin *v* 247/5137 [4.8%] with placebo; HR 0.71, 95% CI 0.59 to 0.86; fatal and non-fatal stroke: 89/5168 [1.7%] with atorvastatin *v* 121/5137 [2.4%] with placebo; HR 0.73, 95% CI 0.56 to 0.96; see comment below).[24] There was no significant difference between atorvastatin and placebo in all cause mortality or cardiovascular mortality at follow up (all cause mortality: 185/5168 [3.6%] with atorvastatin *v* 212/5137 [4.1%] with placebo; HR 0.87, 95% CI 0.71 to 1.06; cardiovascular mortality: 74/5168 [1.4%] with atorvastatin *v* 82/5137 [1.6%] with placebo; HR 0.90, 95% CI 0.66 to 1.23). The third RCT found that pravastatin 40 mg daily significantly reduced the combined end point of coronary death, non-fatal myocardial infarction, and fatal or non-fatal stroke compared with placebo at follow up (5804 people, aged 70–82 years, 513 people with intermittent claudication G or previous peripheral arterial surgery, mean follow up time 3.2 years; combined end point: 408/2891 [14.1%] with pravastatin *v* 473/2913 [16.2%] with placebo; HR 0.85, 95% CI 0.74 to 0.97; see comment below).[25] **Claudication:** We found three RCTs, which compared statins versus placebo.[26–28] The first RCT found that simvastatin 40 mg daily significantly increased time to onset of claudication compared with placebo at 12 months (69 people with intermittent claudication, aged 60–85 years; increase in exercise time: 225 seconds at baseline to 320 seconds with simvastatin *v* 231 seconds at baseline to 221 seconds with placebo; P < 0.0001).[26] The second RCT found that simvastatin 40 mg daily increased pain free walking distance and total walking distance compared with placebo at 6 months (86 people with peripheral arterial

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disease and intermittent claudication; pain free walking distance: 72 m at baseline to 190 m with simvastatin *v* 74 m at baseline to 100 m with placebo; P < 0.0005; total walking distance: 96 m at baseline to 230 m with simvastatin *v* 93 m at baseline to 104 m with placebo; P < 0.005).[27] It also found that simvastatin significantly improved ankle brachial index (ABI) both at rest and after exercise compared with placebo at 6 months (ABI at rest: 0.53 at baseline to 0.65 with simvastatin *v* 0.55 at baseline to 0.56 with placebo; P < 0.01; ABI after exercise: 0.35 at baseline to 0.55 with simvastatin *v* 0.39 at baseline to 0.36 with placebo; P < 0.01). The third RCT found that atorvastatin 80 mg daily improved pain free walking time compared with placebo at 12 months (354 people with peripheral arterial disease and intermittent claudication; mean improvement in pain free walking time from baseline: 81 seconds with atorvastatin *v* 39 seconds with placebo; P = 0.025).[28] However, it found no significant difference between atorvastatin and placebo in maximal walking time after 12 months of treatment (increase in maximal walking time from baseline: 90 seconds with atorvastatin *v* 50 seconds with placebo; P = 0.37). There was no significant difference between treatments in quality of life (measured using the Walking Impairment questionnaire and SF-36; reported as not significant; no further data reported).

Harms:

Vascular events studies: The first RCT found no significant difference between simvastatin and placebo in muscular pain and weakness (32.9% with simvastatin *v* 33.2% with placebo; P value not reported).[23] There was no significant difference between treatments in the proportion of people who discontinued treatment because of adverse effects (4.8% with simvastatin *v* 5.1% with placebo). There was also no significant difference in the rate of new primary cancers between treatment groups (814/10 269 [7.9%] with simvastatin *v* 803/10 267 [7.8%]; RR 1.0, 95% CI 0.91 to 1.11).[23] The second RCT found no difference in serious adverse events between the placebo and statin groups (adverse events not described; significance not reported).[24] The RCT reported one incidence of fatal rhabdomyolysis in the statin group. The third RCT found that the frequency of serious adverse events (including myalgia) was similar with pravastatin and placebo (myalgia: 36/2891 [1.2%] with pravastatin *v* 32/2913 [1.1%] with placebo; significance not reported).[25] However, the study did report a significant increase in the number of new cancers in the pravastatin group (HR 1.25, 95% CI 1.04 to 1.51). **Claudication studies:** The first and second RCTs did not report on harms.[26,27] The third RCT reported four deaths with 10 mg atorvastatin, one with 80 mg atorvastatin, and one with placebo (significance not reported).[28] The study also reported four myocardial infarctions and one stroke with 10 mg atorvastatin, two myocardial infarctions and one stroke with 80 mg atorvastatin, and three myocardial infarctions with placebo (significance not reported). The number of discontinuations from the study was similar between the three groups (33 [27.5%] with 10 mg atorvastatin *v* 25 [20.8%] with 80 mg atorvastatin *v* 28 [24.6%] with placebo; significance not reported).

Comment:

In the three RCTs investigating the effect of statins on prevention of vascular events, people with peripheral arterial disease formed only a small proportion of the total number of people randomised (3728/36 645 [10%]).[23–25] However, similar benefits were observed in this subgroup, suggesting that the results of the three RCTs may be generalisable to people with peripheral arterial disease. In subgroup analysis, the first RCT found that simvastatin significantly reduced first major vascular events (major coronary event, stroke, revascularisation) compared with placebo (2701 people with peripheral vascular disease and no prior coronary heart disease; 327/1325 (24.7%) with simvastatin *v* 420/1376 (30.5%) with placebo, P < 0.0001).[23] The second and third RCTs did not separately analyse or report on the subgroup with peripheral arterial disease alone.[24,25] The second RCT noted that for the prespecified subgroups that it did analyse, the proportional effect of atorvastatin on the primary end point (non-fatal myocardial infarction and fatal coronary heart disease) did not differ significantly from that noted overall in the RCT, although the benefit was not significant in a number of these subgroups.[24] Follow up was complete in more than 90% of people recruited in all three RCTs.

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Peripheral arterial disease

OPTION PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY

Two small RCTs identified by a systematic review, in people with mild to moderate intermittent claudication, found limited evidence that percutaneous angioplasty improved walking distance after 6 months compared with no angioplasty but found no significant difference after 2 or 6 years. Two small RCTs identified by a systematic review and four additional RCTs in people with stenosis between the femoral and popliteal arteries or between the aorta and iliac arteries found no significant difference between angioplasty alone and angioplasty plus stent placement in patency rates, occlusion rates, or clinical improvement. The RCTs may have lacked power to detect a clinically important effect. One RCT found no significant difference between percutaneous transluminal angioplasty plus lovastatin and percutaneous transluminal angioplasty alone in restenosis rates at 12 months. One systematic review found, in people with chronic progressive peripheral arterial disease, that percutaneous transluminal angioplasty was less effective in improving patency compared with surgery after 12–24 months but found no significant difference after 4 years. The review found no difference in mortality after 12–24 months.

Benefits:

Percutaneous transluminal angioplasty (PTA) versus no percutaneous intervention: We found one systematic review (search date not reported), which identified two RCTs.[29] The first RCT identified by the review found that PTA significantly increased the median claudication distance after 6 months compared with no PTA, but found no significant difference in median claudication distance or quality of life after 2 years (1 RCT, 98 people with mild to moderate intermittent claudication⊖; median claudication distance at 6 months: 667 m *v* 172 m; $P < 0.05$; median claudication distance at 2 years: $P = 0.695$; quality of life [assessed using the Nottingham Health Profile]: $P > 0.05$).[30] The second RCT found that PTA significantly increased the absolute claudication distance⊖ at 6 months compared with an exercise programme (1 RCT, 56 people; 130 m *v* 50 m; WMD 80 m; $P < 0.05$), but found no significant difference in absolute claudication distance after 6 years (180 m *v* 130 m; WMD 50 m; $P > 0.05$).[31,32] **PTA versus PTA plus stents:** We found one systematic review (search date 2002, 2 RCTs)[33] and two additional RCTs comparing PTA versus PTA plus stent.[34,35] The RCTs in the systematic review used different techniques and different definitions of restenosis, and data were not pooled.[33] The first RCT identified by the review found no significant difference in patency (assessed by colour flow duplex ultrasound) or in occlusion rate between PTA and PTA plus stent (1 RCT, 51 people with aorto–iliac or femoro–popliteal lesions on angiography who had received an intravenous bolus of heparin and oral aspirin; patency: 74% with PTA alone *v* 62% with PTA plus stent; $P = 0.22$; occlusion rate: 2/27 [7%] with PTA alone *v* 5/24 [21%] with PTA plus stent; $P = 0.16$).[36] The second RCT found no significant difference between PTA and PTA plus stent in patency after 34 months' follow up (53 people who had received an intravenous bolus of heparin and oral aspirin; patency: 68.4% with PTA *v* 62% with PTA plus stent).[37] People in the PTA plus stent group also received a preoperative intravenous heparin bolus of 500 units plus 1 g aspirin. The first additional RCT found no significant difference between PTA and PTA plus stent in "clinical improvement" after 1 year (32 people; 71% with PTA *v* 60% with PTA plus stent; $P = 0.17$).[34] The second additional RCT found no significant difference between PTA and PTA plus stent in patency, as determined by angiography after 1 year (141 people, 154 limbs; 63% with PTA *v* 63% of limbs with PTA plus stent).[35] **PTA plus routine stent versus PTA plus selective stent:** We found two RCTs comparing PTA plus routine stenting versus PTA plus selective stenting.[38,39] The first RCT found no significant difference between treatments in reintervention rates (279 people with intermittent claudication and iliac artery stenosis; reintervention rate: 7% with PTA plus routine stent *v* 4% with PTA plus selective stent; ARR 3%, 95% CI −3% to + 8%).[38] The second RCT found no significant difference between treatments in death or in restenosis after 1 year (227 people with severe claudication or limb threatening stenosis of the superficial femoral artery; death: 8% with PTA plus selective stent *v* 4% with PTA plus routine stent; $P = 0.4$; > 50% restenosis: 32.3% with PTA plus selective stent *v* 34.7% with PTA plus routine stent; $P = 0.85$).[39] **PTA versus PTA plus statins:** One RCT found no significant difference between PTA plus

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lovastatin 20 mg daily and PTA alone in restenosis rates at 12 months (37 people taking aspirin 250 mg/day with critical ischaemia or severe claudication, Fontaine classification G class IIb or III; restenosis: 8/19 [42%] with PTA alone *v* 4/18 [22%] with PTA plus lovastatin; reported as not significant; P value not reported).[40] **PTA versus bypass surgery:** See benefits of bypass surgery, p 11.

Harms: **PTA versus PTA plus stents:** The systematic review did not report on harms.[33] **PTA plus routine stent versus PTA plus selective stent:** One of the RCTs found that routine stenting significantly increased the risk of local vascular events compared with selective stenting after 1 year (P = 0.017).[39] Prospective cohort studies have found that complications of PTA include puncture site major bleeding (3.4%), pseudoaneurysms (0.5%), limb loss (0.2%), renal failure secondary to intravenous contrast (0.2%), cardiac complications such as myocardial infarction (0.2%), and death (0.2%).[41,42] **PTA versus PTA plus statins:** The RCT found that limb loss was higher with PTA alone, but this difference was not significant.[40]

Comment: This limited evidence suggests transient benefit from angioplasty compared with no angioplasty. The longer term effects of angioplasty or stent placement on symptoms, bypass surgery, and amputation remain unclear, and the available RCTs are likely to have been too small to detect clinically important effects of stent placement. The long term patency of femoro–popliteal angioplasties is poor, and there is no evidence that the addition of stents confers any additional benefit.[34,35,37] The small number of RCTs and their small sample sizes and methodological weaknesses suggest that further RCTs are needed to establish clinical effects reliably. The RCT investigating the effect of statins on restenosis rates after angioplasty was very small (37 people) and is likely to have been underpowered to detect a small but clinically significant difference between the two groups.[40]

OPTION SMOKING CESSATION

RCTs of advice to stop smoking would be considered unethical. The consensus view is that smoking cessation improves symptoms in people with intermittent claudication. One systematic review of observational studies found inconclusive results of stopping smoking, both in terms of increasing absolute claudication distance and reducing the risk of symptom progression, compared with people who continue to smoke.

Benefits: **Advice to stop smoking versus no advice:** RCTs of advice to stop smoking are considered unethical. The consensus view is that smoking cessation improves symptoms in people with intermittent claudication G. We found one systematic review (search date 1996, 4 observational studies, 866 people) of advice to stop cigarette smoking versus no advice.[14] One observational study included in the systematic review found no significant increase in absolute claudication distance G after cessation of smoking (46.7 m, 95% CI –19.3 m to 112.7 m). The second and third studies identified by the review found conflicting results about the risk of deteriorating from moderate to severe claudication in people who successfully stopped smoking compared with current smokers. The second study found that significantly more smokers deteriorated from Fontaine stage II to III G compared with people who had stopped smoking (26/304 [8.6%] smokers *v* 0/39 [0%] non-smokers; ARR 8.6%, 95% CI 5.4% to 11.7%). However, the third study found that there was no difference between smokers and people who had stopped smoking in deterioration in ankle brachial index G at 1 year (data not reported). There was also no significant difference in the number of failed revascularisation procedures between smokers and non-smokers (P = 0.07).[14] The fourth study provided no numerical results. Overall, the review found no good evidence to confirm or refute the consensus view that advice to stop smoking improves symptoms in people with intermittent claudication.

Harms: We found no RCTs.

Comment: None.

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Peripheral arterial disease

OPTION CILOSTAZOL

One non-systematic meta-analysis and one additional RCT found that cilostazol improved claudication distance at 12–24 weeks compared with placebo. However, adverse effects of cilostazol were common in the RCTs, and included headache, diarrhoea, and palpitations. One RCT found limited evidence that cilostazol increased initial and absolute claudication distance compared with pentoxifylline.

Benefits: **Cilostazol versus placebo:** We found no systematic review. We found one non-systematic meta-analysis[43] and one additional RCT (see comment below).[44] The meta-analysis (search date not reported) found that cilostazol 100 mg twice daily significantly increased mean maximal treadmill walking distance and pain free treadmill walking distance compared with placebo (5 published RCTs plus data from 1 RCT held on file by a pharmaceutical company; 1751 people with claudication for 6 months or more, treated for between 12 and 24 weeks; 90% were current or previous smokers, 27% had diabetes mellitus, and 60% had hypertension; maximal distance: 250 m at baseline to 350 m with cilostazol *v* 252 m at baseline to 302 m with placebo, P < 0.001; pain free distance: 127 m at baseline to 210 m with cilostazol *v* 132 m at baseline to 185 m with placebo, P < 0.001).[43] One of the RCTs included in the meta-analysis also evaluated a lower dose of cilostazol (100 mg/day).[45] It found no significant difference between this dose of cilostazol and placebo in mean maximum walking distance (167 m with cilostazol 100 mg/day *v* 141 m with placebo; P = 0.18). The additional RCT found that cilostazol 100 mg twice daily significantly increased initial claudication distance G and absolute claudication distance G at 12 weeks compared with placebo (81 people with stable intermittent claudication G for 6 months or more; intention to treat analysis; initial claudication distance: 112.5 m with cilostazol *v* 84.6 m with placebo; P = 0.007; absolute claudication distance: 231.7 m with cilostazol *v* 152.1 m with placebo; P = 0.002).[44] **Cilostazol versus pentoxifylline:** See benefits of pentoxifylline, p 11.[46]

Harms: Harms were not reported in the meta-analysis.[43] Two RCTs included in the meta-analysis found that cilostazol significantly increased the risk of withdrawal from the trial because of adverse effects or concerns about safety compared with placebo (1 RCT: 39/227 [17%] with cilostazol 200 mg *v* 24/239 [10%] with placebo; RR 1.71, 95% CI 1.06 to 2.75; NNH 14, 95% CI 8 to 111; 1 RCT: 22.6% with cilostazol 200 mg *v* 12.1% with cilostazol 100 mg *v* 10.1% with placebo, CI not reported).[45,46] The second of these RCTs found that cilostazol 200 mg increased withdrawal due to headache and cardiovascular events compared with placebo (headache: 4.5% with cilostazol 200 mg *v* 0% with placebo; cardiovascular events: 12/133 with cilostazol *v* 5/129 with placebo; CI not reported). The additional RCT found that cilostazol 100 mg increased gastrointestinal complaints compared with placebo (44% with cilostazol *v* 15% with placebo; CI not reported).[44] Cilostazol is a phosphodiesterase inhibitor; RCTs have found that other phosphodiesterase inhibitors (milrinone, vesnarinone) are associated with increased mortality in people with heart failure. However, results aggregated from other studies have not found an excess of cardiovascular events with cilostazol.[47]

Comment: The meta-analysis comparing cilostazol versus placebo was not based on studies identified systematically, and hence the selection of studies may be biased.[43] However, the meta-analysis included all of the studies identified by our own systematic search except for one.[44] Analysis was on an intention to treat basis. Although the overall results of cilostazol compared with placebo indicate a significant effect of cilostazol on increasing walking distance, the RCTs have some weaknesses in their methods that may limit the applicability of the results.[44,46,48,49] First, none of the RCTs evaluated cilostazol beyond 24 weeks. In addition, some of the RCTs had high withdrawal rates after randomisation (up to 29%).[48] In most of the RCTs withdrawals were more common with cilostazol than with placebo.[44–46,48,49] To allow for these problems, the authors performed intention to treat analyses using "last available observation carried forward". However, the analyses did not include people with no observations to carry forward, and the effect of the difference in withdrawals between the groups was not explored adequately. If people with worsening claudication were more likely to withdraw, then the

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observed differences might have been artefactual. We found one further trial, written in Chinese, which compared cilostazol versus dipyridamole in 32 people with peripheral vascular disease and type 2 diabetes.[50] This study is awaiting translation and appraisal for inclusion in *Clinical Evidence*. Although cilostazol appears promising, the balance of its benefits and harms remains unclear.

OPTION BYPASS SURGERY

One systematic review found that surgery in people with chronic progressive peripheral arterial disease improved primary patency after 12–24 months compared with percutaneous transluminal angioplasty, but it found no significant difference after 4 years. The review found no significant difference in mortality after 12–24 months. Although the consensus view is that bypass surgery is the most effective treatment for people with debilitating symptomatic peripheral arterial disease, we found inadequate evidence from RCTs reporting long term clinical outcomes to confirm this view.

Benefits:

Bypass surgery versus percutaneous transluminal angioplasty (PTA): We found one systematic review, which found no significant difference between surgery and PTA in mortality after 12–24 months (search date 2001, 2 RCTs, 365 people with chronic progressive peripheral arterial disease; OR 1.08, 95% CI 0.61 to 1.89).[51] The review found that surgery significantly improved patency after 12–24 months compared with PTA (OR 0.62, 95% CI 0.39 to 0.99), but it found no significant difference in primary patency after 4 years (primary patency: P = 0.14). **Bypass surgery versus PTA plus stent placement:** We found no RCTs comparing surgery versus PTA plus stent placement that reported long term outcomes.

Harms:

Surgery increased early postprocedural complications compared with PTA. Among people undergoing aorto–iliac surgery, perioperative mortality (within 30 days of the procedure) was 3.3%, and complications having a major health impact occurred in 8.3%.[52] Among people undergoing infrainguinal bypass surgery, perioperative mortality was about 2% and serious complications occurred in 8%.[53] Among people undergoing PTA with or without stent placement, perioperative mortality was about 1% and serious complications occurred in about 5%.[54]

Comment:

The RCTs are small, have different follow up periods, and assessed different outcomes. Too few people with infrainguinal lesions were included in the RCTs to provide good evidence about surgical management. Indirect comparisons of proxy outcomes in people with infrainguinal lesions suggest worse results after PTA (after 5 years; patency: 38%, range 34–42%) compared with surgery (patency: 80%).[55] Although the consensus view is that bypass surgery is the most effective treatment for people with debilitating symptomatic peripheral arterial disease, we found inadequate evidence from RCTs reporting long term clinical outcomes to confirm this view.

OPTION PENTOXIFYLLINE

One systematic review and one subsequent RCT found insufficient evidence to compare pentoxifylline versus placebo. One RCT found limited evidence that pentoxifylline was less effective at improving initial and absolute claudication distance compared with cilostazol after 24 weeks.

Benefits:

Pentoxifylline versus placebo: We found one systematic review[56] and one subsequent RCT.[46] The review (search date 1999) identified two RCTs but it did not meta-analyse the results. Neither RCT in the review found any significant difference between pentoxifylline and placebo for change in initial claudication distance G or absolute claudication distance G (2 RCTs, 192 people; follow up time not reported; improvement in mean initial claudication distance for pentoxifylline *v* placebo: 15 m, 95% CI –5 m to + 35 m *v* –30 m, 95% CI –138 to + 78 m; improvement in mean absolute claudication distance: + 21 m, 95% CI –10 m to + 52 m *v* + 69 m, 95% CI –44 to + 182 m).[56] The subsequent RCT compared three treatments: pentoxifylline, cilostazol, and placebo.[46] It found no significant difference between pentoxifylline and placebo in the proportion of people who had no change or deterioration in the

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Peripheral arterial disease

claudication distance (438 people; see comment below; 72/212 [34%] with pentoxifylline *v* 68/226 [30%] with placebo; RR 1.13, 95% CI 0.86 to 1.48). **Pentoxifylline versus cilostazol:** We found one RCT which compared three treatments: pentoxifylline, cilostazol, and placebo.[46] The RCT (see comment below) found that pentoxifylline significantly increased the proportion of people who had no change or deterioration in claudication distance compared with cilostazol (438 people; 72/212 [34%] with pentoxifylline *v* 47/205 [23%] with cilostazol; RR 1.48, 95% CI 1.08 to 2.03; ARR 11%, 95% CI 2.4% to 20.0%; NNT 9, 95% CI 5 to 42). It found that pentoxifylline was less effective at increasing the initial claudication distance and the absolute claudication distance compared with cilostazol after 24 weeks (202 m with pentoxifylline *v* 218 m with cilostazol; mean difference –16 m; P = 0.0001; absolute claudication distance: 308 m with pentoxifylline *v* 350 m with cilostazol; mean difference –42 m; P = 0.0005).

Harms: One RCT found that pentoxifylline significantly increased the risk of withdrawal from the RCT because of adverse effects or concerns about safety compared with placebo (44/232 [19%] with pentoxifylline *v* 24/239 [10%] with placebo; RR 1.89, 95% CI 1.19 to 3.00; NNH 12, 95% CI 7 to 39).[46] Side effects of pentoxifylline included sore throat (14% with pentoxifylline *v* 7% with placebo) and dyspepsia, nausea, and diarrhoea (8% with pentoxifylline *v* 5% with placebo; P = 0.31). No life threatening adverse effects of pentoxifylline have been reported, although to date RCTs have been too small to assess this reliably.

Comment: The subsequent RCT had a high withdrawal rate after randomisation, which could be a source of bias (60/232 [26%] with pentoxifylline *v* 61/237 [26%] with cilostazol).[46]

GLOSSARY

Ankle brachial index The ankle brachial index (ABI) is calculated by dividing the blood pressure recorded at the ankle by the blood pressure recorded in the arm. The ABI value is calculated both at rest and after exercise to determine the severity of peripheral arterial disease. A normal ABI value at rest is 1.0. A decrease in the ABI after exercise or a resting ABI below 0.9 indicates that peripheral arterial disease is present.
Absolute claudication distance Also known as the total walking distance; the maximum distance a person can walk before stopping.
Acute limb ischaemia An ischaemic process that threatens the viability of the limb, and is associated with pain, neurological deficit, inadequate skin capillary circulation, and/or inaudible arterial flow signals by Doppler examination. This acute process often leads to hospitalisation.
Critical limb ischaemia Results in a breakdown of the skin (ulceration or gangrene) or pain in the foot at rest. Critical limb ischaemia corresponds to the Fontaine classification III and IV (see below).
Fontaine classification I: asymptomatic; II: intermittent claudication (see below); II-a: pain free, claudication walking more than 200 m; II-b: pain free, claudication walking less than 200 metres; III: rest/nocturnal pain; IV: necrosis/gangrene.
Initial claudication distance The distance a person can walk before the onset of claudication symptoms.
Intermittent claudication Pain, stiffness, or weakness in the leg that develops on walking, intensifies with continued walking until further walking is impossible, and is relieved by rest.

Substantive changes

Antiplatelet agents Two systematic reviews added;[10,12] benefits and harms data enhanced, categorisation unchanged (beneficial).
Exercise One RCT added;[19] benefits and harms data enhanced, categorisation unchanged (beneficial).

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Search date November 2003

Michael Pignone

QUESTIONS

INTERVENTIONS

Key Messages

Drug treatment in low risk people (<0.6% annual CHD risk)

- **Fibrates** We found no RCTs examining the effects of fibrates in people at low risk of coronary heart disease events.
- **Niacin** We found no RCTs examining the effects of niacin for lowering cholesterol in people at low risk of coronary heart disease events.
- **Resins** We found no RCTs examining the effects of resins in people at low risk of coronary heart disease events.
- **Statins** We found no RCTs examining the effects of statins in people at low risk of coronary heart disease events.

Drug treatment in medium risk people (0.6%–1.4% annual CHD risk)

- **Fibrates** One large RCT in men found that gemfibrozil reduced coronary heart disease events, but not overall mortality, over 5 years compared with placebo.
- **Resins** One RCT in men found that that cholestyramine reduced non-fatal myocardial infarction and coronary heart disease death compared with placebo at 7 years, although the difference did not reach conventional significance.

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Primary prevention: dyslipidaemia

- **Statins** One RCT found that lovastatin reduced cardiovascular events in men at medium risk of coronary heart disease events after 5 years. The RCT found no significant difference between statins and placebo for all cause mortality, but it may have been underpowered to detect a clinically important difference in this outcome. Another RCT found no significant difference between pravastatin and usual care for all cause mortality or a combined outcome of nonfatal myocardial infarction or coronary heart disease death after a mean follow up of 4.8 years among men and women at medium risk. However, about 30% of people in the usual care group started lipid lowering drugs during the study, thus diluting the treatment effect.
- **Niacin** We found no RCTs examining niacin for lowering cholesterol in people at medium risk of coronary heart disease events.

Drug treatment in high risk people (≥ 1.5% annual CHD risk)

- **Statins** Two RCTs and one meta-regression analysis provided evidence that, in people at high risk for future CHD events, statins reduced coronary heart disease events and all cause mortality. The magnitude of the benefit with statin treatment is related to an individual's baseline risk of coronary heart disease events and to the degree of cholesterol lowering, rather than to the initial cholesterol concentration. One systematic review and meta-regression analysis of all of the major primary and secondary prevention statin RCTs found that mortality benefits of statins outweigh risks in people with a 10 year coronary heart disease risk of more than 13%.
- **Fibrates** We found no RCTs examining effects of fibrates in people at high risk of coronary heart disease events.
- **Niacin** We found no RCTs examining effects of niacin in people at high risk of coronary heart disease events.
- **Resins** We found no RCTs examining effects of resins in people at high risk of coronary heart disease events.

Dietary modification

- **Reduced or modified fat diet** One systematic review of people in all risk groups found limited evidence that reduced or modified fat diet reduced primary cardiovascular events compared with usual diet, but it found no significant difference in mortality.

DEFINITION

Dyslipidaemia, defined as elevated total or low density lipoprotein (LDL) cholesterol levels or low levels of high density lipoprotein (HDL) cholesterol, is an important risk factor for coronary heart disease (CHD) and stroke (cerebrovascular disease). This chapter examines the evidence for treatment of dyslipidaemia for primary prevention of cardiovascular disease. Primary prevention in this context is defined as long term management of people at increased risk but with no clinically overt evidence of cardiovascular disease, such as acute myocardial infarction, angina, stroke, and peripheral vascular disease, and who have not undergone revascularisation. Most adults at increased risk of cardiovascular disease have no symptoms or obvious signs, but they may be identified by assessment of their risk factors (see aetiology/risk factors below). We have divided people with no known cardiovascular disease into three groups: low risk (< 0.6% annual CHD risk), medium risk (0.6–1.4% annual CHD risk) and high risk (≥1.5% annual CHD risk). Prevention of cerebrovascular events is discussed in detail elsewhere in *Clinical Evidence* (see stroke prevention chapter, p 173).

INCIDENCE/ PREVALENCE

Dyslipidaemia, defined as elevated total or LDL cholesterol, or low HDL cholesterol, is common. Data from the US NHANES survey conducted in 1999–2000 found that 25% of adults had total cholesterol greater than 6.2 mmol/L or were taking a lipid lowering medication. [1] According to the World Health Report 1999, ischaemic heart disease was the leading single cause of death in the world, the leading single cause of death in high income countries, and second only to lower respiratory tract infections in low and middle income countries. In 1998 it was still the leading cause of death, with nearly 7.4 million estimated deaths a year in member states of the World Health Organization and the eighth highest burden of disease in the low and middle income countries (30.7 million disability adjusted life years).[2]

AETIOLOGY/ RISK FACTORS

Major risk factors for ischaemic vascular disease include increasing age, male sex, raised LDL cholesterol, reduced HDL cholesterol, raised blood pressure, smoking, diabetes, family history of cardiovascular disease, obesity, and sedentary lifestyle. For many of these risk factors, observational studies show a continuous gradient of increasing risk of cardiovascular disease with increasing levels of the risk factor, with no obvious threshold level. Although by definition event rates are higher in high risk people, most ischaemic vascular events that occur in the population are in people with intermediate levels of absolute risk because there are many more of them than there are people at high risk; see Appendix 1.[3]

PROGNOSIS

One Scottish study found that about half of people who suffer an acute myocardial infarction die

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Primary prevention: dyslipidaemia

within 28 days, and two thirds of acute myocardial infarctions occur before the person reaches hospital.[4] People with known cardiovascular disease are at high risk for future ischaemic heart disease events (see topic on secondary prevention of ischaemic cardiac events, p 01) as are people with diabetes (see topic on prevention of cardiovascular disease in diabetes, p 501). For people without known cardiovascular disease, the absolute risk of ischaemic vascular events is generally lower but varies widely. Estimates of absolute risk can be based on simple risk equations or tables; see Appendix 1.[5,6] Such information may be helpful in making treatment decisions.

AIMS OF INTERVENTION To reduce morbidity and mortality from coronary heart disease, with minimum adverse effects.

OUTCOMES Incidence of fatal and non-fatal ischaemic heart disease events (angina, myocardial infarction, sudden death).

METHODS *Clinical Evidence* search and appraisal November 2003. Study population annual baseline CHD risk was defined as low (<0.6%), medium (0.6%–1.4%), or high (≥1.5%) according to the rate of CHD events observed in their placebo control group.

QUESTION **What are the effects of pharmacological cholesterol lowering interventions in people at low risk (< 0.6% annual coronary heart disease [CHD] risk)?** New

OPTION FIBRATES New

We found no RCTs examining the effects of fibrates in people at low risk of coronary heart disease events.

Benefits: We found no RCTs examining the effects of fibrates in people at low risk of coronary heart disease events.

Harms: We found no RCTs.

Comment: The effect of lipid lowering therapies in people at low risk of coronary heart disease events has not been well studied to date.

OPTION NIACIN New

We found no RCTs examining the effects of niacin for lowering cholesterol in people at low risk of coronary heart disease events.

Benefits: We found no RCTs examining the effects of niacin in people at low risk of coronary heart disease events.

Harms: We found no RCTs.

Comment: The effect of lipid lowering therapies in people at low risk of coronary heart disease events has not been well studied to date.

OPTION RESINS New

We found no RCTs examining the effects of resins in people at low risk of coronary heart disease events.

Benefits: We found no RCTs examining the effects of resins in people at low risk of coronary heart disease events.

Harms: We found no RCTs.

Comment: The effect of lipid lowering therapies in people at low risk of coronary heart disease events has not been well studied to date.

OPTION STATINS New

We found no RCTs examining the effects of statins in people at low risk of coronary heart disease events.

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Primary prevention: dyslipidaemia

Benefits: We found no RCTs examining the effects of statins in people at low risk of coronary heart disease events.

Harms: See harms of statins in people at medium risk of coronary heart disease events, p 4.

Comment: The effect of lipid lowering therapies in people with low short to medium term risk of coronary heart disease events (< 0.6%/year) has not been well studied to date.

QUESTION **What are the effects of pharmacological cholesterol lowering interventions in people at medium risk (0.6–1.4% annual coronary heart disease [CHD] risk)?** New

OPTION **FIBRATES** New

One large RCT in men found that gemfibrozil reduced coronary heart disease events, but not overall mortality, over 5 years compared with placebo.

Benefits: **Fibrates versus placebo:** We found no systematic reviews but we found one RCT (4081 middle aged Finnish men with non-high density lipoprotein cholesterol > 200 mg/dL).[7] It found that gemfibrozil 600 mg twice daily significantly reduced coronary heart disease events, but not all cause mortality, over 5 years compared with placebo (coronary heart disease events: 56/2051 [2.7%] with gemfibrozil *v* 84/2030 [4.1%] with placebo; P < 0.02; RR 0.66, 95% CI 0.47 to 0.92; all cause mortality: 45/2051 [2.2%] with gemfibrozil *v* 42/2030 [2.1%] with placebo; difference reported as not significant; P value or CI not reported).

Harms: The RCT found no significant difference between gemfibrozil and placebo for overall cancer rates (15.1 per 1000 for gemfibrozil *v* 12.8 per 1000 for placebo; P value not reported).[7] It found that gemfibrozil significantly increased severe upper gastrointestinal symptoms in the first year compared with placebo (11.3% *v* 7.0%; P < 0.001). It found no significant difference between treatments for constipation, diarrhoea, nausea, or vomiting.

Comment: None.

OPTION **RESINS** New

One RCT in men found that that cholestyramine reduced non-fatal myocardial infarction and coronary heart disease death compared with placebo at 7 years, although the difference did not reach conventional significance.

Benefits: **Resins versus placebo:** We found no systematic reviews but we found one RCT (3806 men aged 35–59 with low density lipoprotein cholesterol > 190 mg/dL).[8] It found that cholestyramine 24 g daily reduced the combined outcome of non-fatal myocardial infarction and coronary heart disease death compared with placebo at 7.4 years, although the difference did not reach conventional significance (8.1% with cholestyramine *v* 9.8% with placebo; RR 0.81, 90% CI 0.68 to 0.97; P>0.05).

Harms: The RCT did not report on harms.[8]

Comment: None.

OPTION **STATINS** New

One RCT found that lovastatin reduced cardiovascular events in men at medium risk of coronary heart disease events after 5 years. The RCT found no significant difference between statins and placebo for all cause mortality, but it may have been underpowered to detect a clinically important difference in this outcome. Another RCT found no significant difference between pravastatin and usual care for all cause mortality or a combined

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outcome of nonfatal myocardial infarction or coronary heart disease death after a mean follow up of 4.8 years among men and women at medium risk. However, about 30% of people in the usual care group started lipid lowering drugs during the study, thus diluting the treatment effect.

Benefits: **Statins versus placebo or usual care:** We found two RCTs that compared the effects of long term (≥ 6 months) 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) versus placebo.[9,10] The first RCT (5608 men and 997 women with average total and low density lipoprotein cholesterol levels but low high density lipoprotein cholesterol; AFCAPS/TexCAPS study) compared lovastatin 20–40 mg daily versus placebo for 5.2 years.[9] It found that lovastatin significantly reduced first major coronary events and cardiovascular events compared with placebo (first coronary event: RR 0.63, 95% CI 0.50 to 0.79; cardiovascular events: RR 0.75, 95% CI 0.62 to 0.91). It found no significant difference between treatments for all cause mortality but the RCT was not powered to detect a difference in this outcome (80/3304 [2.4%] with lovastatin *v* 77/3301 [2.3%] with placebo; difference reported as not significant; P value and CI not reported) (see figure 1, p 9). The second RCT (10 355 people with hypertension plus one other risk factor and low density lipoprotein cholesterol from 120–189 mg/dL; about 50% male) compared pravastatin 40 mg daily versus usual care.[10] Most people (86%) had no previous history of vascular disease. It found no significant difference between pravastatin and usual care for all cause mortality or a combined outcome of nonfatal myocardial infarction or coronary heart disease death after a mean follow up of 4.8 years (% are 6 year incidence rates; all cause mortality: 631/5170 [14.9%] with pravastatin *v* 641/5185 [15.3%] with usual care; RR 0.99, 95% CI 0.89 to 1.11; combined outcome: 380/5170 [9.3%] with pravastatin *v* 421/5185 [10.4%] with usual care; RR 0.91, 95% CI 0.79 to 1.04). See comment below.

Harms: We found one systematic review (search date 1998, 5 RCTs, 31 817 people, including 2 primary prevention studies: AFCAPS/TexCAPS[9] in medium risk people and WOSCOPS[11] in high risk people) that looked at the effects of long term statin treatment in both primary and secondary prevention settings.[12] The review found no significant difference between statins and placebo in terms of non-cardiovascular mortality, cancer incidence, asymptomatic elevation of creatine kinase (> 10 times upper reference limit), or elevation of transaminases (> 3 times upper reference limit) during a mean of 5.4 years of treatment (OR of event, statin *v* placebo for non-cardiovascular mortality 0.93, 95% CI 0.81 to 1.07; for cancer 0.99, 95% CI 0.90 to 1.08; for creatine kinase increase 1.25, 95% CI 0.83 to 1.89; for transaminase increase 1.13, 95% CI 0.95 to 1.33.

Comment: In the second RCT, low density lipoprotein cholesterol was reduced by only 16.7% after 4 years with pravastatin compared with usual care, in part because 30% of the control group began lipid lowering drugs during the trial.[10] This may have contributed to the finding of no significant difference between treatments.

OPTION NIACIN New

We found no RCTs examining niacin for lowering cholesterol in people at medium risk of coronary heart disease events.

Benefits: We found no RCTs examining niacin for lowering cholesterol in people at medium risk of coronary heart disease events.

Harms: We found no RCTs.

Comment: None.

QUESTION What are the effects of pharmacological cholesterol lowering interventions in people at high risk (annual coronary heart disease [CHD] risk ≥ 1.5%)? New

OPTION STATINS New

Two RCTs and one meta-regression analysis provided evidence that, in people at high risk for future CHD events, statins reduced coronary heart disease events and all cause mortality. The magnitude of the benefit with statin treatment is related to an individual's baseline risk

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Primary prevention: dyslipidaemia

of coronary heart disease events and to the degree of cholesterol lowering, rather than to the initial cholesterol concentration. One systematic review and meta-regression analysis of all of the major primary and secondary prevention statin RCTs found that mortality benefits of statins outweigh risks in people with a 10 year coronary heart disease risk of more than 13%.

Benefits: **Statins versus placebo:** We found no systematic reviews but we found two RCTs.[11,13] The first RCT (6595 men, age 45–64 years, mean plasma cholesterol 272 mg/dL, equivalent to 7.0 mmol/L; WOSCOPS study) found that pravastatin 40 mg daily significantly reduced the combined outcome of non-fatal myocardial infarction or coronary heart disease (CHD) death at 5 years compared with placebo (RR 0.69, 95% CI 0.57 to 0.83) (see figure 1, p 9).[11] It found that pravastatin reduced all cause mortality compared with placebo but the reduction only achieved borderline significance (RR 0.78, 95% CI 0.60 to 1.00). The second RCT (3239 men and women, age 70–82 years, no history of vascular disease) found no significant difference between pravastatin 40 mg daily and placebo for the combined outcome of CHD death or non-fatal myocardial infarction or stroke (181/1585 [11.4%] with pravastatin *v* 200/1654 [12.1%] with placebo; HR 0.94, 95% CI 0.77 to 1.15).[13]

Harms: The second RCT found no difference in serious adverse events between pravastatin and placebo (> 1 event reported by 56% people with pravastatin *v* 55% with placebo).[13] See harms of statins in people at medium risk of coronary heart disease events, p 4.

Comment: We found evidence that the magnitude of the benefit with statin treatment is related to an individual's baseline risk of CHD events and to the degree of cholesterol lowering, rather than to the initial cholesterol concentration. One systematic review carried out regression analysis of all of the major statin trials (including both primary and secondary prevention settings and a variety of CHD risk levels) and found that mortality benefits of statins outweigh risks in people with a 10 year CHD risk of more than 13% (see figure 1, p 9).[17]

OPTION FIBRATES New

We found no RCTs examining effects of fibrates in people at high risk of coronary heart disease events.

Benefits: We found no RCTs examining effects of fibrates in people at high risk of coronary heart disease events.

Harms: We found no RCTs.

Comment: None.

OPTION NIACIN New

We found no RCTs examining effects of niacin in people at high risk of coronary heart disease events.

Benefits: We found no RCTs examining effects of niacin in people at high risk of coronary heart disease events.

Harms: We found no RCTs.

Comment: None.

OPTION RESINS New

We found no RCTs examining effects of resins in people at high risk of coronary heart disease events.

Benefits: We found no RCTs examining effects of resins in people at high risk of coronary heart disease events.

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Harms: We found no RCTs.

Comment: None.

QUESTION What are the effects of reduced or modified fat diet? New

OPTION REDUCED OR MODIFIED FAT DIET New

One systematic review of people in all risk groups found limited evidence that reduced or modified fat diet reduced primary cardiovascular events compared with usual diet, but it found no significant difference in mortality.

Benefits: **Reduced or modified diet versus no dietary modification:** We found one systematic review (search date 1999, 27 RCTs), which examined the effect of reduced or modified fat diet (diet advice, advice plus a supplement, or diet provided) on cardiovascular events.[18] The RCTs included in the review were conducted in people at high and low risk of cardiovascular events. In the review, initial levels of risk were generally high (in control groups, people at low risk had 2.57 events per 100 people per year and people at high risk had 7.62 events per 100 people per year). Overall, the review found no significant difference between diet and control for all cause mortality (RR 0.98, 95% CI 0.86, 1.12). It found that the diet significantly reduced cardiovascular events for all people (RR 0.84, 95% CI 0.72 to 0.99; see comment below). Relative risks for combined cardiovascular events were similar for people at high or low risk of cardiovascular events (RR for high risk people 0.84, 95% CI 0.70 to 0.99; RR for low risk people 0.82, 95% CI 0.56 to 1.20).

Harms: The review did not address harms.[18]

Comment: The review found that, after excluding one RCT that used fish oil in addition to dietary advice, there was no significant difference between treatments for total mortality, cardiovascular mortality, or cardiovascular events (RR for total mortality 1.02, 95% CI 0.91 to 1.14; RR for cardiovascular mortality 0.94, 95% CI 0.79 to 1.11; RR for combined cardiovascular events 0.86, 95% CI 0.72 to 1.03).[18] The effect of diet on combined cardiovascular events was greater for RCTs with mean follow up greater than 2 years (> 2 years RR 0.76, 95% CI 0.65 to 0.90; < 2 years 0.96, RR 0.75 to 1.23). The only low risk trials were in institutionalised people using controlled diets. Other types of diets, such as the Mediterranean diet, have not been well studied for people without known cardiovascular disease.

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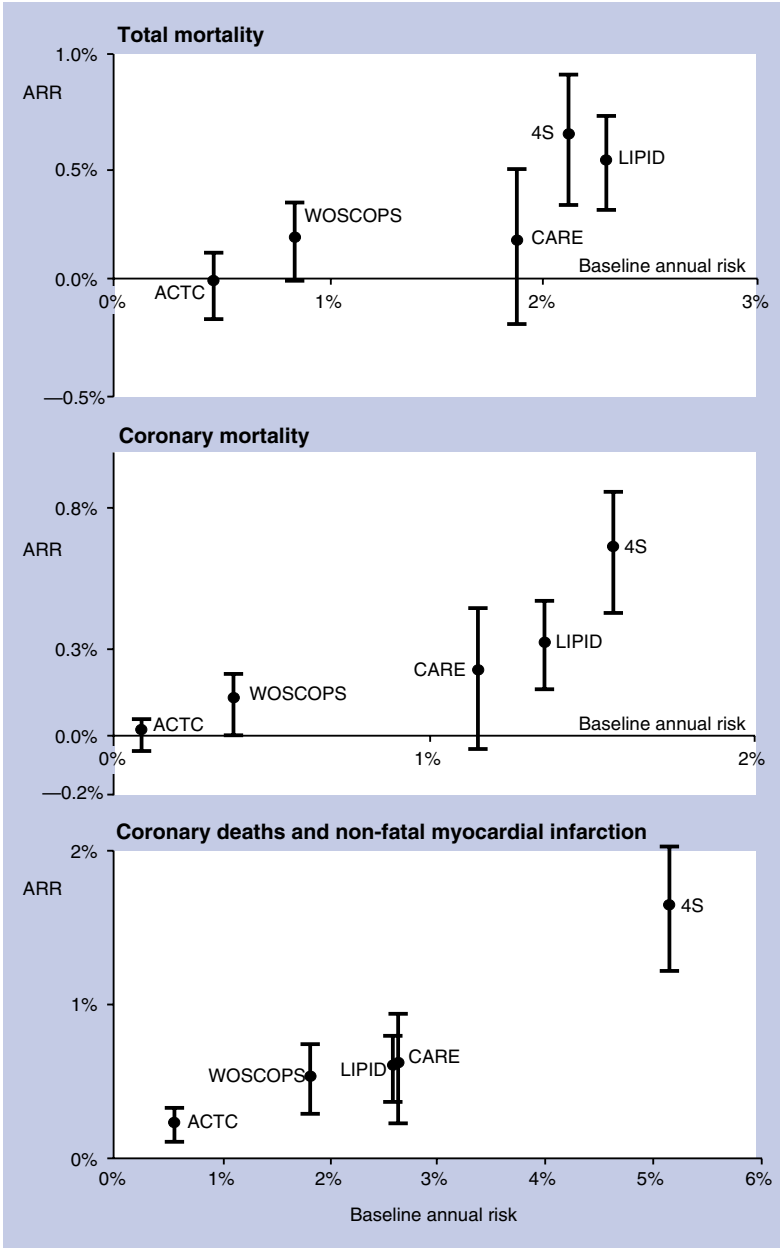

FIGURE 1 **Effects of cholesterol lowering: relation between the ARR (for annual total mortality, coronary heart disease mortality, coronary deaths, and non-fatal myocardial infarction) and the baseline risk of those events in the placebo group for five large statin trials in primary and secondary care settings (ACTC = AFCAPS/TexCAPS,[9] 4S,[14] LIPID,[15] CARE,[16] WOSCOPS[11]) (see text, p 5).**

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Primary prevention: hypertension

Search date December 2003

Stacey L Sheridan and Michael Pignone

QUESTIONS

INTERVENTIONS

Key Messages

Treating hypertension

- **Antihypertensive drugs versus placebo** Systematic reviews found that antihypertensive drug treatment decreased the risk of fatal and non-fatal stroke, cardiac events, and total mortality in people with essential hypertension compared with placebo.

Antihypertensive drugs *v* each other

- **Antihypertensive drugs versus each other** Systematic reviews and large subsequent RCTs found no significant difference in the ability of different antihypertensive agents to reduce total mortality, cardiovascular mortality, and myocardial infarction. Compared with other antihypertensive drugs, however, ACE inhibitors and alpha–blockers were less effective in reducing rates of stroke and combined cardiovascular events; ACE inhibitors, calcium channel blockers and alpha–blockers were less effective in reducing heart failure; and calcium channel blockers were more effective in reducing stroke.

Dietary supplements to prevent hypertension

- **Fish oil supplementation** We found no systematic review or RCTs examining the effects of fish oil on morbidity or mortality in people with hypertension. One systematic review found that fish oil supplementation in large doses of 3 g daily modestly lowered blood pressure compared with placebo in people with hypertension.
- **Low salt diet** One systematic review found that too few RCTs assessed the effects of salt restriction on cardiovascular morbidity and mortality to draw conclusions. Systematic reviews found that dietary intervention to reduce salt intake modestly reduced blood pressure compared with usual diet in people with hypertension.

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Primary prevention: hypertension

- **Potassium supplementation** We found no systematic review or RCTs examining the effects of potassium supplementation on morbidity or mortality in people with hypertension. One systematic review and one subsequent RCT found that daily potassium supplementation of about 60 mmol (approximately the amount contained in 5 bananas) reduced blood pressure by small amounts compared with placebo or no supplements.
- **Calcium supplementation** We found no systematic review or RCTs examining the effects of calcium supplementation on morbidity or mortality in people with hypertension. One systematic review in people both with and without hypertension found that calcium supplementation may reduce systolic blood pressure by small amounts compared with placebo or no supplements.
- **Magnesium supplementation** We found no systematic review or RCTs examining the effects of magnesium supplementation on morbidity or mortality in people with hypertension. One systematic review found no significant difference in blood pressure between magnesium supplementation and placebo in people with hypertension.

DEFINITION	Hypertension, a clinically important elevation in blood pressure, is usually defined in adults as a diastolic blood pressure of 90 mm Hg or higher or a systolic blood pressure of 140 mm Hg or higher.[1,2] The World Health Organization defines grade 1 hypertension as office blood pressures ranging from 140–159 mm Hg systolic or 90–99 mm Hg diastolic, grade 2 hypertension as pressures of 160–179 mm Hg systolic or 100–109 mm Hg diastolic, and grade 3 hypertension as pressures equal to or greater than 180 mm Hg systolic and 110 mm Hg diastolic.[1] It is usually recommended that clinicians diagnose hypertension only after obtaining two or more elevated blood pressure readings at each of two or more separate visits over a period of one or more weeks.[2] This recommendation follows the pattern of blood pressure measurement in the RCTs of antihypertensive therapy and represents a compromise between reliable detection of elevated blood pressure and clinical practicality. This review focuses on the effects and treatment of essential hypertension, namely the elevation of systolic and diastolic blood pressures (in isolation or combination) with no secondary underlying cause.
INCIDENCE/ PREVALENCE	Coronary heart disease is a major cause of morbidity and mortality throughout the world.[3] It is a leading cause of disability and rising health care costs, and it is responsible for 13% of deaths worldwide. Most of this burden of heart disease can be linked to several "traditional" risk factors, including age, sex, increasing blood pressure, increasing cholesterol, smoking, diabetes, and left ventricular hypertrophy.[4] Of these, hypertension is most common, affecting 20% of the world adult population.[5] The relative risk of adverse events associated with hypertension is continuous and graded.[6] The absolute risk of adverse outcomes from hypertension depends on the presence of other cardiovascular risk factors, including smoking, diabetes, and abnormal blood lipid levels, as well as the degree of blood pressure elevation.[7] Even modest elevations in blood pressure in young adulthood are associated with increased risk of cardiovascular events in middle age.[8]
AETIOLOGY/ RISK FACTORS	Identified risk factors for hypertension include age, sex, race/ethnicity, genetic predisposition, diet, physical inactivity, obesity, and psychological and social characteristics.[9]
PROGNOSIS	People with hypertension have a two to four times increased risk of stroke, myocardial infarction, heart failure, and peripheral vascular disease than those without hypertension.[6] Additionally, they have an increased risk of end stage renal disease, retinopathy, and aortic aneurysm.[10–12] The absolute risk of adverse outcomes from hypertension depends on other cardiovascular risk factors and the degree of blood pressure elevation (see incidence/prevalence section).[7]
AIMS OF INTERVENTION	To reduce morbidity and mortality from hypertension, with minimum adverse effects.
OUTCOMES	Incidence of fatal and non-fatal cardiovascular events (including coronary, cerebrovascular, renal, and heart failure). Surrogate outcomes include changes in levels of individual risk factors, such as blood pressure, when morbidity and mortality related outcomes are not available.
METHODS	*Clinical Evidence* search and appraisal December 2003.

QUESTION **What are the effects of treating hypertension with single drug therapy?** New

OPTION **ANTIHYPERTENSIVE DRUGS VERSUS PLACEBO** New

Systematic reviews found that antihypertensive drug treatment decreased the risk of fatal and non-fatal stroke, cardiac events, and total mortality in people with essential hypertension compared with placebo.

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Benefits:

Mortality and morbidity: We found three systematic reviews, of which one performed separate analyses of the effects of antihypertensive drugs in people with varying severities of hypertension,[13] one assessed antihypertensive drugs in people with all severities of hypertension,[14] and a third assessed the effects of treatments for isolated systolic hypertension (see comment below).[15] The first review (search date 1997, 15 RCTs, 18 397 people with hypertension) found that, in people with diastolic blood pressure greater than 110 mm Hg, the centrally acting antihypertensive drugs reserpine and methyldopa significantly reduced congestive heart failure by 86% compared with placebo (3 RCTs, 171 people; OR 0.14, 95% CI 0.05 to 0.41).[13] Other events were too infrequent over the 1–2 year durations of included trials to determine the effects of treatment on stroke, major coronary events, cardiovascular disease, mortality, or total mortality. The review also found that, for people younger than 60 years with diastolic blood pressure of 90–109 mm Hg, reserpine or methyldopa significantly reduced stroke over 1.4–7 years compared with placebo (5 RCTs, 11528 adults younger than 60 years; OR 0.51, 95% CI 0.39 to 0.69) but had no effect on coronary heart disease events, cardiovascular disease deaths, or total mortality. In people older than 60 years, methyldopa or beta–blockers significantly reduced total mortality (7 RCTs, 6698 people; OR 0.90, 95% CI 0.81 to 1.00), cardiovascular disease mortality (OR 0.77, 95% CI 0.67 to 0.89), stroke (OR 0.66, 95% CI 0.56 to 0.77), coronary heart disease events (OR 0.79, 95% CI 0.68 to 0.92), and congestive heart failure (OR 0.54, 95% CI 0.43 to 0.68) compared with placebo. The second review (search date not reported, 16 RCTs, 8 included in the first review, 45 019 people with hypertension) found that antihypertensive drugs, including angiotensin converting enzyme (ACE) inhibitors, diuretics, beta–blockers, and calcium channel blockers, significantly reduced stroke and ischaemic heart disease events compared with placebo (stroke: RR 0.62, 95% CI 0.54 to 0.70; ischaemic heart disease events: RR 0.85, 95% CI 0.78 to 0.93).[14] The third review (search date 1999, 8 RCTs, 6 RCTs included in the previous reviews, 15 693 people aged over 60 years with isolated systolic hypertension) compared antihypertensive drugs, including ACE inhibitors, diuretics, beta–blockers, and calcium channel blockers versus placebo in people older than 60 years with isolated systolic hypertension.[15] It found that, compared with placebo, antihypertensive drugs significantly reduced stroke (RR 0.70, 95% CI 0.59 to 0.82), coronary heart disease events (RR 0.70, 95% CI 0.66 to 0.90), cardiovascular disease mortality (RR 0.82, 95% CI 0.71 to 0.96), and total mortality (RR 0.87, 95% CI 0.78 to 0.98). The number needed to treat over 5 years to prevent one cardiovascular event was 18 (95% CI 17 to 19) in men and 38 (95% CI 36 to 40) in women. **Quality of life:** We found one systematic review (search date 1990, 9 RCTs, 1620 people with hypertension) comparing the effects of antihypertensive drugs (beta–blockers, vasodilators, calcium channel blockers, diuretics, ACE inhibitors, centrally acting antihypertensive drugs, and centrally acting alpha–agonists) versus placebo or no treatment.[16] Results were analysed for five quality of life constructs: sexual function, sleep, psychomotor, general well being, and mood. The review found no negative effects of treatment on any construct.

Harms:

The first systematic review gave no information on adverse effects.[13] The second systematic review (354 RCTs in people with hypertension with and without cardiovascular disorders) of calcium channel blockers, ACE inhibitors, angiotensin receptor blockers, diuretics, and beta–blockers alone or in combination (including 40 000 treated individuals and 16 000 controls) found that adverse effects varied significantly among different antihypertensives compared with placebo.[14] It found that standard doses of beta–blockers, calcium channel blockers, and diuretics significantly increased adverse effects compared with placebo (proportion with adverse effects with beta–blockers: 7.5%, 95% CI 4% to 11%; with calcium channel blockers: 8.3%, 95% CI 4.8% to 11.8%; with diuretics: 9.9%, 95% CI 6.6% to 13.2%). The adverse effects included flushing, ankle oedema and dizziness for calcium channel blockers, dizziness, impotence, nausea and muscle cramps for diuretics, and cold extremities, fatigue and nausea for beta–blockers. However, the review found no significant increase in adverse effects between standard doses of angiotensin II receptor antagonists or ACE inhibitors

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and placebo (proportion with adverse effects; angiotensin II receptor antagonists: 0.0%, 95% CI –5.4% to +5.4%; ACE inhibitors: 3.9%, 95% CI –0.5% to +8.3%). Withdrawal from treatment due to adverse effects occurred in ≥1% of people taking any antihypertensive.[14] Two further systematic reviews gave no information on adverse effects.[15,16] For standard doses, see web table A.

Comment: RCTs included people who were healthier than the general population, with lower rates of cardiovascular risk factors, cardiovascular disease, and comorbidity.[13–16] People with higher cardiovascular risk can expect greater short term absolute risk reduction than is seen in the RCTs, whereas people with major competing risks such as terminal cancer or end stage Alzheimer's disease can expect smaller risk reduction.

QUESTION **What are the effects of different antihypertensive drugs for people with hypertension?** New

OPTION **ANTIHYPERTENSIVE DRUGS VERSUS EACH OTHER** New

Systematic reviews and large subsequent RCTs found no significant difference in the ability of different antihypertensive agents to reduce total mortality, cardiovascular mortality, and myocardial infarction. Compared with other antihypertensive drugs, however, ACE inhibitors and alpha–blockers were less effective in reducing rates of stroke and combined cardiovascular events; ACE inhibitors, calcium channel blockers and alpha–blockers were less effective in reducing heart failure; and calcium channel blockers were more effective in reducing stroke.

Benefits: We found two systematic reviews[35,17] and one subsequent RCT (published in 2 reports).[18,19] The first review (search date 2003, 15 RCTs, 120,574 people with hypertension) compared newer (calcium channel blockers, ACE inhibitors, angiotensin receptor blockers, and alpha blockers) versus older (diuretics and beta-blockers) antihypertensive drugs.[35] It found no significant difference between newer and older antihypertensive drugs in total mortality (OR 0.98, 95% CI, 0.94 to 1.02), cardiovascular mortality (OR 1.00, 95% CI, 0.95 to 1.07), myocardial infarction (OR 1.00, 95% CI, 0.95 to 1.06), all cardiovascular events (OR 1.01, 95% CI 0.95 to 1.09), and stroke (OR 0.98, 95% CI 0.88 to 1.08). However, compared with older drugs, newer agents offered significantly less protection against heart failure (OR 1.23, 95% CI 1.03 to 1.47). The second review (search date 2000, 8 RCTs, 4 RCTs included in the first review, 37,872 people with hypertension) compared newer (calcium channel blockers and ACE inhibitors) versus older (beta–blockers and diuretics) antihypertensive drugs.[17] It found no significant difference between newer and older antihypertensive drugs in coronary heart disease, heart failure, major cardiovascular events, or total mortality ($P > 0.1$ for all outcomes). However, it found that calcium channel blockers significantly reduced stroke compared with diuretics or beta–blockers (RR 0.87, 95% CI 0.77 to 0.98) and showed a trend toward decreasing cardiovascular disease (RR 1.12, 95% CI 1.0 to 1.26). The subsequent RCT (33 357 people with hypertension and at least one other cardiovascular risk factor) compared four interventions: the diuretic chlorthalidone (25 mg/day), the calcium channel blocker amlodipine (2.5–10 mg/day), the ACE inhibitor lisonipril (10–40 mg/day), and the alpha–blocker doxazosin (2, 4, or 8 mg/day).[18,19] The RCT dichotomised outcomes comparing diuretics versus any other antihypertensive drug. It found no significant difference between diuretics and other antihypertensives in fatal coronary heart disease or non-fatal myocardial infarction (diuretics *v* calcium channel blockers: RR 0.98, 95% CI 0.90 to 1.07; diuretics *v* ACE inhibitors: RR 0.99, 95% CI 0.91 to 1.08; diuretics *v* alpha–blockers: RR 1.02, 95% CI 0.92 to 1.15). However, it found that compared with diuretics, ACE inhibitors and alpha–blockers significantly increased stroke and combined cardiovascular events and ACE inhibitors, calcium channel blockers and alpha–blockers significantly increased heart failure (ACE inhibitors *v* older: OR 1.19, 95% CI 1.07 to 1.31; calcium channel blockers *v* older; OR 1.38, 95% CI 1.25 to 1.52; alpha–blockers *v* older: OR 1.8, 95% CI 1.61 to 2.02).
Beta–blockers versus diuretics: We found two systematic reviews.[20,21] The first review (search date 1995, 18 RCTs, > 48 000 people) compared high and low dose diuretics versus beta–blockers.[20] The second systematic review (search date 1998, 10

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RCTs, 8 included in the first review) was limited to trials in the elderly (16 164 people aged over 60 years).[21] In these reviews, diuretics consistently reduced stroke, cardiovascular disease, and total mortality. Beta–blockers showed similar reductions in stroke, and trends toward reductions in cardiovascular disease and mortality, although confidence intervals were wide and results were not significant. **ACE inhibitors versus calcium channel blockers:** We found one systematic review (search date 2000, 2 RCTs, 4871 people with hypertension) comparing ACE inhibitors versus calcium channel blockers. [17] It found no significant difference between ACE inhibitors and calcium channel blockers in all cause mortality or stroke (all cause mortality: RR 1.03, 95% CI 0.91 to 1.18; stroke: RR 1.02, 95% CI 0.85 to 1.21). However, ACE inhibitors significantly decreased coronary events (RR 0.81, 95% CI 0.68 to 0.97) and showed a trend toward decreasing heart failure (RR 0.81, 95% CI 0.67 to 1.0) compared with calcium channel blockers. **Angiotensin receptor blockers versus other newer antihypertensive drugs:** We found no systematic reviews or RCTs comparing angiotensin receptor blockers versus other newer antihypertensive agents.

Harms: Identified reviews suggest that intermediate and long acting calcium channel blockers do not increase the risk of stroke, cardiovascular disease, heart failure or total mortality compared with placebo. [17] However, compared with other agents (e.g. diuretics, beta–blockers, and ACE inhibitors), calcium channel blockers may increase cardiovascular disease, chronic heart failure, and major cardiovascular disease events (see above). Too few studies are available to determine the adverse effects of short acting calcium channel blockers in those without cardiovascular disease, although the use of these agents has been discouraged based on their dose-related adverse effects in people with known cardiovascular disease. [22]

Comment: None.

QUESTION **What are the effects of dietary modification for people with hypertension?** New

OPTION **FISH OIL SUPPLEMENTATION** New

We found no systematic review or RCTs examining the effects of fish oil on morbidity or mortality in people with hypertension. One systematic review found that fish oil supplementation in large doses of 3 g daily modestly lowered blood pressure compared with placebo in people with hypertension.

Benefits: **Mortality or morbidity:** We found no systematic review or RCTs examining the effects of fish oil supplementation on morbidity or mortality in people with hypertension. **Blood pressure:** We found one systematic review (search date 2001, 36 RCTs, 2114 people, 50% with hypertension) comparing the effects of fish oil (median 3.7 g/day [0.2–15 g/day] as capsules, mostly eicosapentaenoic acid and docosahexaenoic acid) versus no supplements or "placebo" on blood pressure.[23] The review performed a separate analysis in people with hypertension (defined as blood pressure ≥140/90 mm Hg). It found that fish oil supplements significantly reduced blood pressure compared with placebo in people with hypertension (mean decrease systolic blood pressure: –3.65 mm Hg, 95% CI –5.73 mm Hg to –1.58 mm Hg; mean decrease in diastolic blood pressure: –2.51 mm Hg, 95% CI –3.70 mm Hg to –1.33 mm Hg). Benefits were independent of the dose of fish oil, although only one trial reported fish oil doses consistent with the doses that are habitual in Western diets (< 250 mg/day).

Harms: The review gave no information on adverse effects.[23] An earlier systematic review (search date not reported; published 1993) of RCTs and controlled clinical trials found that belching, bad breath, fishy taste, and abdominal pain occurred in about a third of people taking high doses of fish oil.[24]

Comment: The RCTs were of short duration (< 12 weeks) and used high doses of fish oil (median 3.7 g/day). Such high intake may be difficult to maintain in westernised populations, in which habitual intake of fish oil is below 250 mg/day (1 fatty fish meal/week).

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OPTION **LOW SALT DIET** New

One systematic review found that too few RCTs assessed the effects of salt restriction on cardiovascular morbidity and mortality to draw conclusions. Systematic reviews found that dietary intervention to reduce salt intake modestly reduced blood pressure compared with usual diet in people with hypertension.

Benefits: **Mortality or morbidity:** We found one systematic review (search date 1998, 8 RCTs, 5 RCTs in 387 people with untreated hypertension, 3 RCTs in 801 people with treated hypertension) comparing the effects of dietary interventions to restrict salt versus usual diet on morbidity or mortality in people with normal and elevated blood pressures over 6 months to 7 years. [25] It found that RCTs had insufficient data on cardiovascular morbidity and mortality to draw conclusions. **Blood pressure:** We found three systematic reviews[25,26,27] and one subsequent RCT. [30] Each review assessed different reductions in salt intake (-48.94 mmol, 78 mmol, 118 mmol), so we report all of them here. All found that salt restriction reduced blood pressure, but two of the reviews[26,27] found mixed results regarding the relationship between the magnitude and duration of sodium reduction and the degree of blood pressure reduction. The subsequent RCT tested the magnitude of salt restriction directly over 3 months of follow up. The first review (search date 1998, 8 RCTs, 1188 people with hypertension) found that intensive dietary and behaviour change interventions that lowered salt intake (by –48.94, 95% CI –65.4 to +32.46 within 24 hours) significantly reduced systolic blood pressure at 6–12 months compared with usual diet (4 RCTs, 179 people: WMD –8.01 mm Hg, 95% CI –15.78 to –0.23). It found no significant difference in diastolic blood pressure (2 RCTs, 87 people: WMD –4.65 mm Hg, 95% CI –9.33 to + 0.04).[25] The meta-analysis of diastolic blood pressure may have been underpowered to detect clinically important differences between groups. There were also too few RCTs that followed up people with hypertension beyond 12 months to draw definitive conclusions on long term outcomes. However, the review found that, in people with or without hypertension, salt restriction significantly reduced systolic blood pressure at 13–60 months compared with no salt restriction (4 RCTs, 2347 people: WMD–1.12 mm Hg, 95% CI –1.83 to –0.41) but found no significant difference in diastolic blood pressure (WMD –0.62 mm Hg, 95% CI –1.54 to +0.31). The second review (search date 2001, 17 RCTs, none included in the first review, 734 people with hypertension) found that a –78 mmol reduction in salt intake (95% CI –117 mmol to –53 mmol) significantly reduced blood pressure over a median 6 weeks (range 4 weeks to 1 year; mean reduction in systolic blood pressure: –4.97 mm Hg, 95% CI –5.75 to –4.17; mean reduction in diastolic blood pressure: –2.73 mm Hg, 95% CI –3.21 to –2.25).[26] The third review (search date 2002, 58 RCTs, 12 included in the second review, 2161 people with hypertension) found that a 118 mmol reduction in salt intake significantly reduced blood pressure over a mean 28 days (range 4 days to 1 year; WMD in systolic blood pressure: –4.18 mm Hg, 95% CI –5.08 to –3.27; WMD in diastolic blood pressure: –1.98 mm Hg, 95% CI –2.46 to –1.32).[29] We found one subsequent RCT (412 people with systolic/diastolic blood pressure > 120/80 mm Hg, mean age 48 years, duration 30 days) that assessed the relationship between sodium and blood pressure levels.[28] People were assigned to receive prepared food with three different target levels of sodium intake (150, 100, and 50 mmol/day [8.6, 5.7, and 2.9 g/day]) in a crossover design.[28] The RCT found that for both people eating a typical American diet, those in the lowest salt intake group (i.e. those with the greatest salt restriction) had significantly reduced systolic (mean difference –6.7 mm Hg, 95% CI –5.4 to –8.0; $P < 0.001$) and diastolic (mean difference –3.5 mm Hg, 95% CI –0.8 to –2.5; $P < 0.001$) blood pressures compared to those with the highest salt intake. Although the greatest effect of salt reduction occurred after 1 week, blood pressures continued to decline throughout the duration of the study, suggesting that effects may be greater with longer term follow up. [29]

Harms: We found no evidence of harms.

Comment: Small RCTs tended to report larger reductions in systolic and diastolic blood pressure than larger RCTs. This may be explained by publication bias or less rigorous methodology in small RCTs.

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OPTION POTASSIUM SUPPLEMENTATION New

We found no systematic review or RCTs examining the effects of potassium supplementation on morbidity or mortality in people with hypertension. One systematic review and one subsequent RCT found that daily potassium supplementation of about 60 mmol (approximately the amount contained in 5 bananas) reduced blood pressure by small amounts compared with placebo or no supplements.

Benefits: **Mortality or morbidity:** We found no systematic review or RCTs examining the effects of potassium supplementation on morbidity or mortality in people with primary hypertension. **Blood pressure:** We found one systematic review[30] and one subsequent RCT.[31] The review (search date 1995, 21 RCTs, 1560 adults with hypertension, age 19–79 years) compared the effects of potassium supplements (60–100 mmol/day [2–3 g/day] potassium chloride) versus placebo or no supplements on blood pressure.[30] It found that, compared with placebo or no supplements, potassium supplements significantly reduced systolic blood pressure (mean decrease in systolic blood pressure with potassium supplements *v* placebo: 3.11 mm Hg, 95% CI 1.91 to 4.31) and diastolic blood pressure (mean decrease in diastolic blood pressure with potassium supplements *v* placebo: 1.97 mm Hg, 95% CI 0.52 to 3.42). The subsequent RCT (150 adults living in China, age 35–64 years, blood pressure 130–159/80–94 mm Hg) found similar significant reductions in systolic blood pressure compared with placebo in people who received potassium chloride (60 mmol/day) for 12 weeks (mean decrease with potassium chloride *v* placebo: –5 mm Hg, 95% CI –2.13 to –7.88). However, it found no significant difference in mean diastolic blood pressure between potassium chloride and placebo (mean decrease with potassium *v* placebo: –0.63 mm Hg, 95% CI –2.49 to +1.23). [31]

Harms: Gastrointestinal adverse effects such as belching, flatulence, diarrhoea, and abdominal discomfort occurred in 2–10% of people in the systematic review.[30] The subsequent RCT gave no information on adverse effects.[31] We found no direct evidence of more substantial harms in people without kidney failure and in people not taking drugs that increase serum potassium concentration.

Comment: None.

OPTION CALCIUM SUPPLEMENTATION New

We found no systematic review or RCTs examining the effects of calcium supplementation on morbidity or mortality in people with hypertension. One systematic review in people both with and without hypertension found that calcium supplementation may reduce systolic blood pressure by small amounts compared with placebo or no supplements.

Benefits: **Mortality or morbidity:** We found no RCTs examining the effects of calcium supplementation on morbidity or mortality in people with primary hypertension. **Blood pressure:** We found one systematic review (search date 1994, 42 RCTs, 4560 middle aged people with and without hypertension) comparing the effects of calcium supplementation 500–2000 mg daily versus placebo or no supplements on blood pressure.[32] The review did not perform separate analysis for people with and without hypertension. It found that calcium supplements reduced blood pressure by a small but significant amount compared with placebo or no supplements (mean systolic blood pressure reduction; supplement *v* control: –1.44 mm Hg, 95% CI–2.20 to –0.68; mean diastolic blood pressure reduction: –0.8 mm Hg, 95% CI –1.44 to –0.24). There were similar results in trials of dietary and non-dietary calcium supplementation.

Harms: The review found that adverse gastrointestinal effects, such as abdominal pain, were generally mild and varied among preparations.[32]

Comment: Data relating specifically to people with hypertension are limited by few studies with small sample sizes and short durations.

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OPTION **MAGNESIUM SUPPLEMENTATION** New

We found no systematic review or RCTs examining the effects of magnesium supplementation on morbidity or mortality in people with hypertension. One systematic review found no significant difference in blood pressure between magnesium supplementation and placebo in people with hypertension.

Benefits: **Mortality or morbidity:** We found no systematic review or RCTs examining the effects of magnesium supplementation on morbidity or mortality. **Blood pressure:** We found one systematic review[33] and one subsequent RCT.[34] The review (search date 2001, 20 RCTs, 1220 people with and without hypertension and with normal magnesium) compared the effects of magnesium supplementation versus placebo on blood pressure.[33] The review performed a separate analysis in people with hypertension (defined as average baseline systolic blood pressure > 140 mm Hg and diastolic blood pressure > 90 mm Hg). It found that every 10 mmol/day increase in magnesium, non significantly reduced systolic blood pressure (3.3 mm Hg, 95% CI -0.1 to + 6.8) and diastolic blood pressure (2.3 mm Hg, 95% CI -1.0 to +5.6). The subsequent RCT (36 mildly hypertensive patients) found no significant effect of 600 mg magnesium on blood pressure in 36 people who received supplementation for 10 weeks compared with placebo controls (P = 0.081).[34]

Harms: The systematic review and subsequent RCT gave no information on adverse effects.[33,34]

Comment: Larger studies with higher dose magnesium supplementation are still needed.

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Secondary prevention of ischaemic cardiac events

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QUESTIONS

INTERVENTIONS

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To be covered in future updates
Alcohol intake
Implantable cardioverter defibrillators

Key Messages

Antithrombotic treatment

- **Aspirin** Two systematic reviews found that aspirin reduced the risk of serious vascular events and reduced all cause mortality compared with placebo. One of the reviews found that doses of 75–325 mg daily were as effective as higher doses (500–1500 mg).
- **Oral anticoagulants in the absence of antiplatelet treatment** One systematic review found that moderate or high intensity oral anticoagulation reduced the risk of cardiovascular events in people with coronary artery disease but substantially increased the risks of haemorrhage compared with placebo or aspirin.
- **Thienopyridines** Two systematic reviews and two RCTs found that thienopyridines were more effective than aspirin for reducing the risk of further cardiovascular events.
- **Combinations of antiplatelets** One RCT found that clopidogrel reduced serious cardiovascular events in people already taking aspirin compared with aspirin alone. One systematic review and one RCT found that adding oral glycoprotein IIb/IIIa inhibitor to aspirin increased mortality and serious bleeding compared with aspirin alone.
- **Oral anticoagulants in addition to antiplatelet treatment** One systematic review found that when added to aspirin, moderate or high intensity oral anticoagulation reduced the risk of serious cardiovascular events compared with aspirin alone but increased the risk of major haemorrhage. One RCT found that adding fixed, low dose warfarin to aspirin had no effect on cardiovascular outcomes compared with aspirin alone. Another RCT found that fixed dose ximelagatran reduced serious cardiovascular events compared with aspirin alone. We found no RCTs comparing oral anticoagulants plus aspirin versus any other drugs.
- **Oral glycoprotein IIb/IIIa receptor inhibitors** One systematic review found that oral glycoprotein IIb/IIIa receptor inhibitors (in people not taking aspirin) increased mortality, myocardial infarction, and haemorrhage compared with aspirin alone. We found no comparisons between oral glycoprotein IIb/IIIa receptor inhibitors and placebo or anticoagulants.

Other drugs

- **Amiodarone** Two systematic reviews found that amiodarone (a class III antiarrhythmic agent) significantly reduced the risk of all cause and cardiac mortality compared with placebo in people with recent myocardial infarction and high risk of death from cardiac arrhythmia (including left ventricular dysfunction).
- **Angiotensin converting enzyme inhibitors (in people with and without left ventricular dysfunction)** Two large RCTs found that angiotensin converting enzyme inhibitors reduced the risk of serious cardiac events in people at high risk of cardiovascular events (but with normal ventricular function and without heart failure). Two systematic reviews found that angiotensin converting enzyme inhibitors reduced mortality in people with recent myocardial infarction or left ventricular dysfunction, one finding a smaller benefit in women, but equal benefit in people with and without diabetes and in black and white people.
- **Angiotensin II receptor blockers** One RCT found a reduction in cardiovascular events and a death with use of low dose angiotensin II receptor blockers compared with usual care in people with coronary artery disease, most of whom were not taking angiotensin converting enzyme inhibitors.
- **Beta–blockers** Systematic reviews have found strong evidence that beta–blockers reduce the risk of all cause mortality, coronary mortality, recurrent non-fatal myocardial infarction, and sudden death in people after myocardial infarction. One systematic review found no differences in effect between men and women. Another systematic review found that beta–blockers reduced risk of death from heart failure compared with placebo in people with left ventricular dysfunction and that relative benefit was similar in people with and without diabetes. Relative efficacy of different types of beta–blockers is not clear.

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- **Angiotensin II receptor blockers added to angiotensin converting enzyme inhibitors** We found no systematic review or RCTs comparing angiotensin II blockers plus angiotensin converting enzyme inhibitors versus placebo. Two RCTs found conflicting evidence about the effects on mortality and morbidity of adding angiotensin II receptor blockers to treatment for people already taking angiotensin converting enzyme inhibitors versus angiotensin converting enzyme inhibitors alone, though one of these RCTs may have lacked power to detect a clinically important effect.
- **Calcium channel blockers** One systematic review found no significant difference in mortality between calcium channel blockers and placebo in people after myocardial infarction or with chronic coronary heart disease. However, subgroup analysis by drug type found that diltiazem and verapamil reduced rates of refractory angina in people without heart failure after myocardial infarction. The review found non-significantly higher mortality with dihydropyridines compared with placebo.
- **Class I antiarrhythmic agents (quinidine, procainamide, disopyramide, encainide, flecainide, and moracizine)** One systematic review found that class I antiarrhythmic agents after myocardial infarction increased the risk of cardiovascular mortality and sudden death compared with placebo. One RCT found that in people with myocardial infarction and symptomatic ventricular arrhythmia, class I antiarrhythmic drugs increased risk of cardiac arrest or death compared with placebo.
- **Hormone replacement therapy** Two RCTs found no significant difference between combined oestrogen and progestin and placebo in cardiac events among postmenopausal women with coronary artery disease. A third RCT found no significant difference between oestrogen and placebo on mortality in women after myocardial infarction. A fourth RCT found that in men with pre-existing coronary heart disease, high dose oestrogen increased the risk of cardiac events compared with placebo. Hormone replacement therapy led to higher rates of venous thromboembolism, gall bladder disease, and vaginal bleeding in women.
- **Sotalol** One RCT found that, in people with myocardial infarction and left ventricular dysfunction, sotalol increased mortality compared with placebo.

Cholesterol reduction

- **Non-specific cholesterol reduction** One systematic review and one RCT found that multiple lipid lowering treatments in people with coronary heart disease substantially reduced overall mortality, cardiovascular mortality, and non-fatal cardiovascular events compared with not lowering cholesterol.
- **Statins** One systematic review and subsequent RCTs found that, compared with control, statins reduced the risk of mortality and cardiac events in people at high risk of cardiovascular events or with evidence of prior disease. Two RCTs found that intensive statin treatment was more effective than moderate statin treatment in reducing mortality and cardiac events. One RCT found that pravastatin reduced the risk of cardiac outcomes in men, but not in women. Another RCT found that simvastatin was associated with similar relative risk reductions in women and the elderly compared with that in younger men. Pravastatin was shown by one RCT to be effective in reducing cardiovascular events in the elderly.
- **Fibrates** One RCT found that gemfibrozil reduced the risk of cardiac mortality and cardiac events in people with coronary heart disease compared with placebo. Three RCTs found different results regarding the effect of clofibrate on cardiac or all cause mortality in men with a history of myocardial infarction. A large RCT found no significant difference between bezafibrate and placebo in all cause mortality or cardiac events in people with myocardial infarction or stable angina and a low density lipoprotein level less than 4.7 mmol/L (180mg/dl). A smaller RCT found that bezafibrate reduced cardiac events (mortality, reinfarction, revascularisation, or a combination of these) compared with placebo in men with a history of myocardial infarction and elevated serum cholesterol.

Blood pressure reduction

- **Blood pressure reduction** One systematic review found that the magnitude of cardiovascular risk reduction in people with coronary artery disease correlated directly with the magnitude of blood pressure reduction and there was little evidence for significant differences of treatment effect for different drugs classes.

Non-drug treatments

- **Cardiac rehabilitation (including exercise)** One systematic review found that, compared with usual care, cardiac rehabilitation reduced mortality and cardiac events in people with coronary heart disease. Adverse events during or after exercise were rare.

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- **Mediterranean diet** One RCT found that advising people with coronary heart disease to eat a Mediterranean diet (more fruit and vegetables, bread, pasta, potatoes, olive oil, and rapeseed margarine) had a substantial survival benefit over a Western diet.
- **Psychosocial treatment** One systematic review and two subsequent RCTs provided limited evidence that psychological treatment improved symptoms and reduced the risk of serious cardiac events compared with usual care in people with coronary artery disease.
- **Smoking cessation** We found no RCTs of the effects of smoking cessation on cardiovascular events in people with coronary heart disease. Observational studies have found that smoking cessation significantly reduced the risk of myocardial infarction and death in people with coronary heart disease.
- **Advice to eat less fat** We found no strong evidence from RCTs on the effect on secondary ischaemic cardiac events of advising people to eat a low fat diet.
- **Advice to eat more fibre** There was no evidence from one RCT included in a systematic review that high fibre diets had any effect on cardiac or all cause mortality.
- **Fish oil consumption (from oily fish or capsules)** Three RCTs, one included in a systematic review, found conflicting evidence that advice to people with coronary heart disease to eat more fish (particularly oily fish) or to take fish oil capsules reduced cardiac events. One RCT found that use of fish oil capsules reduced mortality at 3.5 years.
- **Antioxidant vitamin combinations** Three RCTs included in a systematic review found no benefit of antioxidant combinations on cardiovascular events or cardiac mortality.
- **Multivitamins** One RCT included in a systematic review found a reduction in cardiac events with multivitamins but no effect on cardiac mortality.
- **Vitamin C** We found no RCTs examining the effects of vitamin C on risk of cardiovascular events or death.
- **Beta-carotene** One RCT from a systematic review found no effect of beta carotene on cardiovascular events or death in people with mild angina. It found that in people with previous myocardial infarction beta carotene increased cardiac mortality.
- **Vitamin E** Two systematic reviews found inconclusive evidence about the benefits of vitamin E, two RCTs finding that high doses increased cardiac and all cause mortality.

Surgical treatments

- **Coronary artery bypass grafting versus medical treatment alone** One systematic review and one subsequent RCT found that coronary artery bypass grafting reduced revascularisations and angina after 1 year and reduced cardiac and all cause mortality up to 10 years after surgery compared with medical treatment. People with left ventricular dysfunction had a larger absolute reduction in mortality than people with normal ventricular function, though relative benefits were similar. A significant survival benefit was observed in people with left main stem or three vessel disease, but not in people with single or double vessel disease.
- **Intracoronary stents (versus percutaneous coronary transluminal angioplasty alone)** One systematic review found no significant difference between routine stenting and standard percutaneous angioplasty in mortality rates, risk of myocardial infarction or risk of future coronary artery bypass grafting. However it found that stenting reduced rates of restenosis and future percutaneous transluminal angioplasty. One subsequent RCT found that stents increased event free survival but not mortality after 5 years compared with percutaneous transluminal angioplasty. One systematic review found that stenting significantly reduced cardiac events, restenosis, and revascularisation compared with percutaneous transluminal angioplasty in small (< 3 mm) coronary arteries. However, a subsequent RCT found similar rates of restenosis and cardiac events following either treatment in small coronary arteries. One RCT found that stents reduced cardiac events after 6 months compared with percutaneous transluminal angioplasty in saphenous vein graft lesions in people with prior coronary artery bypass grafting. Three RCTs found that stents reduced restenosis and improved angina in people with total occlusions. There is conflicting evidence from two RCTs about effects of stents compared with percutaneous transluminal angioplasty in people with stenosis after initial percutaneous transluminal angioplasty on further restenosis and cardiac events.

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Secondary prevention of ischaemic cardiac events

- **Coronary artery bypass grafting (versus percutaneous transluminal angioplasty with or without stenting for multivessel disease)** One systematic review found no significant difference in mortality or myocardial infarction between percutaneous transluminal angioplasty (with or without stenting) and coronary artery bypass grafting after 3 years. However, percutaneous transluminal angioplasty (with or without stenting) led to a higher rate of repeat revascularisation and recurrent angina. The review lacked power to detect less than a 20–30% relative difference in mortality.
- **Coronary percutaneous transluminal angioplasty versus medical treatment** One systematic review found no significant difference between coronary percutaneous transluminal angioplasty and medical treatment in survival. However, percutaneous transluminal angioplasty improved physical functioning and general health and vitality after 1 year and reduced angina severity in those with severe or moderate angina compared with medical treatment alone. The review found an increase in subsequent coronary artery bypass grafting with percutaneous transluminal angioplasty. One RCT in elderly people found that percutaneous transluminal angioplasty reduced anginal symptoms and adverse cardiac events, but not mortality or non-fatal myocardial infarction.

DEFINITION	Secondary prevention in this context is the long term treatment to prevent recurrent cardiac morbidity and mortality and to improve quality of life in people who either had a prior acute myocardial infarction or are at high risk of ischaemic cardiac events for other reasons, such as severe coronary artery stenoses, angina, or prior coronary surgical procedures.
INCIDENCE/ PREVALENCE	Coronary artery disease is the leading cause of mortality in developed countries and is becoming a major cause of morbidity and mortality in developing countries. There are international, regional, and temporal differences in incidence, prevalence, and death rates. In the USA, the prevalence of coronary artery disease is over 6%, and the annual incidence is over 0.33%.[1]
AETIOLOGY/ RISK FACTORS	Most ischaemic cardiac events are associated with atheromatous plaques that can lead to acute obstruction of coronary arteries. Coronary artery disease is more likely in people who are older or have risk factors, such as smoking, hypertension, high cholesterol, and diabetes mellitus.
PROGNOSIS	Within 1 year of having a first myocardial infarction, 25% of men and 38% of women will die. Within 6 years of having a first myocardial infarction, 18% of men and 35% of women will have another myocardial infarction, 22% of men and 46% of women will have heart failure, and 7% of men and 6% of women will have sudden death.[1]
AIMS OF INTERVENTION	To prevent (recurrent) acute coronary syndromes (myocardial infarction or unstable angina), left ventricular dysfunction, heart failure, sudden cardiac death, and overall mortality; and to maintain or improve quality of life.
OUTCOMES	Morbidity (recurrent cardiovascular events including myocardial infarction, angina, stroke, coronary artery disease); mortality; quality of life.
METHODS	*Clinical Evidence* search and appraisal July 2004.

QUESTION What are the effects of antithrombotic treatment?

OPTION ASPIRIN New

Two systematic reviews found that aspirin reduced the risk of serious vascular events and reduced all cause mortality compared with placebo. One of the reviews found that doses of 75–325 mg daily were as effective as higher doses (500–1500 mg).

Benefits: **Aspirin versus no aspirin:** We found two systematic reviews. The first (search date 1997, 195 RCTs, > 140 000 high risk people owing to evidence of pre-existing disease) compared an antiplatelet regimen (aspirin by far the most common) versus no antiplatelet treatment (including placebo).[2] Among almost 60 000 people (excluding those with acute ischaemic stroke) aspirin significantly reduced serious vascular events compared with control (OR 0.77, 95% CI 0.73 to 0.81).[2] The second systematic review (search date 2002, 6 RCTs, 6300 people with cardiovascular disease) compared low dose aspirin (≤ 325 mg/day) with placebo. It found that low dose aspirin reduced all cause mortality (OR 0.82, 95% CI 0.70 to 0.99) and myocardial infarctions (OR 0.70, 95% CI 0.60 to 0.80).[3] **Different doses of aspirin:** We found one systematic review (search date 1997). Direct comparisons (3197 high risk people owing to evidence of pre-existing disease) between daily doses of 500–1500 mg versus 75–325 mg of aspirin found no significant difference in prevention of myocardial infarction, stroke, or death with higher dose aspirin compared with lower dose aspirin (OR 0.97, 95% CI 0.79 to

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1.19); and direct comparisons (3570 people) between daily doses of 75 mg or more and less than 75 mg daily found no significant effect on rates of myocardial infarction, stroke, and death, but the confidence interval included a potentially clinically important effect (OR 1.08, 95% CI 0.90 to 1.31).[2] **Aspirin versus thienopyridines:** See benefits of thienopyridines, p 9 **Aspirin in addition to thienopyridines:** See benefits of combination antiplatelet treatments, p 9. **Aspirin versus oral glycoprotein IIb/IIIa receptor inhibitors:** See benefits of oral glycoprotein IIb/IIIa receptor inhibitors, p 9. **Aspirin in addition to oral glycoprotein IIb/IIIa receptor inhibitors:** See benefits of combinations of antiplatelets, p 6 **Aspirin versus anticoagulants:** See benefits of oral anticoagulants in absence of antiplatelet treatment, p 8. **Aspirin in addition to anticoagulants:** See benefits of oral anticoagulants in addition to antiplatelet treatment, p 7.

Harms: **Overall haemorrhage:** A systematic review of bleeding complications with antiplatelet agents (search date 2002, 25 RCTs, 287 616 people) found that low dose aspirin (< 100 mg/day) was associated with the lowest risk of bleeding (3.6%, 95% CI 3.3% to 3.9%) compared with other antiplatelet treatments, and that higher doses of aspirin were associated with higher haemorrhagic event rates (100–325 mg/day: 9.1%, 95% CI 8.7% to 9.4%; > 325 mg/day: 9.9%, 95% CI 8.4% to 11.4%).[4] **Intracranial haemorrhage:** A systematic review comparing aspirin versus control (search date 1997, 16 RCTs, 55 462 people) found that aspirin increased risk of intracranial haemorrhage in about 1/1000 (0.1%) people treated for 3 years.[5] A systematic review (search date 2002) found no significant differences in risk of intracranial haemorrhage with lower aspirin doses (< 325 mg/day) compared with control (19 RCTs, 165 616 people, event rate: 0.3%, 95% CI 0.2% to 0.4%), but an increased risk of intracranial haemorrhage with aspirin doses greater than 325 mg daily compared with control (3 RCTs, 2224 people, event rate: 1.1%, 95% CI 0.7% to 1.5%).[4] **Extracranial haemorrhage:** One systematic review (search date 1997) found that aspirin slightly increased the risk of major extracranial haemorrhage, similar to the risk for antiplatelet treatment in general (see harms of combinations of antiplatelet treatments, p 7), compared with control. It found that the risk of major extracranial haemorrhage was similar with different daily doses (numerical results not reported).[2] **Gastrointestinal haemorrhage:** A systematic review (search date 1999, 24 RCTs, 65 987 people, a mixed primary and secondary prevention population) comparing aspirin versus control found an increased risk of gastrointestinal haemorrhage with aspirin (OR 1.68, 95% CI 1.51 to 1.88), with no definite variation in risk between doses or different formulations.[6] A second systematic review (search date 2002) found that the risk of gastrointestinal bleeding was increased with low dose aspirin (≤ 325 mg/day) compared with placebo (OR 2.5, 95% CI 1.4 to 4.7).[3] A third systematic review (search date 2002) found a lower risk of gastrointestinal haemorrhage with aspirin doses of less than 100 mg daily (5 RCTs, 13 337 people, event rate: 1.1%, 95% CI 0.9% to 1.3%) than with aspirin doses of 100–325 mg daily (7 RCTs, 30 413 people, event rate: 2.4%, 95% CI 2.2% to 2.6%) and aspirin doses of greater than 325 mg daily (3 RCTs, 2224 people, event rate: 2.5%, 95% CI 1.8% to 3.1%).[4]

Comment: Among people at high risk of cardiac events, the large absolute reductions in serious vascular events associated with aspirin far outweigh any absolute risks.

OPTION COMBINATIONS OF ANTIPLATELET TREATMENTS

One RCT found that clopidogrel reduced serious cardiovascular events in people already taking aspirin compared with aspirin alone. One systematic review and one RCT found that adding oral glycoprotein IIb/IIIa inhibitor to aspirin increased mortality and serious bleeding compared with aspirin alone.

Benefits: **Aspirin plus thienopyridines versus aspirin alone:** We found no systematic review, but found one RCT. The RCT (12 562 people taking aspirin after acute coronary syndrome) compared clopidogrel (300 mg initially, then 75 mg/day) versus placebo. It found that adding clopidogrel to aspirin significantly reduced the absolute risk of cardiac death, myocardial infarction, or stroke after an average of 9 months (composite outcome: RR 0.82, 95% CI 0.70 to 0.95).[7] **Aspirin plus oral glycoprotein IIb/IIIa**

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receptor inhibitors versus aspirin alone: We found one systematic review[8] and one subsequent RCT.[9] The review (search date 2001, 2 RCTs, people having percutaneous coronary intervention) found that addition of oral glycoprotein IIb/IIIa receptor inhibitor to aspirin increased mortality compared with aspirin alone (2 RCTs, OR 1.38, 95% CI 1.15 to 1.67).[8] The subsequent RCT (9190 people, 59% with coronary artery disease and 49% with cerebrovascular disease) assessed the effects of adding oral glycoprotein IIb/IIIa receptor inhibitor to aspirin for 2 years.[9] It found no significant difference in risk of cardiovascular events with aspirin plus oral glycoprotein IIb/IIIa receptor inhibitors compared with aspirin alone, but found an increase in risk of haemorrhage (see harms below). The subsequent RCT found that combination treatment increased all cause mortality, most of which was vascular related, compared with aspirin alone (all cause mortality: 3.0% with combination treatment *v* 2.3% with aspirin alone; HR 1.33, 95% CI 1.03 to 1.72).

Harms: **Aspirin plus thienopyridines:** The addition of clopidogrel to aspirin after acute coronary syndrome for 3–12 months did not significantly increase the risk of life threatening haemorrhage compared with aspirin alone (RR 1.09, 95% CI 0.75 to 1.59).[7] **Aspirin plus oral glycoprotein IIb/IIIa receptor inhibitors versus aspirin alone:** Both RCTs included in the review found that adding aspirin to oral glycoprotein IIb/IIIa receptor inhibitors increased bleeding compared with aspirin alone. The first RCT found greater rates of moderate/severe bleeding with xemilofiban plus aspirin compared with aspirin alone (7.1% with 20 mg/day xemilofiban plus aspirin *v* 1.8% with aspirin alone).[8] The second RCT also found greater bleeding rates with orbofiban (50 mg twice daily for 30 days, then 50 mg twice daily) plus aspirin compared with aspirin alone (4.5% with orbofiban plus aspirin *v* 2.0% with aspirin alone).[8] The subsequent RCT found that combination treatment significantly increased serious bleeding risk compared with aspirin alone (8.0% with combination treatment *v* 2.8% with aspirin alone; $P < 0.001$).[9]

Comment: None.

OPTION ORAL ANTICOAGULANTS IN ADDITION TO ANTIPLATELET TREATMENTS New

One systematic review found that when added to aspirin, moderate or high intensity oral anticoagulation reduced the risk of serious cardiovascular events compared with aspirin alone but increased the risk of major haemorrhage. One RCT found that adding fixed, low dose warfarin to aspirin had no effect on cardiovascular outcomes compared with aspirin alone. Another RCT found that fixed dose ximelagatran reduced serious cardiovascular events compared with aspirin alone. We found no RCTs comparing oral anticoagulants plus aspirin versus any other drugs.

Benefits: **Aspirin plus anticoagulants versus aspirin alone:** We found one systematic review[10] and two subsequent RCTs.[11,12] The review (search date 2002, 22 RCTs) examined the effects of adding oral anticoagulants to aspirin in people with coronary artery disease.[10] It identified seven RCTs (12 333 people) of moderate or high intensity (international normalised ratio [INR]G > 2) anticoagulation plus aspirin compared with aspirin alone, and three RCTs (8435 people) of low intensity (INR < 2) anticoagulation plus aspirin compared with aspirin alone. Moderate or high intensity anticoagulation plus aspirin reduced the composite outcome of mortality, myocardial infarction, or stroke (composite measure: OR 0.88, 95% CI 0.80 to 0.97). Adding low intensity anticoagulation to aspirin, however, did not significantly reduce risk (composite measure: OR 0.91, 95% CI 0.79 to 1.06).[10] The first subsequent RCT (2300 people with coronary artery disease, 5 year follow up) compared the effects of adding warfarin 1.25 mg daily to aspirin 75 mg daily versus aspirin 75 mg daily alone. It found no significant difference between the groups in the risk of cardiovascular death, myocardial infarction, or stroke (event rate: 28.1% with warfarin plus aspirin *v* 28.8% with aspirin alone; $P = 0.67$).[11] The second subsequent RCT (1883 people) compared the effect of adding ximelagatran (24–60 mg twice/day) to aspirin 160 mg daily for 6 months versus aspirin 160 mg daily alone.[12] It found that adding ximelagatran to aspirin significantly reduced the risk of death, myocardial infarction, or recurrent ischaemia (HR 0.76, 95% CI 0.59 to 0.98). There was no evidence of a dose response.[12]

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Harms: **Aspirin plus anticoagulants versus aspirin alone:** One systematic review (search date 2002, 22 RCTs) found a significant increase in major haemorrhage with moderate or high intensity anticoagulation plus aspirin compared with aspirin alone (OR 1.74, 95% CI 1.39 to 2.17). The review found that low intensity anticoagulation plus aspirin did not significantly increase major haemorrhage compared with aspirin alone (OR 1.25, 95% CI 0.93 to 1.70).[10] The first subsequent RCT of low dose warfarin added to low dose aspirin showed a significant increase in risk of major haemorrhage (2.2% with warfarin plus aspirin *v* 1.0% with aspirin alone; $P < 0.001$).[11] The second subsequent RCT of ximelagatran and aspirin found no significant increase in risk of major haemorrhage with addition of ximelagatran compared with aspirin alone (HR 1.97, 95% CI 0.80 to 4.84, see comment below).[12]

Comment: Moderate to high intensity oral anticoagulants provide substantial protection against cardiovascular events, but the risks of serious haemorrhage are higher than for aspirin alone and regular monitoring is required. Aspirin provides similar protection, but is safer and easier to use. Ximelagatran was an investigational drug at the time of this summary.

OPTION ORAL ANTICOAGULANTS IN THE ABSENCE OF ANTIPLATELET TREATMENT New

One systematic review found that moderate or high intensity oral anticoagulation reduced the risk of cardiovascular events in people with coronary artery disease but substantially increased the risks of haemorrhage compared with placebo or aspirin.

Benefits: **Oral anticoagulants versus placebo:** We found one systematic review (search date 2002, 22 RCTs) of the effects of oral anticoagulants in people with coronary artery disease.[10] The review compared high intensity anticoagulation (international normalised ratio [INR]◐ > 2.8) versus control (13 RCTs, 8140 people, either no anticoagulation or placebo) and moderate intensity anticoagulation (INR 2–3) versus control (3 RCTs, 982 people). Aspirin was not used by most people in these comparisons. The review found that high intensity anticoagulation reduced the combined outcome of mortality, myocardial infarction, or stroke compared with control (20% with high intensity anticoagulation *v* 30% with control, OR 0.43, 95% CI 0.37 to 0.49; $P < 0.0001$) and that moderate intensity anticoagulation was associated with a smaller, non-significant reduction in this composite outcome.[10] **Oral anticoagulants versus antiplatelet drugs:** We found one systematic review (as above, search date 2002, 22 RCTs). The review compared high or moderate intensity oral anticoagulation (INR > 2) versus aspirin (6 RCTs, 4155 people). It found that oral anticoagulants significantly reduced risk of cardiovascular events (mortality, myocardial infarction, or stroke) compared with aspirin (OR 0.79, 95% CI 0.67 to 0.94).[10]

Harms: **Oral anticoagulants versus placebo:** The same review found that high intensity anticoagulation substantially increased major (mainly extracranial) haemorrhage compared with control (11 RCTs, 7933 people; 4.6% with high intensity anticoagulation *v* 0.7% with control, OR 4.5, 95% CI 2.5 to 6.0; $P < 0.00001$).[10] Moderate intensity anticoagulation also increased major haemorrhage compared with control (OR 7.7, 95% CI 3.3 to 17.6; $P < 0.0001$). **Oral anticoagulants versus antiplatelet drugs:** The review found that high or moderate intensity oral anticoagulation increased major haemorrhage compared with aspirin (10 RCTs, 6655 people; OR 2.1, 95% CI 1.7 to 2.7; $P < 0.00001$).[10]

Comment: Oral anticoagulants provide substantial protection against cardiovascular events, but the risks of serious haemorrhage are higher than for aspirin alone and regular monitoring is required. Aspirin provides similar protection, but is safer and easier to use.

OPTION ORAL GLYCOPROTEIN IIB/IIIA RECEPTOR INHIBITORS New

One systematic review found that oral glycoprotein IIb/IIIa receptor inhibitors (in people not taking aspirin) increased mortality, myocardial infarction, and haemorrhage compared with aspirin alone. We found no comparisons between oral glycoprotein IIb/IIIa receptor inhibitors and placebo or anticoagulants.

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Secondary prevention of ischaemic cardiac events

Benefits: **Oral glycoprotein IIb/IIIa receptor inhibitors versus placebo:** We found no systematic review or RCTs. **Oral glycoprotein IIb/IIIa receptor inhibitors versus aspirin:** We found one systematic review (search date 2001, 2 RCTs, people having percutaneous coronary intervention).[8] The review found that oral glycoprotein IIb/IIIa receptor inhibitors (without aspirin) significantly increased mortality and risk of myocardial infarction compared with aspirin alone after 3–10 months (mortality: 2 RCTs, OR 1.37, 95% CI 1.00 to 1.86; myocardial infarction: 1 RCT, AR 6.9% with high dose glycoprotein IIb/IIIa receptor inhibitors *v* 5.3% with aspirin; P = 0.03).[8] **Oral glycoprotein IIb/IIIa receptor inhibitors versus anticoagulants:** We found no systematic review or RCTs.

Harms: The systematic review found that oral glycoprotein IIb/IIIa receptor inhibitors (without aspirin) significantly increased mortality compared with aspirin alone.[8] Another systematic review (7 RCTs, 34 447 people) compared haemorrhage rates following treatment with aspirin, dipyridamole, ADP receptor blockers, and glycoprotein IIb/IIIa receptor inhibitors (given intravenously or orally). It found that oral glycoprotein IIb/IIIa receptor inhibitors resulted in the highest rates of haemorrhage (44.6%, 95% CI 43.7% to 45.4%; P value not reported).[4]

Comment: None.

OPTION THIENOPYRIDINES (TICLOPIDINE OR CLOPIDOGREL) New

Two systematic reviews and two RCTs found that thienopyridines were more effective than aspirin for reducing the risk of further cardiovascular events.

Benefits: **Ticlopidine versus aspirin:** We found one systematic review[2] and one subsequent RCT.[13] The review (search date 1997, 4 RCTs, 3791 high risk people owing to evidence of prior disease) found that ticlopidine non-significantly reduced serious vascular events compared with aspirin (RR 0.88, 95% CI 0.75 to 1.03).[2] The subsequent RCT (1470 people with previous myocardial infarction) also found that ticlopidine did not significantly reduce the risk of a vascular event compared with aspirin (OR 0.69, 95% 0.31 to 1.48).[13] **Clopidogrel versus aspirin:** We found no systematic review but found one RCT that compared clopidogrel versus aspirin. The RCT (19 185 people with a history of myocardial infarction, stroke, or peripheral arterial disease) compared clopidogrel 75 mg daily versus aspirin 325 mg daily and found that clopidogrel reduced the risk of a serious vascular event by 10% (OR 0.90, 95% CI 0.82 to 0.99).[14] **Any thienopyridine versus aspirin:** We found one systematic review (search date 1999, 4 RCTs, 22 656 people at high risk owing to previous cardiovascular disease).[15] The review found that ticlopidine or clopidogrel modestly but significantly reduced vascular events compared with aspirin (OR 0.91, 95% CI 0.84 to 0.98; average 11 events prevented/1000 people treated with a thienopyridine instead of aspirin for 2 years, 95% CI 2 events prevented/1000 people treated to 19 events prevented/1000 people treated).[15] **Ticlopidine versus clopidogrel:** We found no RCTs that compared long term use of ticlopidine and clopidogrel for secondary prevention of cardiac events.

Harms: One systematic review (search date 1999, 4 RCTs) comparing thienopyridines (ticlopidine or clopidogrel) versus aspirin found that ticlopidine or clopidogrel resulted in significantly less gastrointestinal haemorrhage and upper gastrointestinal symptoms than aspirin (gastrointestinal haemorrhage: 198/11128 [1.8%] with thienopyridine *v* 276/11126 [2.5%] with aspirin; OR 0.71, 95% CI 0.59 to 0.86).[15] However, the incidence of skin rash and diarrhoea doubled with ticlopidine and increased by about a third with clopidogrel. Ticlopidine increased the risk of neutropenia. Observational studies have also found that ticlopidine is associated with thrombocytopenia and thrombotic thrombocytopenic purpura.[16,17] A systematic review (search date 2002, 10 RCTs, 42 502 people) found that thienopyridines were associated with the highest rate of bleeding complications (44.6% with thienopyridines *v* 3.6% with low dose aspirin *v* 6.7% with dipyridamole).[4]

Comment: None.

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Secondary prevention of ischaemic cardiac events

QUESTION What are the effects of other drug treatments?

OPTION BETA–BLOCKERS New

Systematic reviews have found strong evidence that beta–blockers reduce the risk of all cause mortality, coronary mortality, recurrent non-fatal myocardial infarction, and sudden death in people after myocardial infarction. One systematic review found no differences in effect between men and women. Another systematic review found that beta–blockers reduced risk of death from heart failure compared with placebo in people with left ventricular dysfunction and that relative benefit was similar in people with and without diabetes. Relative efficacy of different types of beta–blockers is not clear.

Benefits:

Survival: We found one systematic review (search date 1993, 26 RCTs, > 24 000 people), which compared oral beta–blockers versus placebo within days or weeks of an acute myocardial infarction and continued for between 6 weeks and 3 years.[18] Most RCTs followed people for 1 year. The review found that beta–blockers reduced mortality compared with placebo (RR 0.77, 95% CI 0.70 to 0.86).[18] **Anginal symptoms:** We found no systematic review and no good RCTs assessing the antianginal effects of beta–blockers in people after myocardial infarction. Beta–blockers have been found to be effective in people with stable angina. See stable angina, p 60. **Different types of beta–blockers:** We found one systematic review[19] and one subsequent RCT. The review (search date not reported, 24 RCTs) found no differences between beta–blockers with and without cardioselectivity or membrane stabilising properties, but it raised concerns about the lack of efficacy of beta–blockers with intrinsic sympathomimetic activity in long term management after myocardial infarction.[19] The subsequent RCT (607 people after myocardial infarction) found that acebutolol, a beta–blocker with moderate partial agonist activity, decreased mortality at 1 year compared with placebo (AR of death: 6% with acebutolol *v* 11% with placebo; RR 0.52, 95% CI 0.29 to 0.91).[20] **Effects in different subgroups:** We found one systematic review (search date 1983, 9 RCTs, 13 679 people), which compared beta–blockers versus placebo started more than 24 hours after onset of symptoms of acute myocardial infarction and continued for 9–24 months.[21] It found that the survival benefits of beta–blockers were similar in men and women. The highest absolute benefit from beta–blockers was found in people over 50 years of age; with a higher heart rate at study entry; with a history of myocardial infarction, angina pectoris, hypertension, or treatment with digitalis; and with transient signs or symptoms of mechanical or electrical failure in the early phases of myocardial infarction.[21] **In people with left ventricular dysfunction:** We found one systematic review (search date 2003, 7 RCTs, 12 727 people), which compared the effects of beta–blockers versus placebo in people with left ventricular dysfunction.[22] It found that beta–blockers reduced the risk of death from heart failure compared with placebo, and that the magnitude of benefit was similar for men and women (men: RR 0.66, 95% CI 0.59 to 0.75; women: RR 0.63, 95% CI 0.44 to 0.91).[22] The relative risk of death from heart failure was similar for people with and without diabetes, though absolute benefit is likely to be greater in people with diabetes (without diabetes: RR 0.65, 95% CI 0.57 to 0.74; with diabetes: RR 0.77, 95% CI 0.61 to 0.96; absolute risks not presented). Pooled analysis of studies examining bisoprolol, metoprolol, or carvedilol found that the magnitude of benefit was similar for black and white people (black people: RR 0.67, 95% CI 0.38 to 1.16; white people: RR 0.63, 95% CI 0.52 to 0.77). However, pooled analysis that included the one identified RCT of bucindolol found that the magnitude of benefit was greater in white people than black people (black people: RR 0.97, 95% CI 0.68 to 1.37; white people: RR 0.69, 95% CI 0.55 to 0.85).[22]

Harms:

Beta–blockers versus placebo: We found one systematic review (search date 2001, 15 RCTs, > 35 000 people) that examined harms of beta–blockers compared with placebo in people with previous myocardial infarction, heart failure, or hypertension.[23] It found no significant difference between beta–blockers and placebo in depressive symptoms or sexual dysfunction (depressive symptoms: RR 1.12, 95% CI 0.89 to 1.41; sexual dysfunction 1.10, 95% CI 0.96 to 1.25). However, it found a small but significant increase in fatigue with beta–blockers compared with placebo (RR 1.15, 95% CI 1.05 to 1.25).[23]

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Comment: None.

OPTION ANGIOTENSIN CONVERTING ENZYME INHIBITORS New

Two large RCTs found that angiotensin converting enzyme inhibitors reduced the risk of serious cardiac events in people at high risk of cardiovascular events (but with normal ventricular function and without heart failure). Two systematic reviews found that angiotensin converting enzyme inhibitors reduced mortality in people with recent myocardial infarction or left ventricular dysfunction, one finding a smaller benefit in women, but equal benefit in people with and without diabetes and in black and white people.

Benefits:

Angiotensin converting enzyme inhibitors in people with normal left ventricular function or no heart failure: We found no systematic review but found two RCTs that assessed the effect of angiotensin converting enzyme (ACE) inhibitors on cardiovascular events in people without ventricular dysfunction or heart failure.[24,25] The first RCT (9297 people at high risk of cardiovascular events owing to pre-existing vascular disease or diabetes plus at least 1 other cardiovascular risk factor) found that ramipril 10 mg daily reduced the composite primary outcome of cardiovascular death, myocardial infarction, or stroke compared with placebo over an average of 4.7 years (RR for composite outcome 0.78, 95% CI 0.70 to 0.86; NNT 27, 95% CI 20 to 45; RR for cardiovascular death 0.74, 95% CI 0.64 to 0.87; NNT 50, CI not reported; RR for myocardial infarction 0.80, 95% CI 0.70 to 0.90; NNT 42, CI not reported; RR for stroke 0.68, 95% CI 0.56 to 0.84; NNT 67, CI not reported; RR for death from all causes 0.84, 95% CI 0.75 to 0.95; NNT 56, CI not reported).[24] It also found that ramipril reduced the need for revascularisation procedures (RR 0.85, CI not reported) and reduced events related to heart failure (RR 0.77, CI not reported).[24] The second RCT (12 218 people with coronary artery disease, 4 years' follow up) found that perindopril 8 mg daily reduced the composite outcome of cardiovascular death, myocardial infarction, or cardiac arrest compared with placebo (8% with perindopril *v* 10% with placebo, RRR 20%, 95% CI 9% to 29%; P = 0.0003), and that these benefits were seen in all defined subgroups.[25]
Angiotensin converting enzyme inhibitors in people with left ventricular dysfunction: We found two systematic reviews.[22,26] The first review (search date not reported, 3 RCTs, 5966 people with recent myocardial infarction and heart failure or left ventricular ejection fraction < 35–40%)[26] compared ACE inhibitors (captopril, ramipril, or trandolapril) versus placebo started 3–16 days after acute myocardial infarction and continued for 15–42 months. ACE inhibitors significantly reduced mortality compared with placebo (702/2995 [23.4%] with ACE inhibitors *v* 866/2971 [29.1%] with placebo; OR 0.74, 95% CI 0.66 to 0.83; NNT 17 people treated for about 2 years to prevent 1 death, CI not reported), admission to hospital for congestive heart failure (355/2995 [11.9%] with ACE inhibitors *v* 460/2971 [15.5%] with placebo; OR 0.73, 95% CI 0.63 to 0.85; NNT 28, CI not reported), and recurrent non-fatal myocardial infarction (324/2995 [10.8%] with ACE inhibitors *v* 391/2971 [13.1%] with placebo; OR 0.80, 95% CI 0.69 to 0.94; NNT 43, CI not reported).[26] The second review (search date 2003, 6 RCTs, 12 586 people) assessed mortality in subgroups of people with left ventricular dysfunction.[22] It found that ACE inhibitors reduced mortality compared with placebo. The magnitude of this benefit was smaller in women than in men, similar in people with and without diabetes, and similar in white and black people (women: RR 0.90, 95% CI 0.78 to 1.05; men: 0.80, 95% CI 0.68 to 0.93; with diabetes: RR 0.84, 95% CI 0.70 to 1.00; without diabetes: RR 0.85, 95% CI 0.78 to 0.92; white people: RR 0.89, 95% CI 0.82 to 0.97; black people: RR 0.89, 95% CI 0.74 to 1.06).[22] **Angiotensin converting enzyme inhibitors plus angiotensin II receptor blockers:** See benefits of angiotensin receptor blockers added to angiotensin converting enzyme inhibitors, p 12.

Harms: Major adverse effects reported in these trials were cough (ARI 5–10% with ACE inhibitors *v* placebo), dizziness, hypotension (ARI 5–10% with ACE inhibitors *v* placebo), renal failure (ARI < 3% with ACE inhibitors *v* placebo), hyperkalaemia (ARI < 3% with ACE inhibitors *v* placebo), angina, syncope, diarrhoea (ARI 2% with ACE inhibitors *v* placebo), and, for captopril, alteration in taste (2% of captopril users).[26]

Comment: None.

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Secondary prevention of ischaemic cardiac events

OPTION ANGIOTENSIN II RECEPTOR BLOCKERS New

One RCT found a reduction in cardiovascular events and a death with use of low dose angiotensin II receptor blockers compared with usual care in people with coronary artery disease, most of whom were not taking angiotensin converting enzyme inhibitors.

Benefits: **Angiotensin II receptor blockers versus usual care:** We found no systematic review but found one RCT.[27] The RCT (406 people with previous coronary revascularisation, most of whom were not taking angiotensin converting enzyme inhibitors) found that adding candesartan 4 mg daily to usual care reduced the risk of revascularisation, non-fatal myocardial infarction, or cardiovascular death compared with usual care alone after 2 years (combined cardiovascular outcome: 5.9% with candesartan plus usual care *v* 12.3% with usual care alone; RR 0.47, 95% CI 0.24 to 0.93; P = 0.03).[27] This benefit was observed despite no change in blood pressure in either group during follow up. Subgroup analysis of those not taking angiotensin converting enzyme inhibitors (most participants) found similar results (combined cardiovascular outcome: 10.6% with candesartan plus usual care *v* 21.4% with usual care alone; P = 0.01, see comment below).[27]

Harms: The RCT did not report adverse effects. However, 4% of participants were reported to be intolerant of candesartan.[27]

Comment: The RCT did not stratify allocation by concomitant drug use, and subgroup analyses were not pre-specified.[27]

OPTION ANGIOTENSIN RECEPTOR BLOCKERS ADDED TO ANGIOTENSIN CONVERTING ENZYME INHIBITORS New

We found no systematic review or RCTs comparing angiotensin II blockers plus angiotensin converting enzyme inhibitors versus placebo. Two RCTs found conflicting evidence about the effects on mortality and morbidity of adding angiotensin II receptor blockers to treatment for people already taking angiotensin converting enzyme inhibitors versus angiotensin converting enzyme inhibitors alone, though one of these RCTs may have lacked power to detect a clinically important effect.

Benefits: **Angiotensin receptor blockers plus angiotensin converting enzyme inhibitors versus placebo:** We found no systematic review or RCTs comparing angiotensin receptor blockers plus angiotensin converting enzyme (ACE)-inhibitors versus placebo. **Angiotensin receptor blockers plus angiotensin converting enzyme inhibitors versus angiotensin converting enzyme inhibitors alone:** We found no systematic review but found two RCTs.[27,28] The first RCT (406 people with previous coronary revascularisation, 2 years' follow up, 25% who were already being treated with ACE inhibitors) compared an angiotensin receptor blocker (candasartan) versus usual care. Subgroup analysis in those who were concomitantly treated with ACE inhibitors found that adding candesartan had no significant effect on the combined cardiovascular outcome of risk of revascularisation, non-fatal myocardial infarction, or cardiovascular death compared with usual care alone (14.0% with ACE inhibitors plus angiotensin receptor blockers *v* 15.5% with usual care; P = 0.83).[27] However, the subgroup analysis may have lacked power to detect a clinically important effect.[27] The second RCT (5010 people with heart failure, > 50% with ischaemic heart disease, 93% of whom were receiving concomitant treatment with ACE inhibitors) found that an angiotensin receptor blockers (valsartan) significantly reduced combined mortality and morbidity compared with placebo (723/2511 [29%] with valsartan *v* 801/2499 [32%] with placebo; RR 0.87, 95% CI 0.77 to 0.97; P = 0.009), though had no effect on cardiac death rates.[28]

Harms: See harms of angiotensin converting enzyme inhibitors, p 11 and angiotensin II receptor blockers, p 12.

Comment: None.

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Secondary prevention of ischaemic cardiac events

OPTION CALCIUM CHANNEL BLOCKERS New

One systematic review found no significant difference in mortality between calcium channel blockers and placebo in people after myocardial infarction or with chronic coronary heart disease. However, subgroup analysis by drug type found that diltiazem and verapamil reduced rates of refractory angina in people without heart failure after myocardial infarction. The review found non-significantly higher mortality with dihydropyridines compared with placebo.

Benefits: **Any calcium channel blocker versus placebo:** We found one systematic review and no additional RCTs.[18] The review (search date 1993, 24 RCTs) compared calcium channel blockers (including dihydropyridines, diltiazem, and verapamil) versus placebo given early or late during the course of acute myocardial infarction or unstable angina and continued in the intermediate or long term.[18] Two of the RCTs used angiographic regression of coronary stenosis as an outcome in people with stable coronary heart disease treated with calcium channel blockers. The review found no significant difference in mortality compared with placebo (AR: 9.7% with calcium channel blockers *v* 9.3% with placebo; ARI with calcium channel blockers *v* placebo +0.4%, 95% CI −0.4% to +1.2%; OR 1.04, 95% CI 0.95 to 1.14).[18] **Diltiazem and verapamil:** We found one systematic review and no RCTs. The review (as above, search date 1993, 3 RCTs) found non-significantly lower mortality with diltiazem or verapamil compared with placebo (OR 0.95, 95% CI 0.82 to 1.09).[18] The review found decreased rates of recurrent infarction and refractory angina with active treatment with diltiazem or verapamil but only for those people without signs or symptoms of heart failure.[18] **Dihydropyridines:** We found one systematic review and no additional RCTs.[18] The review (as above, search date 1993) found non-significantly higher mortality with dihydropyridines compared with placebo (OR 1.16, 95% CI 0.99 to 1.35). Several individual RCTs of dihydropyridines found increased mortality, particularly when these agents were started early in the course of acute myocardial infarction and in the absence of beta–blockers.[18]

Harms: Three RCTs of diltiazem or verapamil compared with placebo found a trend toward harm for people with clinical manifestations of heart failure.[29–31]

Comment: Results of the CAMELOT study, which compared amlodipine with placebo for 2 years in about 2000 people with coronary artery disease and normal blood pressure, completed enrolment in 2002 but was not published before our search date. It should provide excellent direct evidence regarding the effect of this newer generation dihydropyridines on recurrent ischaemic events and will be included in future updates.

OPTION CLASS I ANTIARRHYTHMIC AGENTS (QUINIDINE, PROCAINAMIDE, DISOPYRAMIDE, ENCAINIDE, FLECAINIDE, AND MORACIZINE) New

One systematic review found that class I antiarrhythmic agents after myocardial infarction increased the risk of cardiovascular mortality and sudden death compared with placebo. One RCT found that in people with myocardial infarction and symptomatic ventricular arrhythmia, class I antiarrhythmic drugs increased risk of cardiac arrest or death compared with placebo.

Benefits: **Class I antiarrhythmic agents versus placebo:** We found one systematic review (search date 1993, 51 RCTs, 23 229 people with acute myocardial infarction)[18] and one additional RCT (1498 people with myocardial infarction and asymptomatic or mildly symptomatic ventricular arrhythmia).[32] Both found that class I antiarrhythmic drugs were harmful compared with placebo (see harms below).

Harms: The systematic review compared the effects of class I antiarrhythmic drugs versus placebo on mortality.[18] The review found that antiarrhythmic agents increased mortality compared with placebo (AR of death: 5.6% with class I antiarrhythmic drug *v* 5.0% with placebo; OR 1.14, 95% CI 1.01 to 1.28).[18] The additional RCT found that encainide or flecainide compared with placebo increased the risk of death or cardiac arrest after 10 months (RR 2.38, 95% CI 1.59 to 3.57; NNH 17).[32]

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Secondary prevention of ischaemic cardiac events

Comment: The evidence suggests that class I antiarrhythmic drugs should not be used in people after myocardial infarction or with significant coronary artery disease.

OPTION AMIODARONE

Two systematic reviews found that amiodarone (a class III antiarrhythmic agent) significantly reduced the risk of all cause and cardiac mortality compared with placebo in people with recent myocardial infarction and high risk of death from cardiac arrhythmia (including left ventricular dysfunction).

Benefits: We found two systematic reviews.[33,34] The first systematic review (search date not reported, 13 RCTs, 6553 people with recent myocardial infarction or congestive heart failure) compared amiodarone versus control treatments.[33] People were selected with a recent myocardial infarction and a high risk of death from cardiac arrhythmia (based on low left ventricular ejection fraction, frequent ventricular premature depolarisation, or non-sustained ventricular tachycardia, but no history of sustained symptomatic ventricular tachycardia or ventricular fibrillation); 78% of people from eight RCTs had a recent myocardial infarction, and 22% of people from five RCTs had congestive heart failure.[33] Most trials were placebo controlled with a mean follow up of about 1.5 years. The people with congestive heart failure were symptomatic but stable and had not had a recent myocardial infarction, although in most cases the heart failure was ischaemic in origin. All RCTs used a loading dose of amiodarone (400 mg/day for 28 days or 800 mg/day for 14 days) followed by a maintenance dose (200–400 mg/day). Amiodarone significantly reduced total mortality compared with placebo (AR for total mortality: 10.9% a year with amiodarone *v* 12.3% a year with placebo; RR 0.87, 95% CI 0.78 to 0.99) and rates of sudden cardiac death (RR 0.71, 95% CI 0.59 to 0.85). Amiodarone had similar effects in the studies after myocardial infarction and congestive heart failure.[33] The second systematic review (search date 1997, 5864 people with myocardial infarction, congestive heart failure, left ventricular dysfunction, or cardiac arrest) found similar results.[34]

Harms: Adverse events leading to discontinuation of amiodarone were hypothyroidism (expressed as events/100 person-years: 7.0 with amiodarone *v* 1.1 with placebo; OR 7.3), hyperthyroidism (1.4 with amiodarone *v* 0.5 with placebo; OR 2.5), peripheral neuropathy (0.5 with amiodarone *v* 0.2 with placebo; OR 2.8), lung infiltrates (1.6 with amiodarone *v* 0.5 with placebo; OR 3.1), bradycardia (2.4 with amiodarone *v* 0.8 with placebo; OR 2.6), and liver dysfunction (1.0 with amiodarone *v* 0.4 with placebo; OR 2.7).[33]

Comment: The two largest RCTs of amiodarone after myocardial infarction found a favourable interaction between beta–blockers and amiodarone, with additional reduction in cardiac mortality.[36,37]

OPTION SOTALOL New

One RCT found that, in people with myocardial infarction and left ventricular dysfunction, sotalol increased mortality compared with placebo.

Benefits: We found no systematic review but found one RCT.[35] The RCT (3121 people with myocardial infarction and left ventricular dysfunction) found increased mortality with sotalol compared with placebo (AR for death: 5.0% with sotalol *v* 3.1% with placebo; RR 1.65, 95% CI 1.15 to 2.36). The trial was terminated prematurely after less than 1 year.[35]

Harms: The RCT was terminated prematurely after less than 1 year owing to increased mortality among people taking sotalol.[35]

Comment: None.

OPTION HORMONE REPLACEMENT THERAPY New

Two RCTs found no significant difference between combined oestrogen and progestin and placebo in cardiac events among postmenopausal women with coronary artery disease. A third RCT found no significant difference between oestrogen and placebo on mortality in

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women after myocardial infarction. A fourth RCT found that in men with pre-existing coronary heart disease, high dose oestrogen increased the risk of cardiac events compared with placebo. Hormone replacement therapy led to higher rates of venous thromboembolism, gall bladder disease, and vaginal bleeding in women.

Benefits:

Combined oestrogen and progestins versus placebo: We found no systematic review. We found two RCTs (4 publications) that assessed the effect of combined hormone replacement therapy (HRT) on cardiovascular outcomes.[38–41] The first RCT (2763 postmenopausal women with coronary artery disease) found no significant difference in cardiovascular events following use of conjugated equine oestrogen 0.625 mg daily plus medroxyprogesterone acetate 2.5 mg daily compared with placebo for an average of 4.1 years (non-fatal myocardial infarction or death owing to coronary artery disease: 172/1380 [12.5%] with HRT *v* 176/1383 [12.7%] with placebo; ARR +0.3%, 95% CI –2.2% to +2.7%; RR 0.98, 95% CI 0.80 to 1.19).[38] It also found no significant difference in a secondary cardiovascular composite end point (coronary revascularisation, unstable angina, congestive heart failure, resuscitated cardiac arrest, stroke or transient ischaemic attack, and peripheral arterial disease) or in all cause mortality. At the end of the trial, open label treatment was offered to surviving women, according to original treatment allocation.[39] Adherence to HRT was more than 80% for the next 2 years of follow up, but declined to 45% in the final year. Adherence to placebo remained above 90% throughout. Combined analysis of the blinded and open label phases of this RCT found no significant difference between combined HRT and placebo in coronary artery disease events after a mean follow up of 6.8 years (intention to treat analysis: 36.6 events/1000 person-years with HRT *v* 36.8 events/1000 person-years with placebo; HR 0.99, 95% CI 0.84 to 1.17).[39] The second RCT (255 postmenopausal women with congestive heart failure confirmed by angiography) also compared HRT versus placebo.[40] Women allocated to HRT received oestrogen plus progestin (76 women), except if they had a previous hysterectomy, in which case they received oestrogen alone (58 women). The RCT found no significant difference between HRT and placebo in coronary heart disease events after a mean follow up of about 31 months (composite of death owing to heart disease, myocardial infarction, or admission for unstable angina: 15.4 events/100 person-years with hormone replacement *v* 11.9 events/100 person-years with placebo; RR 1.29, 95% CI 0.84 to 1.95).[40] **Oestrogen alone versus placebo:** We found no systematic review and two RCTs, one in women and one in men.[42,43] The first RCT (1017 postmenopausal women who survived a first myocardial infarction, 2 years' follow up) compared oestrogen (17-beta oestradiol 2 mg/day) alone versus placebo for the secondary prevention of coronary artery disease.[42] More women in the oestrogen group (57%) than in the placebo group (37%) discontinued treatment owing to vaginal bleeding (see harms below). It found no difference between oestrogen and placebo groups in the frequency of reinfarction or cardiac death (RR 0.99, 95% CI 0.70 to 1.41), or all cause mortality (RR 0.79, 95% CI 0.50 to 1.27).[42] The RCT in men found that high dose oestrogen (5 mg/day conjugated equine oestrogen) increased the risk of myocardial infarction and thromboembolic events in men with pre-existing coronary heart disease.[43]

Harms:

Combined oestrogen and progestins versus placebo: In one RCT,[38] more women in the HRT group than in the placebo group experienced venous thromboembolism (34/1380 [2.5%] with HRT *v* 12/1383 [0.9%] with placebo; OR 2.65, 95% CI 1.48 to 4.75) and gall bladder disease (84/1380 [6.1%] with HRT *v* 62/1383 [4.5%] with placebo; OR 1.38, 95% CI 0.99 to 1.92). Extended open label follow up of this trial found similar results after a total mean follow up of 6.8 years (combined intention to treat analysis from blind and open label phases; venous thromboembolism: 5.9 events/1000 person-years with HRT *v* 2.8 events/1000 person-years with placebo; HR 2.08, 95% CI 1.28 to 3.40; biliary tract surgery: 19.1 events/1000 person-years with HRT *v* 12.9 events/1000 person-years with placebo; HR 1.48, 95% CI 1.12 to 1.95).[41] **Oestrogen alone versus placebo:** In the one RCT in women,[42] the higher drug discontinuation rate in the oestrogen group (57%) compared with the placebo

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group (37%) was mostly owing to vaginal bleeding, which among women with hysterectomies occurred significantly more with oestrogen treatment (56% with oestrogen *v* 7% with placebo).[42] After 2 years of follow up, there were no cases of endometrial cancer (biopsies obtained in > 90% of oestrogen treated women), and no significant differences between oestrogen and placebo groups in the risk of cerebrovascular events, deep venous thrombosis, pulmonary embolism, or breast cancer.[42]

Comment: Contrary to decades of large observational studies, multiple randomised controlled trials show no cardiovascular benefit from oestrogen with or without progesterone in postmenopausal women.

QUESTION What are the effects of cholesterol reduction?

OPTION FIBRATES New

One RCT found that gemfibrozil reduced the risk of cardiac mortality and cardiac events in people with coronary heart disease compared with placebo. Three RCTs found different results regarding the effect of clofibrate on cardiac or all cause mortality in men with a history of myocardial infarction. A large RCT found no significant difference between bezafibrate and placebo in all cause mortality or cardiac events in people with myocardial infarction or stable angina and a low density lipoprotein level less than 4.7 mmol/L (180mg/dl). A smaller RCT found that bezafibrate reduced cardiac events (mortality, reinfarction, revascularisation, or a combination of these) compared with placebo in men with a history of myocardial infarction and elevated serum cholesterol.

Benefits: **Fibrates versus placebo:** We found one systematic review[44] and two additional RCTs.[45,46] The systematic review (search date not reported, 4 RCTs) compared fibrates versus placebo in people with known coronary heart disease.[44] The review did not perform a meta-analysis. The first RCT included in the review (2531 men with coronary heart disease and a level of high density lipoprotein cholesterol < 1 mmol/L [38 mg/dL]) found that gemfibrozil reduced the composite outcome of non-fatal myocardial infarction plus death from coronary heart disease compared with placebo after a median of 5.1 years (AR: 219/1264 [17%] with gemfibrozil *v* 275/1267 [22%] with placebo; ARR 4.4%, 95% CI 1.4% to 7.0%; RR 0.80, 95% CI 0.68 to 0.94; NNT 23, 95% CI 14 to 73).[44] The second RCT included in the review (men and women with established coronary disease) found that clofibrate reduced risk of cardiac deaths compared with placebo (ARR 42%; P = 0.02, no further data reported).[44] The third RCT included in the review (men and women with a history of angina and myocardial infarction) found that clofibrate reduced cardiac mortality in people with angina plus myocardial infarction (P < 0.05, no further data reported) but found increased risk of cardiac mortality for men with a history of myocardial infarction only (P < 0.02, no further data reported, see comment below) based on a post hoc subgroup analysis.[44] The fourth RCT included in the review (8341 men, aged 30–64 years with previous myocardial infarction) compared the effects of clofibrate on all cause and cardiac mortality. It found no significant difference between clofibrate and placebo (no further details reported).[44] The two additional RCTs compared bezafibrate versus placebo.[45,46] The first RCT (3090 people with previous myocardial infarction or stable angina, high density lipoprotein cholesterol < 1.2 mmol/L [45 mg/dL], and low density lipoprotein cholesterol < 4.7 mmol/L [180 mg/dL]) found that bezafibrate did not significantly reduce all cause mortality or the composite end point of myocardial infarction plus sudden death compared with placebo (AR for myocardial infarction or sudden death: 13.6% with bezafibrate *v* 15.0% with placebo; RR 0.91; P = 0.26).[45] The second RCT (92 men with a history of myocardial infarction, mean serum cholesterol ≥ 5.2 mmol/L) found that bezafibrate significantly reduced the combined outcome of death, reinfarction, plus revascularisation compared with placebo (3/47 [6%] with bezafibrate *v* 11/45 [24%] with placebo; RR 0.26, 95% CI 0.08 to 0.88).[46]

Harms: The systematic review did not report on harms associated with use of fibrates.[44] The first additional RCT reported that there were no significant differences in incidence of adverse events between groups (69% in both groups).[45] The RCT found no significant differences

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in fatal and non-fatal cancers (85/1548 [5.5%] with bezafibrate *v* 91/1542 [5.9%] with placebo; reported as not significant).[45] The second additional RCT reported that the rate of adverse events was similar with bezafibrate compared with placebo (no further details reported). The RCT also found that fewer people with bezafibrate developed diabetes mellitus compared with placebo (3/47 [6.4%] with bezafibrate *v* 5/45 [11.1%] with placebo; no further details reported).[46]

Comment: The largest RCTs suggest that gemfibrozil but not clofibrate or bezafibrate may reduce cardiovascular events or death, but the data are sparse. Benefits of fibrates may be extrapolated from trials of other agents that lower cholesterol concentrations (see option on non-specific cholesterol reduction, p 17).

OPTION NON-SPECIFIC CHOLESTEROL REDUCTION New

One systematic review and one RCT found that multiple lipid lowering treatments in people with coronary heart disease substantially reduced overall mortality, cardiovascular mortality, and non-fatal cardiovascular events compared with not lowering cholesterol.

Benefits: **Cholesterol treatments in general:** We found one systematic review of multiple lipid lowering treatments for secondary prevention. The review (search date 1999, 11 RCTs, 30 018 people with coronary artery disease) combined three RCTs of statins, one RCT of clofibrate, one RCT of gemfibrozil, one RCT of clofibrate plus niacin, one RCT of niacin, and four RCTs of diet therapy.[47] Meta-analysis found that cholesterol lowering treatments reduced all cause mortality, cardiac mortality, and coronary events compared with control (placebo or usual diet) (all cause mortality: RR 0.88, 95% CI 0.83 to 0.93; $P < 0.001$; cardiac mortality: RR 0.85, 95% CI 0.79 to 0.90; $P < 0.001$; coronary events: RR 0.79, 95% CI 0.76 to 0.83; $P < 0.001$). However, significant heterogeneity existed among RCTs of different types of treatment.[47]

Harms: The systematic review did not report on harms associated with cholesterol lowering.

Comment: Multivariate analysis in one systematic review (search date 1996)[48] indicates that in a wide range of clinical contexts, the relative risk reduction depends not on the method by which cholesterol is lowered but on the percent reduction (i.e. the relative reduction) in cholesterol concentration.

OPTION STATINS New

One systematic review and subsequent RCTs found that, compared with control, statins reduced the risk of mortality and cardiac events in people at high risk of cardiovascular events or with evidence of prior disease. Two RCTs found that intensive statin treatment was more effective than moderate statin treatment in reducing mortality and cardiac events. One RCT found that pravastatin reduced the risk of cardiac outcomes in men, but not in women. Another RCT found that simvastatin was associated with similar relative risk reductions in women and the elderly compared with that in younger men. Pravastatin was shown by one RCT to be effective in reducing cardiovascular events in the elderly.

Benefits: **Statins for cholesterol reduction versus control:** We found one systematic review[47] and three subsequent RCTs.[49–51] The systematic review (3 RCTs, 17 617 people with stable angina or myocardial infarction, 5–6 year follow up) compared statins with usual care.[47] It found that statins significantly improved outcomes after 5–6 years (coronary heart disease events: OR 0.75, 95% CI 0.70 to 0.81; $P < 0.001$, cardiac mortality: OR 0.75, 95% CI 0.66 to 0.84; $P < 0.001$, all cause mortality: OR 0.79, 95% CI 0.73 to 0.86; $P < 0.001$).[47] The first subsequent RCT (20 536 high risk adults with total cholesterol > 3.5 mmol/L [> 140 mg/dL; an inclusion threshold lower than previous statin trials], including > 5000 women and > 5000 people aged ≥ 70 years and 5963 people with diabetes) compared simvastatin 40 mg daily versus placebo (see comment below).[49] It found that simvastatin reduced total mortality and major vascular events compared with placebo after a mean of 5.5 years follow up (all cause mortality: 12.9% with simvastatin *v* 14.7% with placebo; RR 0.87, 95% CI 0.81 to 0.94; major vascular events: 19.8% with simvastatin *v* 25.2% with placebo, RR 0.76, 95% CI 0.72 to

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Secondary prevention of ischaemic cardiac events

0.81).[49] The second subsequent RCT (1600 people with established coronary heart disease) found that atorvastatin (10–80 mg/day, titrated to achieve low density lipoprotein (LDL) cholesterol < 2.6 mmol/L [100 mg/dL]) significantly reduced recurrent coronary events or death and all cause mortality compared with non-statin management over 3 years (coronary events or death: 12% with statins *v* 24.5% with placebo; RR 0.49, 95% CI 0.27 to 0.73; all cause mortality: 2.9% with statins *v* 5.0% with placebo; RR 0.57, 95% CI 0.39 to 0.78).[50] The third subsequent RCT (> 10 000 people with hypertension) compared pravastatin 40 mg daily with usual care (see comment below).[51] It found that in people with coronary artery disease (1475 people, mean baseline LDL cholesterol 3.3 mmol/L [129 mg/dL]), pravastatin did not affect all cause mortality or coronary heart disease death plus non-fatal myocardial infarction compared with usual care (all cause mortality: RR 0.95, 95% CI 0.74 to 1.23, coronary heart disease death plus non-fatal myocardial infarction: RR 1.03, 95% CI 0.77 to 1.38).[51]

Intensity of statin treatment: We found no systematic review but found two RCTs.[52,53] The first RCT (1351 people with previous saphenous vein coronary artery bypass grafting) compared intensive LDL cholesterol lowering (to 1.6–2.2 mmol/L [60–85 mg/dL]) with lovastatin and, if necessary, cholestyramine [colestyramine]) versus moderate LDL cholesterol lowering (to 3.4–3.7 mmol/L [130–140 mg/dL]) with the same drugs.[52] It found that intensive treatment significantly reduced the risk of repeat revascularisation compared with moderate treatment over 4 years (6.5% with intensive lowering *v* 9.2% with standard lowering; P = 0.03). The RCT also found that intensive treatment reduced the risk of revascularisation and cardiovascular death more than moderate treatment after 7 years (revascularisation: 19% with intensive lowering *v* 27% with moderate lowering; P = 0.0006; cardiovascular death: 7.4% with intensive lowering *v* 11.3% with moderate lowering; P = 0.03).[52] The second RCT (4162 people with a recent acute coronary syndrome) compared standard LDL cholesterol lowering (to about 2.5 mmol/L [100 mg/dL] with 40 mg/day of pravastatin) versus intensive LDL cholesterol lowering (to about 1.8 mmol/L [70 mg/dl] with 80 mg/day of atorvastatin).[53] It found that intensive treatment significantly reduced the composite outcome of death, myocardial infarction, unstable angina requiring readmission to hospital, revascularisation, and stroke compared with standard cholesterol lowering with pravastatin (composite outcome: HR 0.84, 95% CI 0.74 to 0.95).[53] **Effects of statins in different groups of people:** We found no systematic review but found three RCTs (4 publications).[49,54–56] The first RCT (1516 women and 7498 men with previous myocardial infarction or unstable angina) compared the effects of pravastatin on all cause and cardiac mortality, myocardial infarction, stroke, and admission to hospital for unstable angina in men and women compared with placebo. It found that pravastatin significantly reduced the risk of all cardiac outcomes in men (coronary heart disease [CHD] death: RR 0.74, 95% CI 0.65 to 0.83; all cause mortality: RR 0.75, 95% CI 0.69 to 0.87; myocardial infarction: RR 0.69, 95% CI 0.59 to 0.80) but not in women (CHD death: RR 0.89, 95% CI 0.67 to 1.18; all cause mortality: RR 1.00, 95% CI 0.72 to 1.36; myocardial infarction: RR 0.84, 95% CI 0.59 to 1.19, see comment below).[54] The relative effects of treatment did not differ substantially between women and men and the study may have been underpowered to detect separate effects on relative risks for cardiac outcomes for women.[54] The second RCT (20 536 high risk adults with total cholesterol > 3.5 mmol/L [> 140 mg/dL], including > 5000 women and > 5000 people over 70 years of age and 5963 people with diabetes) found that simvastatin was associated with similar relative risk reductions for secondary prevention in women and the elderly (both compared with younger men) and for people with initial total cholesterol levels of under 5.0 mmol/L (195 mg/dL) compared with people with levels over 5.0 mmol/L .[49] Subgroup analysis found that simvastatin significantly reduced first occurrence of major vascular events in people with diabetes (ARR 22%, 95% CI 13% to 30%; P < 0.0001).[55] While relative risks remain constant, absolute benefits increase linearly with baseline risk. This means that people with higher baseline risk are more likely to benefit, in absolute terms, from statin treatment compared with those at lower baseline risk. The third RCT (5804 people aged 70–82 years, with or at high risk of cardiovascular disease), found that pravastatin 40 mg daily reduced coronary artery disease death, myocardial infarction, or stroke compared with placebo over a mean 3.2 years (ARR 15%, 95% CI 3 to 26%; P = 0.014).[56]

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Harms: The systematic review comparing statin use with usual care did not report on harms associated with statin treatment.[47] An older systematic review of long term statin trials found no significant difference between statins and placebo in terms of non-cardiovascular mortality, cancer incidence, asymptomatic elevation of creatine kinase (> 10 times upper reference limit), or elevation of transaminases (> 3 times upper reference limit) during a mean of 5.4 years of treatment (non-cardiovascular mortality: OR 0.93, 95% CI 0.81 to 1.07; cancer incidence: OR 0.99, 95% CI 0.90 to 1.08; creatine kinase increase: OR 1.25, 95% CI 0.83 to 1.89; transaminase increase: OR 1.13, 95% CI 0.95 to 1.33).[57] We found one meta-analysis of three large RCTs (19 592 people) examining safety of pravastatin compared with placebo in primary or secondary prevention.[58] It found no clinically important difference between pravastatin and placebo for any adverse effects after a mean follow up of 5 years (primary cancer: 9.6% with pravastatin *v* 9.3% with placebo; P = 0.48; musculoskeletal adverse effects: < 0.1% in both groups; P = 0.02; gastrointestinal adverse effects: 1.4% *v* 1.5%; P = 0.48; hepatobiliary adverse effects: ≤ 0.1% in both groups; P = 0.45; dermatological adverse effects: 3.6% *v* 3.4%; P = 0.31; renal adverse effects: 2.7% *v* 2.5%; P = 0.42).[58] We found no evidence of additional harm associated with cholesterol lowering in elderly people, or in people after acute myocardial infarction.

Comment: Some studies compared statin treatment with usual care, which may have included non-study statin treatment. In these cases, the RCTs were not true placebo-controlled trials. People in the large statin trials in both treatment and placebo groups were also given dietary advice aimed at lowering cholesterol. Multivariate analysis in one systematic review (search date 1996)[48] indicates that in a wide range of clinical contexts the relative risk reduction depends not on the method by which cholesterol is lowered but on the percent reduction (i.e. the relative reduction) in cholesterol concentration, a finding that is supported by a subsequent RCT.[53] The absolute benefit over several years of lowering cholesterol is greatest in people with the highest baseline risk of an ischaemic cardiac event. It remains unclear whether any statin has advantages over others. We found only one large direct comparison of statins (atorvastatin *v* pravastatin), but the use of different drug doses in the RCT precludes making inferences about the relative effectiveness of either drug.[53] The main aim of treatment is to reduce absolute risk of clinical events (rather than to reduce the cholesterol to any particular concentration). Treatments aimed at lowering cholesterol need assessment for effectiveness in comparison and in combination with other possible risk factor interventions. At the time of the present search ongoing trials included the Treating New Targets trial (atorvastatin 80 mg/day *v* atorvastatin 10 mg/day), the Incremental Decrease in Endpoints through Aggressive Lipid Lowering trial (atorvastatin 80 mg/day *v* simvastatin 20–40 mg/day), the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine with Simvastatin and Folate/B_{12} (simvastatin 80 mg/day *v* simvastatin 20 mg/day), and the Heart Protection II trial (simvastatin 80 mg/day *v* simvastatin 20–40 mg/day).

QUESTION What are the effects of blood pressure reduction?

OPTION BLOOD PRESSURE REDUCTION

One systematic review found that the magnitude of cardiovascular risk reduction in people with coronary artery disease correlated directly with the magnitude of blood pressure reduction and there was little evidence for significant differences of treatment effect for different drugs classes.

Benefits: **Drugs versus placebo:** We found no systematic review or RCTs comparing drugs to lower blood pressure versus placebo. **Different antihypertensive drugs:** We found one systematic review[59] and one subsequent RCT.[60] The systematic review (search date 2003, 15 RCTs, 120 574 hypertensive people) compared the effects of "new" blood pressure lowering drugs (calcium channel blockers, alpha-blockers, angiotensin converting enzyme inhibitors, and angiotensin I receptor blockers) with "old" drugs (diuretics or beta–blockers) on total mortality, cardiovascular mortality, cardiovascular events, stroke, myocardial infarction, and heart failure. The review found that old and new drugs provided similar reductions in the risk of myocardial infarction, cardiovascular death, and

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Secondary prevention of ischaemic cardiac events

mortality.[59] The review also concluded that the magnitude of cardiovascular risk reduction correlated with the magnitude of blood pressure reduction in people with coronary artery disease.[59] The subsequent RCT (22 576 hypertensive people with coronary artery disease) found no significant difference between verapamil 240 mg daily and atenolol 50 mg daily in the composite outcome of all cause mortality, non-fatal myocardial infarction, or stroke after 2 years (9.9% with verapamil *v* 10.2% with atenolol; RR 0.98, 95% CI 0.90 to 1.06).[60] Additional treatments were given as needed to achieve blood pressure reduction goals (addition of trandolapril, hydrochlorothiazide, or both). This RCT is not purely a comparison between two treatments.[60]

Harms: **Drugs versus placebo:** We found no RCTs. **Different antihypertensive drugs:** The systematic review found that the risk of heart failure was higher with calcium channel blockers than with diuretics (RR 1.33, 95% CI 1.22 to 1.44; $P < 0.0001$).[59] One RCT included in the review also found that angiotensin converting enzyme inhibitors increased the risk of heart failure compared with chlorthalidone (RR 1.19, 95% CI 1.07 to 1.31; $P < 0.001$, see comment below).[51] Some observational studies found increased mortality among those with low diastolic blood pressure,[61] although this was not the case when treating elderly people for hypertension or heart failure.[62]

Comment: Experimental evidence of benefit from lowering of blood pressure in those with coronary heart disease requires extrapolation from primary prevention trials (see Primary prevention: hypertension, p 186). Trials of antihypertensive agents without specific blood pressure outcomes may also provide guidance: mortality benefit has been established for beta–blockers after myocardial infarction (see beta-blockers, p 10), for verapamil and diltiazem after myocardial infarction in those without heart failure (see calcium channel blockers, p 13), and for angiotensin converting enzyme inhibitors after myocardial infarction, especially in those with heart failure (see angiotensin converting enzyme inhibitors, p 11). Prospective epidemiological studies have established that elevated blood pressure is a risk factor for cardiovascular events in people who already have ischaemic heart disease.[63,64] One study (follow up of 5218 women with cardiovascular disease who had reported their blood pressure at baseline in the Women's Antioxidant Cardiovascular Study) found that for every 10 mm Hg increment in systolic blood pressure there was a 9% (95% CI 4% to 15%) increase in secondary cardiovascular events.[64] We found no evidence about the level to which blood pressure must be lowered to achieve the optimal trade off between risks and benefits in people with cardiovascular disease. Results from the ALLHAT study,[51] included in the review[59] must be interpreted with caution as most participants were already taking antihypertensive treatment at randomisation.[51]

QUESTION **What are the effects of non-drug treatments?**

OPTION **ANTIOXIDANT VITAMINS (VITAMIN E, BETA CAROTENE, VITAMIN C)** New

We found no RCTs examining the effects of vitamin C on risk of cardiovascular events or death. Two systematic reviews found inconclusive evidence about the benefits of vitamin E, two RCTs finding that high doses increased cardiac and all cause mortality. One RCT from a systematic review found no effect of beta carotene on cardiovascular events or death in people with mild angina or with previous myocardial infarction. Three RCTs included in a systematic review found no benefit of antioxidant combinations on cardiovascular events or cardiac mortality. One RCT included in a systematic review found a reduction in cardiac events with multivitamins but no effect on cardiac mortality.

Benefits: We found two systematic reviews that compared the effects of vitamin supplementation on cardiovascular outcomes.[65,66] The first review (search date 2001, 12 RCTs, 20 835 people with cardiovascular disease) compared vitamin supplementation (vitamins C or E, beta carotene, folic acid, antioxidant combinations, or multivitamin supplements) versus no supplementation.[65] Only nine of the studies met our inclusion criteria (reported relevant outcomes and were published as full text articles). The review did not perform a meta-analysis and reported that randomised studies have failed to show a consistent or significant effect of supplementation with individual vitamins (C or E, beta

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carotene, or folic acid) or combinations of antioxidants on coronary heart disease outcomes (see table 1 for details of studies meeting our inclusion criteria, p 32).[65] The second systematic review (search date not reported, 8 RCTs, about 45 000 people with or at high risk of cardiovascular disease) compared vitamin E supplementation versus placebo.[66] The review included three RCTs which were included in the first review and five newer ones. It found that supplementation with vitamin E did not affect all cause or cardiovascular mortality or non-fatal myocardial infarction compared with placebo (all cause mortality: RR 0.96, 95% CI 084 to 1.10; cardiovascular mortality: RR 0.97, 95% CI 0.80 to 1.90; non-fatal myocardial infarction: RR 0.72, 95% CI 0.51 to 1.02).[66]

Harms: None of the RCTs that met our inclusion criteria reported harms with vitamin supplementation. One RCT identified by the first systematic review[65] found evidence of an increase in lung cancer incidence and lung cancer mortality with beta carotene supplementation in smokers.[77]

Comment: None.

OPTION CARDIAC REHABILITATION INCLUDING EXERCISE New

One systematic review found that, compared with usual care, cardiac rehabilitation reduced mortality and cardiac events in people with coronary heart disease. Adverse events during or after exercise were rare.

Benefits: **Cardiac rehabilitation versus usual care:** We found one systematic review.[78] The systematic review (search date 2003, 48 RCTs, 8940 people with coronary heart disease) compared exercise based cardiac rehabilitation versus usual care and found that cardiac rehabilitation decreased all cause and cardiac mortality, and improved coronary risk factors (all cause mortality: OR 0.80, 95% CI 0.68 to 0.93; cardiac mortality: OR 0.74, 95% CI 0.61 to 0.96, see comment below).[78] The effect of cardiac rehabilitation on total mortality was independent of coronary heart disease diagnosis, type of cardiac rehabilitation, dose of exercise intervention, length of follow up, trial quality, and trial publication date.

Harms: Rates of adverse cardiovascular outcomes (syncope, arrhythmia, myocardial infarction, or sudden death) were low (2–3/100 000 person-hours) in supervised rehabilitation programmes, and rates of fatal cardiac events during or immediately after exercise training, were reported in two older surveys as ranging from 1/116 400 person-hours to 1/784 000 person-hours.[79]

Comment: The most recent review found that, compared with usual care, cardiac rehabilitation was associated with greater reductions in total cholesterol level (weighted mean difference –0.37 mmol/L [–14.3 mg/dL], 95% CI –0.63 to –0.11 mmol/L [–24.3 to –4.2 mg/dL]), triglyceride level (weighted mean difference –0.23 mmol/L [–20.4 mg/dL], 95% CI: –0.39 to –0.07 mmol/L [–34.5 to –6.2 mg/dL]), and systolic blood pressure (weighted mean difference –3.2 mm Hg, 95% CI: –5.4 mm Hg to –0.9 mm Hg); and lower rates of self reported smoking (OR 0.64, 95% CI 0.50 to 0.83).[78] Other interventions aimed at risk factor modification were often provided in the intervention groups (including nutritional education, counselling in behavioural modification, and, in some trials, lipid lowering medications). The review found no evidence that cardiac rehabilitation improved health related quality of life or the proportion of people returning to work after myocardial infarction.[78]

OPTION DIET New

We found no strong evidence from RCTs on the effect of advising people to eat a low fat diet or a high fibre diet. Three RCTs found conflicting evidence that advice to eat more fish (particularly oily fish) or to take fish oil capsules reduced cardiac events. One RCT found that use of fish oil capsules reduced mortality at 3.5 years. One RCT found that advising people to eat a Mediterranean diet (more fruit and vegetables, bread, pasta, potatoes, olive oil, and rapeseed margarine) had a substantial survival benefit over a Western diet.

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Secondary prevention of ischaemic cardiac events

Benefits:

Low fat diets: We found one systematic review (search date 1994, 10 RCTs, 18 058 people, mainly men with a history of myocardial infarction), which compared the effects of dietary interventions aimed at reducing cholesterol on coronary events and mortality. It found no significant effect of diet on coronary or mortality outcomes, though found a net overall reduction in blood cholesterol levels (10 RCTs, all cause mortality: OR 0.96, 95% CI 0.85 to 1.08; cardiac mortality: OR 0.98, 95% CI 0.83 to 1.15).[80] One large RCT included in the review (2033 middle aged men with a recent myocardial infarction) compared three dietary options: eat less fat, eat more cereal fibre, or eat at least two portions of oily fish a week.[81] The RCT found that advice to reduce fat intake resulted in slightly reduced fat intake and higher fruit and vegetable intake. However, it found no difference in total mortality between those advised to reduce fat intake (to 30% of total energy and to polyunsaturated : saturated ratio of 1 : 0) and those not given advice (111/1018 [10.9%] with advice *v* 113/1018 [11.1%] without advice; RR 1.00, 95% CI 0.77 to 1.30).[81] **High fibre diets:** We found one systematic review and no additional RCTs.[80] The systematic review (search date 1994) included one RCT which examined the effects of a high fibre diet on coronary events and mortality. The RCT (2033 men, < 70 years old, recovering from myocardial infarction) compared advice to reduce fat, advice to increase oily fish intake, and advice to increase fibre intake.[81] The RCT found no significant difference in all cause or cardiac mortality between those advised to increase fibre intake and those who were not advised to increase fibre intake (all cause mortality: 123/1017 [12.1%] with fibre advice *v* 101/1016 [9.9%] without fibre advice; RR 1.27, 95% CI 0.99 to 1.65; cardiac mortality: 109/1017 [10.7%] with fibre advice *v* 85/1016 [8.4%] without fibre advice; RR 1.23, 95% CI 0.97 to 1.57).[81] **High fish diets:** We found one systematic review[81] and two additional RCTs.[67,82] The systematic review (search date 1994) identified one RCT which compared the effects of advice to increase fish in the diet on coronary events and mortality. The RCT (2033 men, < 70 years old, recovering from myocardial infarction) compared advice to reduce fat, advice to increase oily fish intake, and advice to increase fibre intake.[81] The RCT found no significant difference in cardiac mortality between advice to increase fish intake, though found that advice to increase fish intake reduced all cause mortality compared with no advice to increase fish intake (all cause mortality: 94/1015 [9.3%] with fish advice *v* 130/1018 [12.8%] without fish advice; RR 0.71, 95% CI 0.54 to 0.93; cardiac mortality: 78/1015 [7.7%] with fish advice *v* 116/1018 [11.4%] without fish advice; RR 0.84, 95% CI 0.66 to 1.07).[81] The first additional RCT (3114 men with angina) compared advice to eat two or more portions of oily fish or to take three fish oil capsules daily; advice to eat more fruit, vegetables, and oats; advice to do both; or no dietary advice.[82] It found that advice to have a high fish diet did not reduce all cause mortality compared with no advice after 3–9 years. The group given fish advice had a higher risk of cardiac death (RR 1.26, 95% CI 1.00 to 1.58) and sudden cardiac death (RR 1.54, 95% CI 1.06 to 2.23) compared with no advice, which was largely because of events in people given fish oil capsules.[82] The second additional RCT (11 324 people who had survived a recent myocardial infarction) compared 1 g daily of n-3 polyunsaturated fatty acids (fish oil) supplement versus vitamin E supplements versus fish oil plus vitamin E supplements versus placebo. The RCT found that supplementation with fish oil (2836 people) reduced all cause mortality over 3.5 years (RR 0.86, 95% CI 0.76 to 0.97) compared with no supplements.[67] **Mediterranean diet:** We found no systematic review. We found one RCT (2 publications; 605 people with a recent myocardial infarction) which compared advice to eat a Mediterranean diet (more bread, fruit and vegetables, fish, and less meat, and to replace butter and cream with rapeseed margarine) versus Western type diet.[83,84] Adherence to the Mediterranean diet was good during follow up. The RCT found that a Mediterranean diet significantly reduced the combined outcome of cardiac death and non-fatal myocardial infarction and all cause mortality compared with a Western type diet after 46 months (combined outcome: RR 0.28, 95% CI 0.15 to 0.53; total mortality: RR 0.44, 95% CI 0.21 to 0.94).[84]

Harms:

No major adverse effects of dietary advice have been reported, but very high doses of fish oil may increase the risk of bleeding.

Comment:

Effect on cholesterol: See changing behaviour, p 97.

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Secondary prevention of ischaemic cardiac events

OPTION PSYCHOLOGICAL AND STRESS MANAGEMENT New

One systematic review and two subsequent RCTs provided limited evidence that psychological treatment improved symptoms and reduced the risk of serious cardiac events compared with usual care in people with coronary artery disease.

Benefits: **Psychological and stress management versus usual care:** We found one systematic review[85] and two subsequent RCTs.[86,87] The systematic review (search date not reported, 23 RCTs, 3180 people with coronary artery disease) compared a diverse range of psychosocial treatments versus usual treatment.[85] Compared with control interventions, psychosocial interventions significantly reduced mortality and non-fatal events in the first 2 years after myocardial infarction (mortality: 12 RCTs, OR survival 1.70, 95% CI 1.09 to 2.64; non-fatal events: OR for no events 1.84, 95% CI 1.12 to 2.99).[85] The first subsequent RCT (65 people with recent acute myocardial infarction) compared standard care versus a brief in-hospital intervention to alter illness perception, consisting of three 30–40 minute interviews with a psychologist.[86] In these interviews, participants' worries were discussed; participants' causal models of coronary heart disease were discussed and challenged; implications for lifestyle were discussed, and a staged self management plan established and reviewed. The RCT found that the in-hospital intervention significantly reduced angina compared with standard care at 3 months (self report of angina: 14.3% with intervention *v* 39.3% with standard care; $P < 0.05$). However, it was not clear whether this difference was owing to altered perception of symptoms or because of different rates of ischaemia.[86] The second subsequent RCT (2481 people within 1 month of myocardial infarction) compared treatment of depression and low perceived social support with cognitive behaviour therapy (6 months of individual and group sessions), supplemented with a selective serotonin reuptake inhibitor antidepressant when indicated, versus usual medical care.[87] It found significant improvements in psychosocial outcomes with cognitive behaviour therapy and selective serotonin reuptake inhibitor antidepressant compared with usual care (change in Hamilton Rating Scale for Depression score, no further details reported]: –10.7 with intervention *v* –8.4 with usual care; $P < 0.001$). It found no significant difference in event free survival (75.8% with intervention *v* 75.9% with usual care).[87]

Harms: No specific harms were reported.

Comment: The RCTs were generally small, with short follow up, used non-uniform outcome measures, and had other methodological problems. Despite no evidence for effects on cardiovascular morbidity and mortality, most of the RCTs found that psychosocial interventions improved psychosocial outcomes in people with coronary artery disease. One review (search date 2001, 36 RCTs, 12 841 people) found that non-pharmacological psychological interventions (including stress management) reduced non-fatal myocardial infarctions (OR 0.78, 95% CI 0.67 to 0.90) compared with usual medical care, but because of publication bias its conclusion was that there is no strong evidence that psychological interventions (including stress management) affect mortality, cardiac mortality, or revascularisation in patients with coronary artery disease.[88]

OPTION SMOKING CESSATION New

We found no RCTs of the effects of smoking cessation on cardiovascular events in people with coronary heart disease. Observational studies have found that smoking cessation significantly reduced the risk of myocardial infarction and death in people with coronary heart disease.

Benefits: **Smoking cessation versus continuing smoking:** We found no systematic review of controlled trials or RCTs assessing the effects of smoking cessation on coronary morbidity and mortality. One systematic review (search date 2003, 20 prospective studies, 12 603 smokers with coronary artery disease) of prospective observational studies of 2–26 years' follow up (mean 5 years) and with smoking cessation rates of 28–77% (mean 45%) found that smoking cessation led to a significant reduction in mortality and non-fatal myocardial infarction (mortality: RR 0.64, 95% CI 0.58 to 0.71; non-fatal myocardial infarction: RR 0.68, 95% CI 0.57 to 0.82).[89]

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Harms: Two RCTs found no evidence that nicotine replacement using transdermal patches in people with stable coronary heart disease increased cardiovascular events.[90,91]

Comment: None.

QUESTION What are the effects of revascularisation procedures?

OPTION CORONARY ARTERY BYPASS GRAFTING VERSUS MEDICAL TREATMENT ALONE New

One systematic review and one subsequent RCT found that coronary artery bypass grafting reduced revascularisations and angina after 1 year and reduced cardiac and all cause mortality up to 10 years after surgery compared with medical treatment. People with left ventricular dysfunction had a larger absolute reduction in mortality than people with normal ventricular function, though relative benefits were similar. A significant survival benefit was observed in people with left main stem or three vessel disease, but not in people with single or double vessel disease.

Benefits: We found one systematic review[92] and one subsequent RCT,[93] which compared coronary artery bypass grafting (CABG) versus medical treatment. In the systematic review (search date not reported, 7 RCTs, 2649 people with coronary heart disease, mostly male, aged 41–60 years old, 80% with ejection fraction > 50%, 60% with prior myocardial infarction; and 83% with 2 or 3 vessel disease) people assigned to CABG also received medical treatment, and 40% initially assigned to medical treatment underwent CABG in the following 10 years.[92] It found that compared with medical treatment CABG reduced deaths at 5 and 10 years (death at 5 years: RR 0.61, 95% CI 0.48 to 0.77; death at 10 years: RR 0.83, 95% CI 0.70 to 0.98).[92] Most trials did not collect data on recurrent angina or quality of life. The subsequent RCT (people with multivessel disease, stable angina, and preserved ventricular function) compared percutaneous coronary intervention versus CABG versus medical treatment alone.[93] It found that CABG did not significantly improve survival and myocardial infarction free survival after 1 year (survival: 96.0% with CABG *v* 98.5% with medical treatment alone; myocardial infarction free survival: 98% with CABG *v* 97% with medical treatment alone; P reported as not significant). The RCT also found that CABG reduced revascularisations and led to greater elimination of angina compared with medical treatment alone (revascularisations: 0.5% with CABG *v* 8.3% with medical treatment alone; angina elimination: 88% with CABG *v* 46% with medical treatment alone; $P < 0.0001$).[93] **Effects in people with reduced versus normal left ventricular function:** One systematic review (as above, search date not reported, 7 RCTs, 2649 people with coronary heart disease) found that the relative benefits of CABG were similar in people with normal compared with reduced left ventricular function (death: OR 0.61, 95% CI 0.46 to 0.81 if left ventricular function was normal; OR 0.59. 95% CI 0.39 to 0.91 if left ventricular function was reduced).[92] The absolute benefit of CABG was greater in people with a reduced left ventricular function because the baseline risk of death was higher. **Effects in people with different numbers of diseased vessels:** One systematic review (as above, search date not reported, 7 RCTs, 2649 people with coronary heart disease) found that CABG reduced mortality compared with medical treatment in people with single vessel, two vessel, three vessel, and left main stem disease. However, the change in mortality was not significant for people with single vessel and two vessel disease. This may have been because the number of deaths was small (mortality: RR with single vessel disease 0.54, 95% CI 0.22 to 1.33; with two vessel disease 0.84, 95% CI 0.54 to 1.32; with three vessel disease 0.58, 95% CI 0.42 to 0.80; with left main stem disease 0.32, 95% CI 0.15 to 0.70).[92] **Effects in asymptomatic people:** We found no systematic review or RCTs which compared CABG versus medical treatment in asymptomatic people (see comment below).

Harms: In the systematic review, of the 1240 people who had CABG, 40 (3.2%) died and 88 (7.1%) had non-fatal myocardial infarction within 30 days of the procedure. At 1 year, the estimated incidence of death or myocardial infarction was significantly higher with CABG compared with medical treatment (11.6% with CABG *v* 8% with medical treatment; RR 1.45, 95% CI 1.18 to 2.03).[92] The diagnosis of myocardial infarction after CABG is difficult, and true incidence may be higher.

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Comment: The results of the systematic review may not be easily generalised to current practice. People were aged 65 years or younger, but more than 50% of CABG procedures are now performed on people over 65 years of age. In addition, almost all were male and high risk people, such as those with severe angina and left main coronary artery stenosis, were under-represented. Internal thoracic artery grafts were used in fewer than 5% of people. Lipid lowering agents (particularly statins) and aspirin were used infrequently (aspirin used in 3% of people at enrolment). Only about 50% of people were taking beta–blockers. The systematic review may underestimate the real benefits of CABG in comparison with medical treatment alone because medical and surgical treatment for coronary artery disease were not mutually exclusive; by 5 years, 25% of people receiving medical treatment had undergone CABG surgery and by 10 years, 41% had undergone CABG surgery. The underestimate of effect would be greatest among people at high risk. People with previous CABG have not been studied in RCTs, although they now represent a growing proportion of those undergoing CABG.[92] **Effects in asymptomatic people:** We found no systematic review and one RCT. The RCT (558 people with asymptomatic ischaemia identified by exercise test or ambulatory electrocardiogram) compared CABG or percutaneous transluminal angioplasty versus symptom guided treatment versus electrocardiogram and symptom guided treatment and found that a revascularisation strategy versus medical treatment alone reduced death or myocardial infarction at 2 years (death or myocardial infarction: AR: 4.7% with revascularisation *v* 8.8% with symptom guided treatment *v* 12.1% with symptom plus electrocardiogram guided treatment; $P < 0.04$).[94]

OPTION CORONARY ARTERY BYPASS GRAFTING VERSUS PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY WITH OR WITHOUT STENTING FOR MULTIVESSEL DISEASE

New

One systematic review found no significant difference in mortality or myocardial infarction between percutaneous transluminal angioplasty (with or without stenting) and coronary artery bypass grafting after 3 years. However, percutaneous transluminal angioplasty (with or without stenting) led to a higher rate of repeat revascularisation and recurrent angina. The review lacked power to detect less than a 20–30% relative difference in mortality.

Benefits: We found one systematic review and no additional RCTs.[95] The review (search date 2001, 8 RCTs, 5066 people, mainly men with high prevalence of hypertension and angina) compared coronary artery bypass grafting (CABG) with percutaneous transluminal angioplasty ([PTA] with or without stenting). It found no significant differences in survival or myocardial infarction at 3 years (death: ARR +1.1%, 95% CI –0.1% to +2.3%; $P = 0.08$; myocardial infarction: ARI +1.2%, 95% CI –1.8% to +4.2%; $P = 0.42$). It found that PTA (with or without stenting) significantly increased revascularisations and angina symptoms at 3 years (revascularisation: ARI 34%, 95% CI 28% to 40%; $P < 0.001$; angina: ARI 9.7%, 95% CI 4.6% to 15.0%; $P < 0.001$).[95]

Harms: See harms under percutaneous transluminal angioplasty versus medical treatment, p 26. CABG is more invasive than PTA, but PTA is associated with a greater need for repeat procedures.

Comment: Although no significant differences in death or myocardial infarction were observed in the systematic review, the trials enrolled people at relatively low risk of cardiac events. Fewer than 20% of people had left ventricular dysfunction, almost 70% had one or two vessel disease, and observed mortality was only 2.6% for the first year and 1.1% for the second year. People enrolled in the largest trial more closely approximated moderate risk people, owing to its inclusion of a high proportion of people with diabetes mellitus.[96] Even in that trial, nearly 60% of people had two vessel coronary artery disease. The total number of people enrolled in the trials so far is not adequate to show anything less than a 20–30% difference in mortality between PTA and CABG. A subgroup analysis of people with diabetes found that CABG reduced all cause mortality at 4 years, although this effect was not significant at 6.5 years (at 4 years: ARR 8.6%, 95% CI 2.2% to 15.0%; $P < 0.01$; at 6.5 years: ARR +3.9%, 95% CI –17.0% to +25.0%; $P = 0.71$).[95]

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OPTION CORONARY PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY VERSUS MEDICAL TREATMENT ALONE New

One systematic review found no significant difference between coronary percutaneous transluminal angioplasty and medical treatment in survival. However, percutaneous transluminal angioplasty improved physical functioning and general health and vitality after 1 year and reduced angina severity in those with severe or moderate angina compared with medical treatment alone. The review found an increase in subsequent coronary artery bypass grafting with percutaneous transluminal angioplasty. One RCT in elderly people found that percutaneous transluminal angioplasty reduced anginal symptoms and adverse cardiac events, but not mortality or non-fatal myocardial infarction.

Benefits: **Coronary percutaneous transluminal angioplasty versus medical treatment alone:** We found one systematic review (search date 1998, 6 RCTs, 1904 people with stable coronary artery disease), which compared coronary percutaneous transluminal angioplasty (PTA) versus medical treatment alone.[97] Follow up varied from 6 months to 57 months. It found that compared with medical treatment, PTA alone reduced angina, but increased subsequent coronary artery bypass grafting (CABG) (angina: RR 0.70, 95% CI 0.50 to 0.98; CABG: RR 1.59, 95% CI 1.09 to 2.32). It found higher mortality and myocardial infarction with PTA compared with medical treatment alone but the difference was not significant (death: RR 1.32, 95% CI 0.65 to 2.70; myocardial infarction: RR 1.42, 95% CI 0.90 to 2.25). The review found significant heterogeneity between trials. The largest RCT identified by the review (1018 people) found that PTA compared with medical treatment improved physical functioning, vitality, and general health at 1 year (proportion of people rating their health "much improved": 33% of people treated with PTA *v* 22% of people treated with medical treatment alone; P = 0.008), but found no significant difference at 3 years.[98] The improvements were related to breathlessness, angina, and treadmill tolerance. High transfer (27%) from the medical to PTA group may partly explain the lack of difference between groups at 3 years. Long term follow up of the RCT found that PTA significantly reduced future revascularisations, improved angina but had no effect on death or myocardial infarction at 7 years (revascularisations: 27.2% with PTA *v* 35.4% with medical treatment; P value not reported; angina: 19.4% with PTA *v* 35.9% with medical treatment; ARR 16.5%, 95% CI 11.0% to 21.9%, P value not reported; death or myocardial infarction: 14.5% with PTA *v* 12.3% with medical treatment; ARI 2.3%, 95% CI –2.0% to +6.4%).[99] **Effects in elderly people:** We found no systematic review but found one RCT. The RCT (305 people aged > 75 years with chronic refractory angina) compared PTA versus medical treatment alone.[100] It found that PTA reduced all adverse cardiac events and decreased anginal severity compared with medical treatment, but had no significant effect on deaths or non-fatal myocardial infarctions after 6 months (adverse cardiac events, AR: 19% with PTA *v* 49% with medical treatment; P < 0.0001; change in angina class: –2.0 with PTA *v* –1.6 with medical treatment; P < 0.0001; deaths, AR: 8.5% with PTA *v* 4.1% with medical treatment; P = 0.15; non-fatal infarctions, AR: 7.8% with PTA *v* 11.5% with medical treatment, P = 0.46). **Effects in people with different angina severity:** We found one systematic review (as above, search date 1998, 1 RCT, 1904 people with stable coronary artery disease).[97] The RCT included in the systematic review found that antianginal benefit from PTA was limited to people with moderate to severe (grade 2 or worse) angina (20% lower incidence of angina and 1 minute longer treadmill exercise times compared with medical treatment).[101] People with mild symptoms at enrolment derived no significant improvement in symptoms.

Harms: Some RCTs included in the systematic review reported complications of PTA. In multiple RCTs, procedure related rates of CABG were 2–3% and myocardial infarction were 3–5%.[101,102] In one RCT, the higher mortality or rate of myocardial infarction with PTA was attributable to one death and seven procedure related myocardial infarctions.[100] In one RCT, after 6 months the PTA group had higher rates of CABG surgery (7% with PTA *v* 0% with medical treatment alone) and non-protocol PTA (15.2% *v* 10.3%).[101]

Comment: One RCT (people with multivessel disease, stable angina, and preserved ventricular function) compared percutaneous coronary intervention (205 people), CABG (203 people), and medical treatment alone (203 people).[93] After 1 year, there were no

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significant differences for survival (95.6% with PCI *v* 98.5% with medical treatment alone) or survival free of myocardial infarction (92% *v* 97%), and while the PCI group had more revascularisations (13.3% *v* 8.3%; P value not reported), they also had more angina elimination (79% *v* 46%; P < 0.0001).[93] PCI procedures included stenting, lasers, and atherectomy and were not limited to PTA. The findings that PTA improves anginal symptoms but does not reduce death or myocardial infarction in people with stable angina could be because of the risk of peri-procedural complications and the fact that most PTAs are performed for single vessel disease.

OPTION INTRACORONARY STENTS VERSUS CORONARY PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY ALONE

New

One systematic review found no significant difference between routine stenting and standard percutaneous angioplasty in mortality rates, risk of myocardial infarction or risk of future coronary artery bypass grafting. However it found that stenting reduced rates of restenosis and future percutaneous transluminal angioplasty. One subsequent RCT found that stents increased event free survival but not mortality after 5 years compared with percutaneous transluminal angioplasty. One systematic review found that stenting significantly reduced cardiac events, restenosis, and revascularisation compared with percutaneous transluminal angioplasty in small (< 3 mm) coronary arteries. However, a subsequent RCT found similar rates of restenosis and cardiac events following either treatment in small coronary arteries. One RCT found that stents reduced cardiac events after 6 months compared with percutaneous transluminal angioplasty in saphenous vein graft lesions in people with prior coronary artery bypass grafting. Three RCTs found that stents reduced restenosis and improved angina in people with total occlusions. There is conflicting evidence from two RCTs about effects of stents compared with percutaneous transluminal angioplasty in people with stenosis after initial percutaneous transluminal angioplasty on further restenosis and cardiac events.

Benefits:

Stenting versus percutaneous transluminal angioplasty: We found one systematic review[103] and one subsequent RCT.[104] The systematic review (search date 2002, 29 RCTs, 9918 people) compared routine stenting with standard percutaneous transluminal angioplasty (PTA; which included provisional stenting for acute complications or suboptimal results with PTA alone).[103] It found no difference between routine stenting and standard PTA in risk of death or myocardial infarction or future coronary artery bypass grafting (death or myocardial infarction: OR 0.90, 95% CI 0.72 to 1.11; CABG: OR 1.01, CI 0.79 to 1.31). It also found that routine stenting reduced the rate of restenosis and repeat PTA compared with standard PTA (restenosis: OR 0.52, CI 0.37 to 0.69; repeat PTA: OR 0.59, CI 0.50 to 0.68).[103] The subsequent RCT (120 people with angina, ischaemia, or both) compared stenting with PTA for isolated stenosis of the proximal left anterior descending artery. It found that stents increased event free survival (free from myocardial infarction, cerebrovascular accident, and target lesion revascularisation) after 5 years compared with PTA, but had no significant effect on mortality (event free survival: 80% with stents *v* 53% with PTA, OR 0.29, 95% CI 0.13 to 0.69; P = 0.0034; mortality: 7% with stents *v* 17% with PTA, OR 0.36, 95% CI 0.10 to 1.21; P = 0.098).[104] **In small (< 3 mm) coronary arteries:** We found one systematic review[105] and one subsequent RCT[106] comparing stents with PTA specifically in small (< 3 mm) coronary arteries. The review (search date 2003, 11 RCTs, 3541 people) found that stenting reduced rate of restenosis, cardiac events, and repeat target vessel revascularisation compared with PTA (restenosis: 25.8% with stents *v* 34.2% with PTA, RR 0.77, 95% CI 0.65 to 0.92; P = 0.003; cardiac events: 15.0% with stents *v* 21.8% with PTA, RR 0.70, 95% CI 0.57 to 0.87; P = 0.002; revascularisation: 12.5% with stents *v* 17.0% with PTA, RR 0.75, 95% CI 0.61 to 0.91; P = 0.004).[105] The subsequent RCT (496 people) found similar rates of angiographic restenosis at 6 months and major cardiac events at 12 months with stenting and PTA of small vessels (restenosis at 6 months: 21% with stents *v* 25% with PTA; P reported as not significant, cardiac events at 12 months: no further data reported). Twenty-nine per cent of people randomised to PTA crossed over to stenting in this RCT.[106] **In saphenous vein graft lesions in people with prior coronary artery bypass grafting:** We found no systematic review and one RCT.[107] The RCT (220 people) compared stents with PTA alone for stenosed saphenous vein grafts. It found no significant difference in rates of restenosis with stenting

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compared with PTA after 6 months but found that stents reduced cardiac events (death, myocardial infarction, CABG, or repeat PTA) after 6 months (restenosis: 37% with stents *v* 46% with PTA alone; P = 0.24; cardiac events: 27% with stents *v* 42% with PTA alone; P = 0.03).[107] **In people with total occlusions:** We found no systematic review and three RCTs (four publications) that compared stents with PTA alone in people with chronic totally occluded coronary arteries.[108–111] The first RCT (119 people) found that stent reduced angina, angiographic restenosis, and repeat procedures compared with PTA alone at 6 months (angina free: 57% with stents *v* 24% with PTA alone, P < 0.001; > 50% stenosis on follow up angiography: 32% with stents *v* 74% with PTA alone; P < 0.001; repeat procedures: 22% with stents *v* 42% with PTA alone; P = 0.03).[108] The second RCT (110 people) found that stents reduced restenosis and repeat PTA compared with PTA alone after 4 months (restenosis: 26% with stents *v* 62% with PTA alone; P = 0.01; repeat PTA: 24% with stents *v* 55% with PTA alone; P = 0.05). No deaths or CABG operations occurred in either group. The incidence of myocardial infarction was low in both groups (0% with stents *v* 2% with PTA alone; P > 0.05).[109] The third RCT (110 people) found that stents reduced restenosis and repeat procedures after 9 months compared with PTA alone (restenosis: 32% with stents *v* 68% with PTA alone; P < 0.001; repeat procedures: 5% with stents *v* 22% with PTA alone; P = 0.04).[110] Long term follow up found that stenting reduced cardiac events (cardiac death, myocardial infarction, or target lesion revascularisation) and reduced survival free from revascularisation compared with PTA alone at 6 years (cardiac events: 60.4% with stents *v* 76.1% with PTA; P = 0.056; survival free from revascularisation: 65.5% with stents *v* 85.1% with PTA; P = 0.017).[111] **For treatment of restenosis after initial percutaneous transluminal angioplasty:** We found no systematic review and two RCTs which compared coronary stent versus PTA alone for treatment of restenosis.[112,113] The first RCT (383 people) found that stents reduced restenosis and repeat procedures, and increased survival free of myocardial infarction and repeat revascularisation compared with PTA alone after 6 months (restenosis: 18% with stents *v* 32% with PTA alone; P = 0.03; repeat procedures: 10% with stents *v* 27% with PTA alone, P = 0.001; survival free of myocardial infarction or repeat revascularisation: 84% with stent *v* 72% with PTA alone; P = 0.04).[112] The second RCT (450 people) found that stents and PTA had similar outcomes at 1 year (restenosis: 38% with stents *v* 39% with PTA; P reported as not significant; cardiac events: 77% with stents *v* 71% with PTA; P = 0.19).[113] It also found that when treated artery luminal diameter was greater than 3 mm, people treated with stenting had less restenosis and greater event free survival (rate of restenosis: 27% with stents *v* 49% with PTA alone; P = 0.007; event free survival: 84% with stents *v* 62% with PTA alone; P = 0.002).[113]

Harms: The risk of stent thrombosis is less than 1%.[114–116] Haemorrhage (particularly femoral artery haemorrhage) was more frequent after stenting than PTA alone,[117] but occurred in less than 3% after stenting when antiplatelet drugs were used without long term anticoagulants.

Comment: Significant differences in survival were not consistently seen between stents and PTA. The available data are limited by the low numbers of deaths in the trials and the fact that potential differences may be masked by crossover from PTA to stenting after complications (such as dissection) or suboptimal dilation immediately after PTA.

GLOSSARY

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. Therapeutic anticoagulation often aims to achieve an INR value of 2.0–3.5.

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Secondary prevention of ischaemic cardiac events

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TABLE 1 **Effects of different antioxidant vitamins on various cardiac outcomes (see text, p 20).**[67–76]

Ref	Intervention	Study population	Results	Notes
Vitamin C				No studies found that met our inclusion criteria
Vitamin E				
68	Vitamin E 400 IU/day *v* placebo	48 people with stable angina.	Angina improved in more people in the vitamin E group (5/18 with vitamin E *v* 3/18 with placebo; P value not reported).	This study had a short (9 week) follow up
69	Vitamin E 1600 IU/day *v* placebo	52 people with stable angina plus previous MI.	No significant difference in CV events between groups (2/48 with vitamin E *v* 2/48 with placebo; P > 0.05).	
70	High dose vitamin E 400 or 800 IU/day	2002 people with ischaemic heart disease.	Vitamin E reduced non-fatal CHD events (RR 0.23, 95% CI 0.11 to 0.47). Vitamin E non-significantly increased coronary death (RR 1.18, 95% CI 0.62 to 2.27).	
71,72	Vitamin E 50 IU/day *v* beta carotene supplements *v* both *v* placebo	Finnish smokers, aged 50–69 years.	In people with previous MI (n = 1862) there was no significant difference in CV events (RR 0.90, 95% CI 0.67 to 1.22) or cardiac mortality (RR 1.33, 95% CI 0.86 to 2.05).[71] In people with mild angina (n = 1795) there was no significant difference in CV events (RR 0.95, 95% CI 0.68 to 1.33) or cardiac mortality (RR 1.08, 95% CI 0.68 to 1.72).[72]	
67	Vitamin E 300 mg/day *v* 1 g/day n-3 polyunsaturated fat *v* both *v* placebo	11 324 people who had survived a recent MI.	Vitamin E increased all cause mortality (RR 1.16, 1.03 to 1.31).	
Beta Carotene				
71,72	50 IU/day vitamin E *v* beta carotene supplements *v* both *v* placebo	Finnish smokers, aged 50–69 years.	In people with previous MI, there was no significant difference between beta-carotene and placebo in CV events (RR 1.11, 95% CI 0.84 to 1.48), but an increase in cardiac mortality (RR 1.75, 95% CI 1.16 to 2.64).[71] In people with mild angina, there was no significant effect of supplementation on CV events or cardiac mortality (CV events: RR 1.08, 95% CI 0.78 to 1.50, cardiac mortality: 1.18, 95% CI 0.74 to 1.87).[72]	
Antioxidant combinations				
73	Beta carotene 60 000 IU/day, vitamin C 1000 mg/day, tocopherol 1400 IU/day *v* no vitamin supplementation	255 people, ≥ 50% stenosis, successful angioplasty, 70% men.	MI: 1 event with vitamins *v* 0 events with placebo (P value not reported).	

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74	Vitamin E 800 IU/day, vitamin C 1000 mg/day, natural beta carotene 25 mg, selenium 100 mg/day *v* no vitamin supplementation	160 people with coronary disease; > 3 coronary stenoses of > 30% or 1 coronary stenoses of > 50%; and low HDL and high triglyceride levels.	No significant difference between vitamin and placebo groups in CV events (21% with vitamins *v* 24% with placebo; P > 0.05).
75	Vitamin E 400 IU/day, vitamin C 500 mg/day *v* conjugated equine estrogens	423 postmenopausal women with ≥ 1 coronary artery with 15–75% stenosis.	No significant difference between groups in cardiac mortality (4.7% with vitamins *v* 1.9% with placebo; P = 0.17).[75]
Multivitamins			
76	Folic acid 1 mg/day, vitamin B_{12} 400 µg/day, pyridoxine 10 mg/day	206 people with successful coronary angioplasty of ≥ 1 artery with > 50% stenosis.	Significant reduction in cardiac events with vitamins (RR 0.48, 95% CI 0.25 to 0.94). No significant difference in cardiac mortality (1.0% with vitamins *v* 2.1% with placebo; P > 0.2).[76]

CHD, coronary heart disease; CV, cardiovascular; HDL, high density lipoprotein; MI, myocardial infarction; Ref, reference.

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Stroke management

Search date January 2005

Elizabeth Warburton

QUESTIONS

INTERVENTIONS

SPECIALISED CARE IN STROKE
Beneficial
Specialised care (specialist stroke rehabilitation) 3

MEDICAL TREATMENT IN ACUTE ISCHAEMIC STROKE
Beneficial
Aspirin 4

Trade off between benefits and harms
Systemic anticoagulation (unfractionated heparin, low molecular weight heparin, heparinoids, oral anticoagulants, or specific thrombin inhibitors) 6
Thrombolysis (increased overall mortality and fatal haemorrhages but reduced dependency in survivors; beneficial effects on dependency do not extend to streptokinase) 6

Unlikely to be beneficial
Neuroprotective agents (calcium channel antagonists, citicoline, gamma-aminobutyric acid agonists, glycine antagonists, lubeluzole, magnesium, N-methyl-D-aspartate antagonists, tirilazad) 8

Likely to be ineffective or harmful
Acute reduction in blood pressure 5

SURGERY: INTRACEREBRAL HAEMATOMA
Unknown effectiveness
Evacuation 10

To be covered in future updates
Early supported discharge from hospital and other issues pertaining to stroke service organisation
Other treatments for acute ischaemic stroke (corticosteroids, fibrinogen depleting agent, glycerol, haemodilution techniques, mannitol)
Preventing of deep venous thrombosis/pulmonary embolism in people with stroke using aspirin or compression stockings

See glossary G

Key Messages

Specialised care in stroke

- **Specialised care (specialist stroke rehabilitation)** One systematic review found that specialist stroke rehabilitation reduced death or dependency after a median follow up of 1 year compared with conventional (less specialised) care. Prospective observational data suggest that these findings may be reproducible in routine clinical settings. A second systematic review of one RCT provided insufficient evidence to compare care based on in-hospital care pathways versus standard care. One small subsequent pilot study found that intensive monitoring reduced mortality at 3 months compared with standard care. It found no significant difference between intensive monitoring and usual stroke unit care in rates of poor outcome at 3 months but may not have been large enough to detect clinically important differences in function.

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Stroke management

Medical treatment in acute ischaemic stroke

- **Aspirin** One systematic review in people with ischaemic stroke confirmed by computerised tomography scan found that aspirin taken within 48 hours of stroke onset reduced death or dependency at 6 months and increased the proportion of people making a complete recovery compared with placebo. Another systematic review found no significant difference between aspirin and systemic anticoagulants (unfractionated and low molecular weight heparin) taken within 48 hours of stroke onset in death or dependency at 3–6 months and found that the risk of symptomatic intracranial haemorrhage or extracranial haemorrhage was lower with aspirin than systemic anticoagulants.
- **Systemic anticoagulation (unfractionated heparin, low molecular weight heparin, heparinoids, oral anticoagulants, or specific thrombin inhibitors)** Two systematic reviews comparing systemic anticoagulants (unfractionated heparin, low molecular weight heparin, heparinoids, oral anticoagulants, or specific thrombin inhibitors) versus control (placebo or no treatment) or versus aspirin found no significant difference in death or dependency after 3–6 months. Both reviews found that systemic anticoagulation reduced the risk of symptomatic deep venous thrombosis in people with ischaemic stroke compared with control (placebo or no treatment) or aspirin. However, systemic anticoagulants increased the risk of intracranial haemorrhage or extracranial haemorrhage.
- **Thrombolysis (increased overall mortality and fatal haemorrhages but reduced dependency in survivors; beneficial effects on dependency do not extend to streptokinase)** One systematic review in people with confirmed ischaemic stroke found that thrombolysis reduced the risk of the composite outcome of death or dependency after 1–6 months compared with placebo. However, thrombolysis increased the risk of death from intracranial haemorrhage measured in the first 7–10 days and risk of death after 1–6 months. The excess in mortality was offset by fewer people being alive but dependent 6 months after stroke onset, and the net effect was a reduction in people who were either dead or dependent. Systematic reviews that pooled results for specific thrombolytic agents found that benefits and harms of recombinant tissue plasminogen activator were similar to the overall results. However, streptokinase increased mortality compared with placebo, and this harm was not offset by reduced dependency in survivors. Results of the reviews may not extrapolate to people with the most mild or most severe strokes.
- **Neuroprotective agents (calcium channel antagonists, citicoline, gamma-aminobutyric acid agonists, glycine antagonists, lubeluzole, magnesium, N-methyl-D-aspartate antagonists, tirilazad)** RCTs found no evidence that calcium channel antagonists, citicoline, lubeluzole, gamma-aminobutyric acid agonists, tirilazad, glycine antagonists, magnesium, antineutrophil inhibitory factor, or N-methyl-D-aspartate antagonists improved clinical outcomes compared with placebo. One systematic review found that lubeluzole increased the risk of having Q-T prolongation to more than 450 ms on electrocardiography compared with placebo.
- **Acute reduction in blood pressure** One systematic review in people with acute stroke provided insufficient evidence to assess the effects of lowering blood pressure compared with placebo on clinical outcomes. However, other studies found conflicting results. Two RCTs suggested that people treated with antihypertensive agents may have a worse clinical outcome and increased mortality.

Surgery: intracerebral haematoma

- **Evacuation** We found that the balance between benefits and harms has not been clearly established for the evacuation of supratentorial haematomas. We found no evidence from RCTs on the role of evacuation or ventricular shunting in people with infratentorial haematoma whose consciousness level is declining.

DEFINITION	Stroke is characterised by rapidly developing clinical symptoms and signs of focal, and at times global, loss of cerebral function lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin.[1] Ischaemic stroke is stroke caused by vascular insufficiency (such as cerebrovascular thromboembolism) rather than haemorrhage.
INCIDENCE/ PREVALENCE	Stroke is the third most common cause of death in most developed countries.[2] It is a worldwide problem; about 4.5 million people die from stroke each year. Stroke can occur at any age, but half of all strokes occur in people over 70 years old.[3]
AETIOLOGY/ RISK FACTORS	About 80% of all acute strokes are ischaemic, usually resulting from thrombotic or embolic occlusion of a cerebral artery.[4] The remainder are caused either by intracerebral or subarachnoid haemorrhage.
PROGNOSIS	About 10% of all people with acute ischaemic strokes will die within 30 days of stroke onset.[5] Of those who survive the acute event, about 50% will experience some level of disability after 6 months.[6]

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AIMS OF INTERVENTION	To reduce mortality, impairment, disability, and secondary complications, with minimal adverse effects of treatment.
OUTCOMES	Risk of death or dependency (generally assessed as the proportion of people dead or requiring physical assistance for transfers, mobility, dressing, feeding, or toileting 3–6 months after stroke onset);[6] quality of life.
METHODS	*Clinical Evidence* search and appraisal January 2005.

QUESTION What are the effects of specialised care in people with acute stroke?

OPTION SPECIALISED CARE

One systematic review found that specialist stroke rehabilitation reduced death or dependency after a median follow up of 1 year compared with conventional (less specialised) care. Prospective observational data suggest that these findings may be reproducible in routine clinical settings. A second systematic review of one RCT provided insufficient evidence to compare care based on in-hospital care pathways versus standard care. One small subsequent pilot study found that intensive monitoring reduced mortality at 3 months compared with standard care. It found no significant difference between intensive monitoring and usual stroke unit care in rates of poor outcome at 3 months but may not have been large enough to detect clinically important differences in function.

Benefits: We found one systematic review comparing specialised stroke rehabilitation versus conventional care,[7] a second systematic review comparing an integrated care pathway G versus conventional multidisciplinary care in hospital,[8] and one subsequent RCT[9] comparing intensive monitoring versus conventional stroke unit care (see table A on web extra). The first review (search date 2001) found that stroke rehabilitation units significantly reduced death or dependency at 1 and 5 years compared with alternative, less organised care (see also figure 1, p 14).[7] One RCT included in the review extended follow up to 10 years after stroke and found that care in a combined acute and rehabilitation unit increased the proportion of people able to live at home 10 years after their stroke.[13] The duration of stay was calculated differently for many of the trials in the first review, so heterogeneity among results limits generalisability. However, overall, duration of stay in the stroke unit was significantly shorter than duration of stay in a non-stroke unit setting. The second review (search date 2001) analysed one small RCT and found no significant difference in the combined outcome of death or dependency or death alone at 6 months.[8] However, this analysis, based on a single RCT, may have lacked power to detect clinically important differences in effect. The subsequent RCT was a small pilot study that compared care in a stroke care monitoring unit (intensive monitoring of temperature, oxygen saturation, blood pressure, and electrocardiogram) versus conventional stroke unit care.[9] It found that that monitoring significantly reduced mortality at 3 months but found no significant difference between treatments in rates of "poor outcome". The RCT may not have been sufficiently powered to detect clinically important differences in function.

Harms: No detrimental effects attributable to stroke units were reported.[7–9]

Comment: **Clinical guide:** Although the proportional reduction in death or dependency seems larger with thrombolysis (see thrombolysis, p 6), stroke unit care is applicable to most people with stroke, whereas, owing to the risk of haemorrhage associated with thrombolysis and the need to begin treatment within a short time frame (3 hours if possible), it is applicable only to a small proportion of people with stroke. The systematic review did not provide evidence about which aspects of the multidisciplinary approach led to improved outcome,[7] although one limited retrospective analysis of one of the RCTs found that several factors, including early mobilisation, increased use of oxygen, intravenous saline solutions, and antipyretics, might have been responsible.[14] Most RCTs excluded the most mild and most severe strokes. Since publication of the systematic review,[7] prospective observational data have been collected in one large series of over 14 000 people in 80 Swedish hospitals.[15] In this series, people admitted to stroke units had reduced dependence at 3 months (RRR 6%, 95% CI 1% to 11%).

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Stroke management

Although biases are inherent in such observational data, the findings suggest that the results of the meta-analysis may be reproducible in routine clinical settings. One review examined the characteristics of 11 controlled trials identified by the first systematic review,[7] which found benefit from stroke units.[16] It found that most effective units described similar management in terms of: medical, nursing, and treatment assessment; early mobilisation; treatment of hypoxia; hyperglycaemia; and suspected infection; and coordinated goal directed rehabilitation policies.[16] The authors of the review suggested that these elements might form the benchmark for general stroke unit care and future studies.

QUESTION **What are the effects of medical treatment in people with acute ischaemic stroke?**

OPTION **ASPIRIN**

One systematic review in people with ischaemic stroke confirmed by computerised tomography scan found that aspirin taken within 48 hours of stroke onset reduced death or dependency at 6 months and increased the proportion of people making a complete recovery compared with placebo. Another systematic review found no significant difference between aspirin and systemic anticoagulants (unfractionated and low molecular weight heparin) taken within 48 hours of stroke onset in death or dependency at 3–6 months and found that the risk of symptomatic intracranial haemorrhage or extracranial haemorrhage was lower with aspirin than systemic anticoagulants.

Benefits: **Early use of aspirin:** We found one systematic review (search date 2002, 3 RCTs, 40 850 people with definite or presumed ischaemic stroke), which compared aspirin started within 14 days of the stroke versus placebo.[23] Most (> 98%) of the data in the systematic review came from two large RCTs of aspirin 160–300 mg daily started within 48 hours of stroke onset.[11,12] Most people had an ischaemic stroke confirmed by computerised tomography scan before randomisation, but people who were conscious could be randomised before computerised tomography scan if the stroke was very likely to be ischaemic on clinical grounds. Treatment duration varied from 10 days to 28 days. The review found that aspirin started within the first 48 hours of acute ischaemic stroke significantly reduced death or dependency at 6 months' follow up (3 RCTs, 40 850 people: RR 0.97, 95% CI 0.95 to 0.99 (see figure 1, p 14) and increased the proportion of people making a complete recovery (2 RCTs, 40 541 people: RR 1.04, 95% CI 1.01 to 1.07). We found a second meta-analysis[18] of the two large RCTs.[11,12] It found that aspirin significantly reduced further stroke or death compared with placebo (ARR 0.90%, 95% CI 0.75% to 1.85%; NNT 111, 95% CI 54 to 133).[18] The effect was similar across subgroups (older *v* younger; male *v* female; impaired consciousness or not; atrial fibrillation or not; blood pressure; stroke subtype; timing of computerised tomography scanning). **Long term use of aspirin:** See aspirin under stroke prevention, p 243. **Aspirin versus systemic anticoagulation:** See benefits of systemic anticoagulation, p 6.

Harms: **Early use of aspirin:** Aspirin caused an excess of about two intracranial and four extracranial haemorrhages per 1000 people treated, but these small risks were more than offset by the reductions in death and disability from other causes both in the short term[17] and in the long term.[19] Common adverse effects of aspirin (such as dyspepsia and constipation) were dose related.[20] **Long term use of aspirin:** See aspirin under stroke prevention, p 243. **Aspirin versus systemic anticoagulation:** See harms of systemic anticoagulation, p 6.

Comment: We found no clear evidence that any one dose of aspirin is more effective than any other in the treatment of acute ischaemic stroke. One meta-regression analysis of the dose–response effect of aspirin on stroke found a uniform effect of aspirin in a range of doses of 50–1500 mg daily.[21] People unable to swallow safely after a stroke may be given aspirin as a suppository.

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OPTION BLOOD PRESSURE REDUCTION

One systematic review in people with acute stroke provided insufficient evidence to assess the effects of lowering blood pressure compared with placebo on clinical outcomes. However, other studies found conflicting results. Two RCTs suggested that people treated with antihypertensive agents may have a worse clinical outcome and increased mortality.

Benefits: We found one systematic review[22] and two additional RCTs.[23,24] The review (search date 2000, 5 RCTs, 281 people with acute stroke) compared interventions aimed at lowering blood pressure in people with acute stroke versus placebo (see comment below).[22] Several different antihypertensive agents were used. The RCTs identified by the review collected insufficient clinical data to allow an analysis of the relation between changes in blood pressure and clinical outcome to be carried out. We found two additional placebo controlled RCTs that measured blood pressure as an outcome and suggested that people treated with antihypertensive agents may have a worse clinical outcome and increased mortality.[23,24] The first additional RCT (295 people with acute ischaemic stroke) compared nimodipine (a calcium channel antagonist) versus placebo (see comment below).[23] The RCT was stopped prematurely because of an excess in unfavourable neurological outcomes in the nimodipine treated group. Exploratory analyses confirmed that this negative correlation was related to reductions in mean arterial blood pressure (CI not reported; $P = 0.02$) and diastolic blood pressure ($P = 0.0005$). The second additional RCT (302 people with acute ischaemic stroke) assessed beta-blockers (atenolol or propranolol).[24] It found a non-significant increase in mortality in people taking beta-blockers, and no significant difference in the proportion of people achieving a good outcome.

Harms: The RCTs identified by the first review collected insufficient clinical data to allow an analysis of the relation between changes in blood pressure and clinical outcome to be carried out.[25] Two additional placebo controlled RCTs suggested that people treated with antihypertensive agents may have a worse clinical outcome and increased mortality (see benefits section above).[23,24]

Comment: The authors of the systematic review only included RCTs with the specific aim of reducing blood pressure as they felt that there were methodological differences between studies which aimed to alter blood pressure, and those which may, or not, have measured blood pressure as part of their protocol.[22] The review identified several ongoing RCTs. We identified one additional ongoing RCT not included in the review.[26] Although treatment with the calcium channel antagonist nimodipine was intended for neuroprotection, blood pressure was lower in the treatment group in the trial.[23] Calcium channel antagonists are both antihypertensive agents and neuroprotective agents. They are considered specifically in the neuroprotective agents option, p 8. **Clinical guide:** One long term retrospective analysis of data from a large RCT of people with acute ischaemic stroke[27] and population based studies identified by a systematic review[28] suggest a direct and continuous association between blood pressure and the risk of recurrent stroke. However, acute blood pressure lowering in acute ischaemic stroke may lead to increased cerebral ischaemia. The review (search date not reported, 32 population based observational studies, 10 892 people with primary intracranial haemorrhage, acute ischaemic stroke, or mixed stroke) assessed the relationship between blood pressure on admission to hospital and clinical outcome.[28] Follow up varied considerably among the studies (from 6 days to 6 years). The review found that high mean arterial pressure (defined as 110 mm Hg) and high mean diastolic pressure (defined as 90 mm Hg) were associated with a significant increase in mortality (arterial blood pressure; 6 studies, 1211 people with intracranial haemorrhage: OR 1.61, 95% CI 1.12 to 2.31; diastolic blood pressure; 6 studies, 1655 people: OR 1.71, 95% CI 1.33 to 2.48). The authors suggested, therefore, that modest reduction of blood pressure may improve outcome in people with intracranial haemorrhage.[28]

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Stroke management

OPTION ANTICOAGULATION

Two systematic reviews comparing systemic anticoagulants (unfractionated heparin, low molecular weight heparin, heparinoids, oral anticoagulants, or specific thrombin inhibitors) versus control (placebo or no treatment) or versus aspirin found no significant difference in death or dependency after 3–6 months. Both reviews found that systemic anticoagulation reduced the risk of symptomatic deep venous thrombosis in people with ischaemic stroke compared with control (placebo or no treatment) or aspirin. However, systemic anticoagulants increased the risk of intracranial haemorrhage or extracranial haemorrhage.

Benefits: **Death or dependency:** We found four systematic reviews comparing systemic anticoagulants versus usual care, aspirin, or each other.[29–32] Two reviews found no significant difference in death or dependency between anticoagulants and control (placebo or no treatment) or anticoagulants and aspirin after 3–6 months, the other two reviews provided insufficient evidence to compare anticoagulants versus each other for this outcome (see table B on web extra). **Deep venous thrombosis and pulmonary embolism:** We found four systematic reviews comparing anticoagulants versus control, aspirin, or versus each other (see table B on web extra).[29–32] The reviews found that systemic anticoagulation reduced deep vein thrombosis compared with control or aspirin and that low molecular weight heparins or heparinoids were more effective than unfractionated heparin. Results for pulmonary embolism were not definitive.

Harms: **Systemic anticoagulants versus placebo or no treatment:** The first review found that anticoagulation slightly but significantly increased symptomatic intracranial haemorrhages and major extracranial haemorrhages within 14 days of starting treatment compared with control, with a increased risk as dose increased.[29] **Systemic anticoagulants versus aspirin:** The second review found that anticoagulants (unfractionated and low molecular weight heparin) significantly increased symptomatic intracranial haemorrhage compared with aspirin, with a greater increase with higher dose compared with lower dose anticoagulants.[30] **Unfractionated heparin plus aspirin versus aspirin alone:** The second review found that unfractionated heparin plus aspirin significantly increased symptomatic intracranial haemorrhage and major extracranial haemorrhage compared with aspirin alone.[30] **Low molecular weight heparins or heparinoids versus unfractionated heparin:** In the third and fourth reviews, the number of events was too small to compare the effects of low molecular weight heparins or heparinoids with unfractionated heparin on intracranial or extracranial haemorrhage.[31,32]

Comment: Alternative treatments to prevent deep venous thrombosis and pulmonary embolism after acute ischaemic stroke include aspirin and compression stockings. The evidence relating to these will be reviewed in future *Clinical Evidence* updates.

OPTION THROMBOLYSIS

One systematic review in people with confirmed ischaemic stroke found that thrombolysis reduced the risk of the composite outcome of death or dependency after 1–6 months compared with placebo. However, thrombolysis increased the risk of death from intracranial haemorrhage measured in the first 7–10 days and risk of death after 1–6 months. The excess in mortality was offset by fewer people being alive but dependent 6 months after stroke onset, and the net effect was a reduction in people who were either dead or dependent. Systematic reviews that pooled results for specific thrombolytic agents found that benefits and harms of recombinant tissue plasminogen activator were similar to the overall results. However, streptokinase increased mortality compared with placebo, and this harm was not offset by reduced dependency in survivors. Results of the reviews may not extrapolate to people with the most mild or most severe strokes.

Benefits: We found two systematic reviews.[10,33] **Any thrombolytic:** The first review (search date 1999, 17 RCTs, 5216 highly selected people,[10] people with severe stroke and risk of bleeding excluded) compared intravenous or intra-arterial thrombolysis versus placebo given soon after the onset of stroke. In the review, all trials used computerised

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tomography or magnetic resonance imaging before randomisation to exclude intracranial haemorrhage or other non-stroke disorders. Results for three different thrombolytic agents (streptokinase, urokinase, and recombinant tissue plasminogen activator) were included. Two RCTs administered thrombolysis by the intra-arterial route and the rest used the intravenous route. The review found that any type of thrombolysis significantly reduced the composite risk of death or dependency compared with no thrombolysis at the end of the trials (1–6 months: ARR 4.2%, 95% CI 1.2% to 7.2%; NNT 24, 95% CI 14 to 83) (see figure 1, p 14 and figure 2, p 15).[10] **Recombinant tissue plasminogen activator:** The first review also pooled data separately for trials assessing intravenous recombinant tissue plasminogen activator.[10] It found that recombinant tissue plasminogen activator significantly reduced death or dependency compared with no thrombolysis at the end of the studies (ARR 5.7%, 95% CI 2.0% to 9.4%; RR 0.90, 95% CI 0.84 to 0.96; NNT 18, 95% CI 11 to 50). **Streptokinase:** The first review did not pool data separately for trials assessing streptokinase.[10] However, the second review included the same streptokinase RCTs that were included in the first review (search date not reported, 4 RCTs, 1292 people with acute ischaemic stroke), which found no significant difference between streptokinase and placebo in the proportion of people who were dead or dependent at 3 months (RR 0.99, 95% CI 0.92 to 1.06).[33]

Harms:

Any thrombolytic: In the first systematic review, thrombolysis increased fatal intracranial haemorrhage measured in the first 7–10 days (ARI 4.4%, 95% CI 3.4% to 5.4%; RRI 396%, 95% CI 220% to 668%; NNH 23, 95% CI 19 to 29), and increased the risk of death by the end of follow up (death at 1–6 months: ARI 3.3%, 95% CI 1.2% to 5.4%; RRI 23%, 95% CI 10% to 38%; NNH 30, 95% CI 19 to 83) compared with no thrombolysis.[10] This excess of deaths was offset by fewer people being alive but dependent 6 months after stroke onset. The net effect was a reduction in the proportion of people who were dead or dependent. **Recombinant tissue plasminogen activator:** The first review also pooled data separately for recombinant tissue plasminogen activators.[10] It found that recombinant tissue plasminogen activator significantly increased fatal intracranial haemorrhage at 7–10 days compared with no thrombolysis (ARI 2.9%, 95% CI 1.7% to 4.1%; RRI 259%, 95% CI 102% to 536%; NNH 34, 95% CI 24 to 59).[10] **Streptokinase:** The second review found that streptokinase significantly increased mortality compared with placebo after 3 months (RR 1.46, 95% CI 1.24 to 1.73).[33]

Comment:

Limitations of the evidence: In the first review, there was no significant heterogeneity of treatment effect overall, but heterogeneity of results was noted for the outcomes of death, and death or dependency at final follow up among the eight trials of intravenous recombinant tissue plasminogen activator.[10] Explanations may include the combined use of antithrombotic agents (aspirin or heparin within the first 24 hours of thrombolysis), stroke severity, the presence of early ischaemic changes on computerised tomography scan, and the time from stroke onset to randomisation. Most trials reported outcomes at 3 months; only one trial reported 1 year outcome data.[34] **Clinical guide; timing of thrombolysis:** One systematic review (6 RCTs, 2775 people) assessed outcomes in people receiving recombinant tissue plasminogen activator compared with placebo within 3 hours of stroke onset.[35] It confirmed that the major determinant of benefit is time of administration of the drug from stroke onset, that is the sooner the better.[35] The review suggested there may be benefit beyond 3 hours but further trials are needed. An earlier preliminary pooling of three RCTs (1734 people) suggested that recombinant tissue plasminogen activator given between 3 and 6 hours may reduce death or dependency in some people compared with placebo.[36] **Clinical guide; barriers to delivery of thrombolysis:** In most developed stroke services, the aim is to initiate thrombolysis within the 3 hour time frame to ensure as many people as possible who are eligible receive treatment. Problems over recognition of stroke in the community, and failure to admit people quickly to stroke centres means that most arrive too late to be considered for thrombolysis, although about one in four people who arrive within 3 hours of stroke are suitable for treatment. We found two systematic reviews (search date 2001;[37] search date 2002[38]), which analysed barriers to delivery of thrombolysis[37] and assessed methods to improve efficiency of delivery.[38] The second review (10 observational studies, ≥ 6345 people with acute ischaemic stroke) found that interventions that improved delivery of thrombolysis were: education programmes to raise public

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awareness of stroke symptoms, training programmes for paramedics to improve diagnostic skills and hasten rapid triage to hospital, and reorganisation to streamline patient flows, particularly to brain imaging, once in hospital.[38] **Clinical guide; assessing individual patient risk:** Evidence of benefit of thrombolysis to people over the age of 80 years is limited because of the small numbers in this age group included in trials to date. There is currently no consensus about giving thrombolysis after 3 hours in this age group. Newer magnetic resonance imaging techniques, such as diffusion/perfusion weighted imaging, may be helpful in patient selection, but studies using these techniques have so far been small.[39] One systematic review (search date 1996, 8 studies, number of RCTs and people not reported) found that factors associated with increased haemorrhage risk are age older than 70 years, large cortical infarcts, particularly those with mass effect.[40] **Ongoing research:** Several trials of different thrombolytic regimens are underway.[41]

OPTION NEUROPROTECTIVE AGENTS

RCTs found no evidence that calcium channel antagonists, citicoline, lubeluzole, gamma-aminobutyric acid agonists, tirilazad, glycine antagonists, magnesium, antineutrophil inhibitory factor, or N-methyl-D-aspartate antagonists improved clinical outcomes compared with placebo. One systematic review found that lubeluzole increased the risk of having Q-T prolongation to more than 450 ms on electrocardiography compared with placebo.

Benefits:

Calcium channel antagonists: We found two systematic reviews comparing calcium channel antagonists versus placebo.[25,42] The first review (search date 1999, 28 RCTs, 7521 people with acute ischaemic stroke) found that calcium channel antagonists did not significantly reduce the risk of poor outcome (including death) at the end of the follow up period compared with placebo (ARI of poor outcome +4.9%, 95% CI –2.5% to +7.3%; RRI +4%, 95% CI –2% to +9%).[25] The second review (search date 1999)[42] included one additional RCT (454 people)[43] that was stopped prematurely because of publication of the results of first review.[25] Inclusion of its data did not change the results of the first review. **Citicoline:** We found one systematic review (search date not reported, 4 RCTs, 1652 people with moderate to severe stroke) comparing citicoline given within 24 hours of stroke onset versus placebo.[44] It found that citicoline significantly increased the proportion of people who were completely recovered at 3 months (25% with citicoline *v* 20% with placebo; OR 1.33, 95% CI 1.10 to 1.62, P = 0.0034). However, it found no significant difference in mortality between citicoline and placebo (19% with citicoline *v* 18% with placebo; reported as non-significant, P value not reported). **Gamma-aminobutyric acid agonists:** We found one systematic review (search date not reported, 3 RCTs, 1002 people with acute ischaemic stroke)[45] and two subsequent RCTs.[46,47] The systematic review found no significant difference between piracetam (a gamma-aminobutyric acid agonist) and placebo in the proportion of people dead or dependent at the end of follow up (ARI +0.2%, 95% CI –6.0% to +6.4%; RRI 0%, 95% CI –11% to +9%).[45] Similar results were found in the two subsequent RCTs.[46,47] The first subsequent RCT (1360 people with acute stroke) found no significant difference between clomethiazole (a gamma-aminobutyric acid agonist) and placebo in functional independence (ARR +1.5%, 95% CI –4.0% to +6.6%; RRR +3%, 95% CI –7% to +13%).[46] The second subsequent RCT (1198 people with major acute ischaemic stroke treated within 12 hours) found no significant difference between clomethiazole and placebo in neurological recovery at 3 months (Barthel index ≥ 60: 42/586 [7.1%] with clomethiazole *v* 46/583 [7.9%] with placebo; OR 0.81, 95% CI 0.62 to 1.05).[47] **Glycine antagonists (gavestinel):** We found one systematic review (search date 2001, 8 RCTs, 3751 people).[48] It found no significant difference in death or dependency (OR 1.04, 95% CI 0.91 to 1.18) or in mortality (OR 1.12, 95% CI 0.95 to 1.32) between gavestinel and placebo after 1–3 months. We found two RCTs.[49,50] One RCT (1804 conscious people with limb weakness assessed within 6 hours of stroke onset) found no significant difference between gavestinel and placebo in survival and outcome at 3 months, as measured using the Barthel index (ARR +1.0%, 95% CI –3.5% to +6.0%).[49] The second RCT (1367 people with predefined level of limb weakness and functional independence before stroke) also found no significant difference in survival and outcome at 3 months, measured using the Barthel index (ARI +1.9%, 95% CI –3.8% to +6.4%).[50] **Lubeluzole:** We found one systematic review (search date 2001, 5 RCTs,

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3510 people) that compared lubeluzole (5, 10, or 20 mg/day for 5 days) with placebo.[51] It found no significant difference between any dose of lubeluzole and placebo in death or dependency at the end of follow up (after 4–12 weeks' follow up: AR 54.6% with lubeluzole *v* 53.4% with placebo; ARI +1.2%, 95% CI –2.5% to +6.2%). **Magnesium:** We found no systematic review but found one RCT (2589 people with acute ischaemic stroke) comparing magnesium (16 mmol iv for 15 minutes followed by 65 mmol over 24 hours) versus placebo within 12 hours of stroke onset.[52] It found no significant difference in the combined outcome of death or dependency between magnesium and placebo (OR 0.95, 95% CI 0.80 to 1.13).[52] **N-methyl-D-aspartate antagonists:** We found one systematic review (search date 2001, 10 RCTs, 6317 people).[48] It found no significant difference in death or dependence (presented as a combined outcome) between N-methyl-D-aspartate antagonists and placebo (OR 1.05, 95% CI 0.95 to 1.16). Two RCTs assessing the N-methyl-D-aspartate antagonist selfotel found no significant difference in the proportion of people with a Barthel index over 60, but data were limited as the trials were terminated because of adverse outcomes after only 31% of the total planned patient enrolment.[53] Similarly, an RCT comparing the N-methyl-D-aspartate antagonist aptiganel versus placebo was terminated early because of lack of efficacy and a potential imbalance in mortality.[54] The RCT found a larger proportion of people with favourable outcomes in the placebo group and a non-significant trend favouring placebo in mortality.[54] **Tirilazad:** We found one systematic review (search date 2001, 6 RCTs, 1757 people with acute ischaemic stroke) comparing tirilazad (a steroid derivative) versus placebo.[55] Tirilazad increased death and disability at 3 months' follow up when measured using the expanded Barthel index (OR 1.23, CI 1.01 to 1.51).[55]

Harms:

Calcium channel antagonists: The systematic review found no significant difference in overall adverse effects between calcium channel antagonists and placebo (OR 1.19, 95% CI 0.97 to 1.47), although one RCT identified by the review found that flunarizine significantly increased adverse effects, particularly superficial thrombophlebitis, compared with placebo (OR 3.73, 95% CI 2.21 to 6.29; see comment below).[25] Indirect and limited comparisons of intravenous versus oral administration in the review found no significant difference in adverse events (ARI iv *v* oral: +2.3%, 95% CI –0.9% to +3.7%; RRI +17%, 95% CI –3% to +41%). **Citicoline:** The review found comparable rates of overall adverse effects between citicoline and placebo, although citicoline significantly increased leg oedema, falls, anxiety, depression, and urinary incontinence ($P < 0.05$ for all outcomes).[44] **Gamma-aminobutyric acid agonists:** In the systematic review of piracetam, there was a non-significant increase in death with piracetam compared with placebo, which was no longer apparent after correction for imbalance in stroke severity.[45] The second subsequent RCT (1198 people) found that clomethiazole significantly increased somnolence (50.6% with clomethiazole *v* 12.7% with placebo) and rhinitis (6.3% with clomethiazole *v* 1.9% with placebo; P values not reported) compared with placebo.[47] **Glycine antagonists (gavestinel):** The systematic review did not report on harms.[48] **Lubeluzole:** The systematic review of lubeluzole found that, at any dose, lubeluzole was associated with a significant increase in the risk of having a heart conduction disorder (Q-T prolongation to more than 450 ms on electrocardiography) at the end of follow up (AR: 11.9% with lubeluzole *v* 9.7% with control; ARI 2.2%, 95% CI 0.1% to 4.2%; NNH 45, 95% CI 23 to 1000).[51] Lubeluzole did not significantly increase heart rhythm disorders (atrial fibrillation, ventricular tachycardia or fibrillation, torsade de pointes) at the end of the scheduled follow up (OR 1.28, 95% CI 0.97 to 1.69). **N-methyl-D-aspartate antagonists:** The systematic review did not report on harms.[48] The trials of selfotel were terminated after enrolling 567 people because of greater early mortality in the selfotel groups.[53,54] **Magnesium:** The RCT found similar rates of hypotension, cardiac failure, cardiac conduction block, and flushing between magnesium and placebo (CI not reported for any outcome).[52] **Tirilazad:** The systematic review of tirilazad found an increased risk of injection site phlebitis compared with placebo (ARI 12.2%, 95% CI 8.7% to 15.7%).[55]

Comment:

Calcium channel antagonists: Flunarizine is an antihistamine with calcium channel blocking activity. **Applying the evidence; timing of neuroprotective agents:** We found one systematic review (search date 2001, 6 phase III trials, 5345 people with acute ischaemic stroke), which assessed how long from stroke onset neuroprotective

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Stroke management

drug treatment was initiated.[56] It found that only 6% of trial participants received neuroprotective agents within 3 hours of stroke onset. **Ongoing research:** Systematic reviews are being developed for antioxidants and excitatory amino acid modulators.[57] Several RCTs are ongoing, including one of diazepam (a gamma-aminobutyric acid agonist).[58]

QUESTION **What are the effects of surgical treatment for intracerebral haematomas?**

OPTION **EVACUATION**

We found that the balance between benefits and harms has not been clearly established for the evacuation of supratentorial haematomas. We found no evidence from RCTs on the role of evacuation or ventricular shunting in people with infratentorial haematoma whose consciousness level is declining.

Benefits: **In people with supratentorial haematomas:** We found three systematic reviews.[59–61] Overall, none of the reviews found significant short or long term differences between surgical and medical treatment for death or dependency. The first review (search date 1998)[59] and second review (search date 1997)[60] both identified the same four RCTs comparing surgery (craniotomy in 3 trials and endoscopy in 1 trial) versus best medical treatment in 349 people with primary supratentorial intracerebral haemorrhage. Best medical treatment was poorly defined in the RCTs identified by the reviews but included bed rest, antihypertensives, diuretics, and in one trial, dexamethasone. The second review combined data for craniotomy and endoscopy compared with medical treatment and found no significant difference in death or dependency between groups at 6 months (130/173 [75%] with surgery *v* 125/176 with medical treatment; OR 1.23, 95% CI 0.77 to 1.98). The third review (search date 1999) included several analyses comparing surgery versus best medical treatment.[61] The first analysis included results from seven RCTs (530 people), including three RCTs not included in either of the first two systematic reviews. The overall results are similar to those of the first two reviews, with no significant difference in death or dependency for surgically treated people (OR 1.20, 95% CI 0.83 to 1.74). A further analysis of results from only recent, post-computerised tomography, well constructed, balanced RCTs performed by the third review (5 RCTs, 224 people) also found no significant difference between the two groups (ARR +9.3%, 95% CI −2.6% to +21.2%). **In people with infratentorial haematomas:** We found no systematic review or RCTs that assessed the role of surgical evacuation or ventricular shunting in this population. An RCT is unlikely to be conducted (see comment below).[62]

Harms: **In people with supratentorial haematomas:** The reviews gave no information on adverse effects.[59–61] **In people with infratentorial haematomas:** We found no RCTs.

Comment: **In people with supratentorial haematomas:** Current practice is based on the consensus that people with infratentorial (cerebellar) haematomas whose consciousness level is declining probably benefit from evacuation of the haematoma. The author identified one RCT published after the *Clinical Evidence* search date comparing a policy of "early surgical evacuation" of haematoma versus "initial conservative treatment" in people with spontaneous intracerebral haemorrhage.[63] It suggested that there was no overall benefit from early surgery compared with initial conservative treatment; results will be reported in full in the next issue of *Clinical Evidence*.

GLOSSARY

Integrated care pathway A model of care that includes definition of therapeutic goals and specification of a timed plan designed to promote multidisciplinary care, improve discharge planning, and reduce the duration of hospital stay.

N-methyl-D-aspartate antagonist Glutamate can bind to N-methyl-D-aspartate receptors on cell surfaces. One hypothesis proposed that glutamate released during a stroke can cause further harm to neurones by stimulating the N-methyl-D-aspartate receptors. N-methyl-D-aspartate antagonists block these receptors.

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Substantive changes

Thrombolysis Studies assessing barriers to delivery of thrombolysis[37,38] and evaluating individual patient risk[40] when giving thrombolysis added; categorisation unchanged (tradeoff between benefits and harms).

Neuroprotective agents One RCT added of magnesium[52] and one review added of citicoline;[44] ; categorisation unchanged (unlikely to be beneficial).

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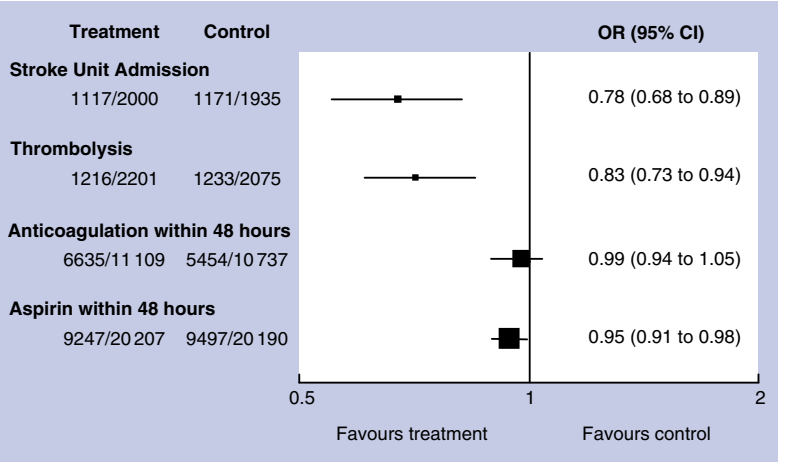

FIGURE 1 **Proportional effects on "death or dependency" at the end of scheduled follow up: results of systematic reviews.[7,10–12] Data refer only to benefits and not to harms (see text, p 4).**

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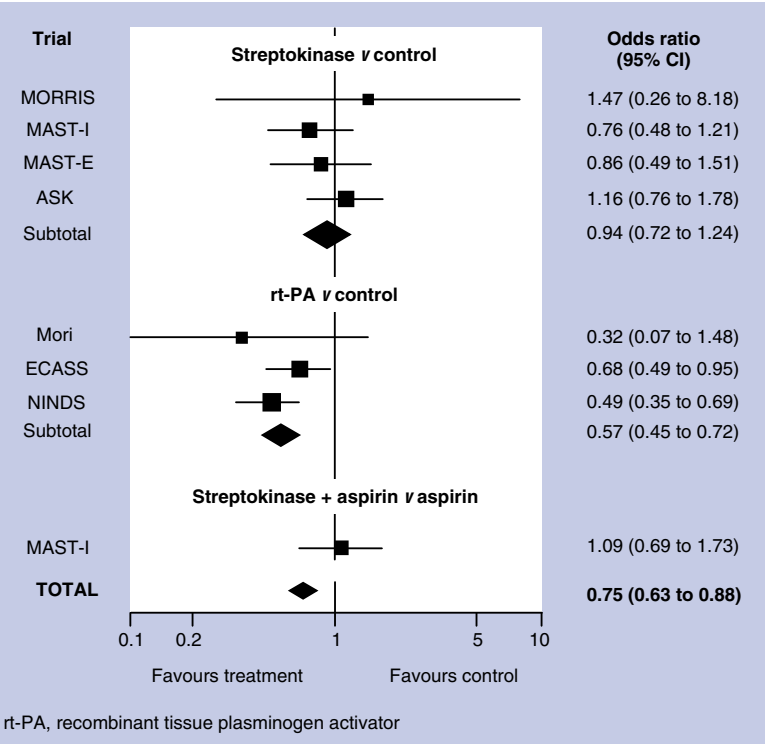

rt-PA, recombinant tissue plasminogen activator

FIGURE 2 **Effect of thrombolysis on death and dependency at end of trial: results of review (see text, p 6). Figure reproduced with permission. Wardlaw JM, Warlow CP, Counsell C. Systematic review of evidence on thrombolytic therapy for acute ischaemic stroke. *Lancet* 1997;350:607–614. © by The Lancet Ltd, 1997.**

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Stroke prevention

Search date September 2004

Gregory YH Lip, Peter Rothwell, and Cathie Sudlow

QUESTIONS

INTERVENTIONS

See glossary

Key Messages

Previous stroke or TIA

- **Antiplatelet treatment** One systematic review found that prolonged antiplatelet treatment reduced the risk of serious vascular events, including stroke, in people with previous stroke or transient ischaemic attack compared with placebo or no antiplatelet treatment.

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- **Blood pressure reduction** One systematic review found that blood pressure lowering treatment reduced stroke, myocardial infarction, and major vascular events (stroke, myocardial infarction, or vascular death) compared with placebo or no treatment in people with a prior stroke or transient ischaemic attack, whether or not they were hypertensive and irrespective of the type of qualifying cerebrovascular event (ischaemic or haemorrhagic).
- **Carotid endarterectomy in people with moderately severe (50–69%) symptomatic carotid artery stenosis** Evidence from a pooled analysis of individual patient data from three RCTs in people with symptomatic carotid artery stenosis found that carotid endarterectomy reduced stroke and death in people with 50–69% carotid stenosis compared with no endarterectomy.
- **Carotid endarterectomy in people with severe (> 70%) symptomatic carotid artery stenosis** Evidence from a pooled analysis of individual patient data from three RCTs in people with symptomatic carotid artery stenosis found that carotid endarterectomy reduced stroke and death compared with no endarterectomy in people with more than 70% carotid stenosis, although no benefit was found in people with near occlusion. Benefit in symptomatic people with more than 70% stenosis was greater than in people with lower grade stenosis.
- **Cholesterol reduction** We found no systematic reviews comparing statins versus placebo which reported results separately for people with previous stroke or transient ischaemic attack. One systematic review found that statins reduced major vascular events, including stroke, compared with placebo or no treatment in various different types of people, including those with prior ischaemic stroke or transient ischaemic attack, irrespective of baseline cholesterol or of the presence or absence of coronary artery disease. We found no systematic reviews comparing non-statin cholesterol lowering treatments versus placebo which reported results separately for people with previous stroke or transient ischaemic attack. One systematic review and three additional RCTs in broader populations found that non-statin cholesterol lowering drug treatments did not reduce stroke compared with placebo or no treatment.
- **Carotid endarterectomy in people with asymptomatic but severe carotid artery stenosis** One systematic review and one subsequent RCT found that carotid endarterectomy reduced perioperative stroke, death, and subsequent ipsilateral stroke in people with asymptomatic but severe stenosis. However, because the risk of stroke without surgery in asymptomatic people is relatively low, the benefit from surgery is small.
- **Alternative antiplatelet regimens to aspirin (no evidence that any regimen is more or less effective than aspirin alone)** Two systematic reviews and one subsequent RCT in people at high risk of vascular events found no good evidence that thienopyridines (ticlopidine or clopidogrel) were superior to aspirin for long term prevention of serious vascular events (stroke, myocardial infarction, or vascular death), but found that clopidogrel was a safe and effective alternative to aspirin. One systematic review in people at high risk of vascular events found that dipyridamole plus aspirin reduced non-fatal stroke compared with aspirin alone, but found no significant difference between treatments in serious vascular events (stroke, myocardial infarction, or vascular death). One systematic review and two subsequent RCTs in people at high risk of stroke found no significant difference between triflusal and aspirin in serious vascular events.
- **Carotid or vertebral percutaneous transluminal angioplasty** RCTs provided insufficient evidence about the effects of carotid or vertebral percutaneous transluminal angioplasty or stenting compared with medical treatment or carotid endarterectomy in people with a recent carotid or vertebral territory transient ischaemic attack or non-disabling ischaemic stroke who have severe stenosis of the ipsilateral carotid or vertebral artery.
- **Different blood pressure lowering regimens (no evidence that any regimen is more or less effective than any other)** We found no RCTs or systematic reviews that compared different blood pressure lowering regimens exclusively in people with a prior stroke or transient ischaemic attack. One systematic review found no significant difference between thiazide diuretics and beta-blockers in death, stroke,

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coronary artery disease, or total cardiovascular events. A second systematic review found that calcium channel blockers reduced stroke compared with angiotensin converting enzyme inhibitors, but the decrease was of borderline significance. It also found that diuretics or beta-blockers reduced stroke compared with angiotensin converting enzyme inhibitors, but the decrease was of borderline significance. Neither of the reviews presented results separately for people with a prior stroke or transient ischaemic attack.

- **Carotid endarterectomy in people with moderate (30–49%) symptomatic carotid artery stenosis** Evidence from a pooled analysis of individual patient data from three RCTs in people with symptomatic carotid artery stenosis found that carotid endarterectomy was of no benefit in people with 30–49% stenosis compared with no endarterectomy.
- **Carotid endarterectomy in people with symptomatic near occlusion of the carotid artery** Three RCTs found no evidence that carotid endarterectomy increased the risk of stroke or death owing to surgery in symptomatic people with near occlusion of the ipsilateral carotid artery.
- **High dose versus low dose aspirin (no additional benefit but may increase harms)** One systematic review and one subsequent RCT in people at high risk of vascular events found that low dose aspirin (75–150 mg/day) was as effective as higher doses for preventing serious vascular events (stroke, myocardial infarction, or vascular death). It also found no significant difference in serious vascular events between doses of 75 mg or more and doses lower than 75 mg. However, the comparison lacked power to detect a clinically important difference. Systematic reviews found no evidence of an association between aspirin dose and risk of intracranial, major extracranial, or gastrointestinal haemorrhage. RCTs found that high dose aspirin (500–1500 mg/day) increased the risk of upper gastrointestinal upset compared with medium dose aspirin (75–325 mg/day).
- **Anticoagulation in people in sinus rhythm** Systematic reviews found no significant difference between oral anticoagulation and placebo or antiplatelet treatment for preventing recurrent stroke after presumed ischaemic stroke in people in normal sinus rhythm. Anticoagulants increased the risk of fatal intracranial and extracranial haemorrhage compared with placebo or no treatment. High intensity anticoagulation increased the risk of intracranial or major bleeding compared with antiplatelet treatment.
- **Carotid endarterectomy in people with less than 30% symptomatic carotid artery stenosis** Evidence from a pooled analysis of individual patient data from three RCTs in people with symptomatic carotid artery stenosis found that carotid endarterectomy did not significantly increase the risk of stroke or death owing to surgery in people with less than 30% carotid stenosis compared with no endarterectomy.

Atrial fibrillation and previous stroke or TIA

- **Oral anticoagulants** One systematic review found that adjusted dose warfarin reduced the risk of stroke compared with control in people with previous stroke or transient ischaemic attack. The best time to begin anticoagulation after an ischaemic stroke is unclear. One systematic review provided insufficient evidence to compare warfarin versus aspirin.
- **Aspirin** One RCT found no significant difference between aspirin and placebo in stroke or death in people with previous stroke or transient ischaemic attack. One systematic review provided insufficient evidence to compare aspirin versus warfarin.

Atrial fibrillation without previous stroke or TIA

- **Aspirin in people with contraindications to anticoagulants** One systematic review found that aspirin reduced the risk of stroke compared with placebo. However, another review found no significant difference. These findings support the use of aspirin in people with atrial fibrillation and contraindications to anticoagulants.

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Stroke prevention

- **Oral anticoagulation** One systematic review found that warfarin reduced fatal and non-fatal ischaemic stroke compared with placebo in people at high risk of stroke, provided that there was a low risk of bleeding and careful monitoring. One overview in people less than 65 years old found no significant difference in the annual stroke rate between warfarin and placebo in people at low risk of stroke. One systematic review found that warfarin reduced the risk of stroke compared with aspirin in people at high risk of stroke. One RCT found no significant difference in stroke between warfarin and the anticoagulant ximelagatran.

DEFINITION	Prevention in this context is the long term management of people with previous stroke or transient ischaemic attack, and of people at high risk of stroke for other reasons such as atrial fibrillation. **Stroke:** See definition under stroke management, p 00. **Transient ischaemic attack:** This is similar to a mild ischaemic stroke, except that symptoms last for less than 24 hours.[1]
INCIDENCE/ PREVALENCE	See incidence/prevalence under stroke management, p 00.
AETIOLOGY/ RISK FACTORS	See aetiology under stroke management, p 00. Risk factors for stroke include previous stroke or transient ischaemic attack, increasing age, hypertension, diabetes, cigarette smoking, and emboli associated with atrial fibrillation, artificial heart valves, or myocardial infarction. The relationship with cholesterol is less clear. Overviews of prospective studies of healthy middle aged people found no association between total cholesterol and overall stroke risk.[2–4] However, two of the overviews found that increased cholesterol increased the risk of ischaemic stroke but reduced the risk of haemorrhagic stroke.[3,4]
PROGNOSIS	People with a history of stroke or transient ischaemic attack are at high risk of all vascular events, such as myocardial infarction, but are at particular risk of subsequent stroke (about 10% in the first year and about 5% each year thereafter); see figure 1, p 30, and figure 1 in secondary prevention of ischaemic cardiac events, p 00.[5–7] People with intermittent atrial fibrillation treated with aspirin should be considered at similar risk of stroke, compared with people with sustained atrial fibrillation treated with aspirin (rate of ischaemic stroke/year: 3.2% with intermittent *v* 3.3% with sustained).[8]
AIMS OF INTERVENTION	To prevent death or disabling stroke, as well as other serious non-fatal outcomes, especially myocardial infarction, with minimal adverse effects from treatment.
OUTCOMES	Stroke, myocardial infarction, mortality, and dependency.
METHODS	*Clinical Evidence* search and appraisal September 2004.

QUESTION What are the effects of preventive interventions in people with previous stroke or transient ischaemic attack?

OPTION BLOOD PRESSURE REDUCTION

Cathie Sudlow

One systematic review found that blood pressure lowering treatment reduced stroke, myocardial infarction, and major vascular events (stroke, myocardial infarction, or vascular death) compared with placebo or no treatment in people with a prior stroke or transient ischaemic attack, whether or not they were hypertensive and irrespective of the type of qualifying cerebrovascular event (ischaemic or haemorrhagic).

Benefits: We found one systematic review (search date not stated, 7 RCTs, 15 527 people with a prior stroke or transient ischaemic attack, followed up for 2–5 years), which compared blood pressure lowering treatment (beta-receptor antagonists, diuretics, and angiotensin converting enzyme [ACE] inhibitors) versus placebo or no treatment.[9] The review found that antihypertensive treatment reduced blood pressure by a mean of 8 mm Hg systolic/4 mm Hg diastolic, and significantly reduced stroke, myocardial infarction (MI), and total vascular events compared with placebo or no treatment, after a mean of 3 years of treatment (stroke: 689/7779 [9.0%] with treatment *v* 888/7748

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[11.5%] with control; OR 0.76, 95% 0.63 to 0.92; myocardial infarction: 244/7729 [3.2%] with treatment *v* 311/7699 [4.0%] with control; OR 0.79, 95% CI 0.63 to 0.98; total vascular events [stroke, MI, or vascular death]: 993/7729 [12.8%] with treatment *v* 1232/7699 [16.0%] with control; OR 0.79, 95% CI 0.66 to 0.95). However, blood pressure lowering treatments did not significantly reduce vascular death or all cause mortality compared with placebo or no treatment (vascular death: OR 0.86, 95% CI 0.70 to 1.06; all cause mortality: OR 0.91, 95% CI 0.79 to 1.05).[9] **ACE inhibitors:** The review found that, compared with placebo, ACE inhibitors significantly reduced MI, but did not significantly reduce stroke or vascular events (2 RCTs; 3574 people; OR for MI: 0.74, 95% CI 0.56 to 0.98; OR for stroke: 0.92, 95% CI 0.75 to 1.13; OR for vascular events: 0.83, 95% CI 0.61 to 1.12).[9] **Diuretics:** The review found that, compared with placebo or no treatment, diuretics significantly reduced stroke and vascular events, but did not significantly reduce MI (3 RCTs; 6216 people; OR for stroke: 0.68, 95% CI 0.50 to 0.92; OR for vascular events: 0.75, 95% CI 0.63 to 0.90; OR for MI: 1.06, 95% CI 0.63 to 1.78).[9] **Diuretic plus ACE inhibitor:** The review found that a diuretic plus an ACE inhibitor significantly reduced stroke, myocardial infarction, and vascular events compared with placebo or no treatment (1 RCT; 3544 people; OR for stroke: 0.55, 95% CI 0.45 to 0.68; OR for vascular events: 0.58, 95% CI 0.48 to 0.69; OR for MI: 0.55, 95% CI 0.38 to 0.79).[9] **Beta-blockers:** The review found that beta-blockers did not significantly reduce stroke, MI, or vascular events compared with placebo (2 RCTs; 2193 people; OR for stroke: 0.93, 95% CI 0.72 to 1.20; OR for MI: 0.94, 95%CI 0.60 to 1.45; OR for all vascular events: 1.01, 95% CI 0.81 to 1.27).[9]

Harms: The systematic review did not report on harms.[9] Two RCTs identified by the systematic review found that atenolol increased the risk of adverse events leading to discontinuation of treatment compared with placebo (first RCT: 108/732 [15%] with atenolol *v* 56/741 [8%] with placebo; significance data not reported; second RCT: 63/372 [17%] with atenolol *v* 35/348 [10%] with placebo; significance data not reported).[10,11] The largest RCT identified by the review found that perindopril with or without added indapamide slightly but significantly increased the risk of discontinuing treatment compared with placebo (714/3051 [23%] with treatment *v* 636/3054 [21%] with placebo; P = 0.02).[12] Another RCT identified by the review found that ramipril slightly increased the risk of discontinuing treatment compared with placebo (1343/4645 [28.9%] *v* 1268/4652 [27.3%]; significance data not reported). These adverse event data were based on analyses of people with and without prior cerebrovascular events.[13]

Comment: The systematic review found that a larger reduction in blood pressure was associated with a greater relative reduction in stroke and in vascular events.[9] The review also found that the effects of blood pressure lowering treatments on stroke and on all vascular events varied according to the antihypertensive regimen used; those drug regimens which reduced blood pressure the most also achieved the greatest reduction in stroke or vascular events.[9] It found that, across all control groups, the average risk of stroke was 11.5% and of vascular events 16% (ARR for stroke and for vascular events with treatment compared with control: 3%, about 1% per year).[9] The largest RCT included in the review compared 4 years of the ACE inhibitor perindopril plus the diuretic indapamide (added at the discretion of the treating physician) versus placebo. The relative risk reduction of stroke and vascular events remained similar, regardless of baseline blood pressure and the type of qualifying cerebrovascular event (ischaemic or haemorrhagic).[12] It found that, compared with placebo, perindopril plus the diuretic indapamide reduced blood pressure by 9/4 mm Hg and reduced stroke and

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Stroke prevention

major vascular events (stroke: RR 0.72, 95% CI 0.62 to 0.83; major vascular events: RR 0.74, 95% CI 0.66 to 0.84).[12] Overviews of observational studies in healthy middle aged and elderly people, as well as in those with a history of a cerebrovascular events, found no evidence of a threshold below which treatment was ineffective for reducing stroke, at least down as far as about 115/75 mm Hg.[3,14–16] However, it seems appropriate to be particularly cautious about lowering blood pressure in people with known severe stenosis of the carotid or vertebral arteries because of the possibility of precipitating a stroke.[17] Observational studies in people with severe bilateral stenosis found that lower blood pressure was associated with an increasing risk of stroke, suggesting that aggressive blood pressure lowering may not be advisable in this group.[18]

OPTION DIFFERENT BLOOD PRESSURE LOWERING REGIMENS

Cathie Sudlow

We found no RCTs or systematic reviews that compared different blood pressure lowering regimens exclusively in people with a prior stroke or transient ischaemic attack. One systematic review found no significant difference between thiazide diuretics and beta-blockers in death, stroke, coronary artery disease, or total cardiovascular events. A second systematic review found that calcium channel blockers reduced stroke compared with angiotensin converting enzyme inhibitors, but the decrease was of borderline significance. It also found that diuretics or beta-blockers reduced stroke compared with angiotensin converting enzyme inhibitors, but the decrease was of borderline significance. Neither of the reviews presented results separately for people with a prior stroke or transient ischaemic attack.

Benefits: We found no systematic reviews or RCTs that compared different blood pressure lowering regimens exclusively in people who have had a prior stroke or transient ischaemic attack (TIA). We found two systematic reviews, which compared different blood pressure lowering regimens in people with hypertension or vascular disease.[19,20] Neither of the reviews presented results separately for people with a prior stroke or TIA. The first systematic review (search date 1997) compared thiazide diuretics (bendrofluazide 2.5 mg, 5 mg, or 10 mg; hydrochlorthiazide 25 mg or 50 mg) versus beta-blockers (propranolol 80 or 160 mg; atenolol 50 mg).[20] Meta-analysis found that thiazide diuretics did not significantly reduce death, stroke, coronary artery disease, or total cardiovascular events compared with beta-blockers (5 RCTs, 17 952 people with hypertension; treatment duration between 1 and 10 years; death: 367/8915 [4.1%] with thiazide *v* 387/9037 [4.3%] with beta-blocker; RR 0.97, 95% CI 0.84 to 1.11; stroke: 107/8862 [1.2%] with thiazide *v* 130/8984 [1.4%] with beta-blocker; RR 0.84, 95% CI 0.65 to 1.08; coronary artery disease: 285/8862 [3.2%] with thiazide *v* 317/8984 [3.5%] with beta-blocker; RR 0.91, 95% CI 0.78 to 1.07; total cardiovascular events [including stroke, coronary artery disease, congestive heart failure, and other vascular events]: 431/8862 [4.9%] with thiazide *v* 495/8984 [5.5%] with beta-blocker; RR 0.88, 95% CI 0.78 to 1.00).[20] The second systematic review (search date 2003,16 RCTs, 142 341 people, the proportion with previous stroke or TIA not reported) assessed the effects on major cardiovascular outcomes of different blood pressure lowering regimens (based on angiotensin converting enzyme inhibitors, calcium channel blockers, diuretics, and beta-blockers) using only direct comparisons.[19] The mean duration of follow up ranged from 2.0–8.4 years. Most people had pre-existing cardiovascular disease or more than one cardiovascular risk factor at baseline. In the analysis, diuretics and beta-blockers were combined. It found that calcium channel blockers reduced stroke compared with diuretics or

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beta-blockers, but the decrease was of borderline significance (RR 0.93, 95% CI 0.86 to 1.00). It found that calcium channel blockers reduced stroke compared with angiotensin converting enzyme inhibitors, but the decrease was of borderline significance (RR 0.89, 95% CI 0.80 to 0.99). It found that diuretics or beta-blockers reduced stroke compared with angiotensin converting enzyme inhibitors, but the decrease was of borderline significance (RR 0.92, 95% CI 0.85 to 1.00).

Harms: The first systematic review found that withdrawal from treatment owing to adverse effects was significantly more common with beta-blockers than with thiazide diuretics (924/8984 [10.3%] with beta-blockers *v* 624/8862 [7.0%] with diuretics; RR 1.45, 95% CI 1.32 to 1.59).[20] See harms under blood pressure reduction, p 5.The second systematic review did not report on harms.[19]

Comment: The second systematic review found that the relative risk of stroke and of all other major vascular outcomes apart from heart failure was directly proportional to the blood pressure reduction achieved.[19] One overview (search date 2003) of published meta-analyses of RCTs of blood pressure lowering treatment versus placebo or no treatment, more versus less intensive blood pressure lowering drug regimens, and one blood pressure lowering drug regimen versus another, found similar results for the outcome of stroke.[21] Together with the results of a systematic review[9] in people with a prior stroke or TIA (See benefits of blood pressure reduction, p 4), these findings suggest that, in general, it is probably the size of the blood pressure reduction rather than the specific drug regimen used that determines the benefit of the treatment.

OPTION CHOLESTEROL REDUCTION

Cathie Sudlow

We found no systematic reviews comparing statins versus placebo which reported results separately for people with previous stroke or transient ischaemic attack. One systematic review found that statins reduced major vascular events, including stroke, compared with placebo or no treatment in various different types of people, including those with prior ischaemic stroke or transient ischaemic attack, irrespective of baseline cholesterol or of the presence or absence of coronary artery disease. We found no systematic reviews comparing non-statin cholesterol lowering treatments versus placebo which reported results separately for people with previous stroke or transient ischaemic attack. One systematic review and three additional RCTs in broader populations found that non-statin cholesterol lowering drug treatments did not reduce stroke compared with placebo or no treatment.

Benefits: **Statins:** We found one systematic review, which assessed the effect of statins on stroke in people with coronary heart disease, raised and normal cholesterol levels, diabetes, prior ischaemic stroke or transient ischaemic attack (TIA), and the elderly.[22] The review did not present results separately for people with a previous ischaemic stroke or TIA. The review (search date 2003, 26 RCTs, 97 981 people) found that statins significantly reduced stroke compared with placebo or no treatment after a mean of 4.3 years (1285/47 090 [2.7%] with statins *v* 1605/47 038 [3.4%] with control; OR 0.79, 95% CI 0.73 to 0.85).[22] The review also found that the effect of statins on stroke was closely associated with the reduction in low density lipoprotein (LDL)-cholesterol, such that each 10% reduction in LDL-cholesterol reduced the risk of stroke by about 16%.[22] One RCT identified by the review (20 536 people) conducted a subgroup analysis in 3280 people with prior ischaemic stroke or TIA.[23] The subgroup analysis found that

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simvastatin significantly reduced major vascular events (major coronary events, strokes, and coronary or non-coronary revascularisations) compared with placebo after 5 years' follow up (24.7% with simvastatin *v* 29.8% with placebo; RR 0.80, 95% CI 0.71 to 0.92). This result was similar to the reduction in major vascular events for the other 17 256 people in the trial, and occurred irrespective of the presence or absence of known coronary disease.[23] The RCT also found that simvastatin did not significantly reduce the risk of stroke compared with placebo in people with prior stroke or TIA (RR 0.98, 95% CI 0.79 to 1.22), but this retrospective subgroup analysis was not supported by the definite benefit observed in the prespecified analysis of major vascular events in people with a prior stroke or TIA.[23] **Non-statin drug treatments:** We found no systematic reviews that reported results separately for people with previous stroke or TIA. We found one systematic review (search date not stated), which compared the effects of both statin and non-statin drug treatments versus placebo on stroke in people with and without prior stroke or TIA.[4] The review found no significant difference between non-statin drug treatments and placebo in the risk of stroke (12 relevant RCTs; 169/12 143 [1.4%] with non-statins *v* 270/15 376 [1.8%] with placebo; OR 1.04, 95% CI 0.85 to 1.28).[4] We found one additional RCT[24] and two subsequent RCTs[25,26] that assessed the outcome of stroke. The additional RCT (532 men who had a previous stroke or TIA) found no significant difference between clofibrate and placebo in death after 3.5 years (AR 13% with clofibrate *v* 16% with placebo; P value not reported).[24] The first subsequent RCT (2531 men with coronary heart disease) found no significant difference between gemfibrozil and placebo in the risk of stroke (AR 5% with gemfibrozil *v* 6% with placebo; RRR + 25%, 95% CI –6% to + 47%).[25] The second subsequent RCT (3090 people with previous myocardial infarction or stable angina, including 58 people with previous stroke or TIA) found no significant difference between bezafibrate 400 mg and placebo in the risk of stroke after follow up for about 6 years (AR 4.6% with bezafibrate *v* 5.0% with placebo; P = 0.66).[26]

Harms:

Statins: One systematic review found no significant difference between statins and placebo in haemorrhagic stroke (0.32% with statins *v* 0.36% with placebo; OR 0.90, 95% CI 0.65 to 1.22).[22]Another systematic review (35 000 people and 158 000 person years of observation) found no significant difference in adverse events between treatments (48 RCTs;1063/14 197 [7.5%] with statins *v* 923/10 568 [8.7%] with placebo; ARR 1%, 95% CI –1% to + 3%).[27] It also found that rhabdomyolysis was reported in eight people treated with statins and five people with placebo (no further data reported). No cases of liver failure were reported in any of the RCTs. Raised serum creatine kinase levels (≥ 10 times the upper limit of normal) were reported in 55 people (0.17%) with statins and 43 people (0.13%) with placebo, with muscle symptoms reported by 13 people with statins and four people with placebo (no further data reported for either outcome). Raised alanine aminotransferase levels (≥ 3 times upper limit of normal) were reported in 449 people (1.3%) with statins and 383 people (1.1%) with placebo (no further data reported).[27] **Statin or non-statin drug treatments:** One systematic review found no significant difference between statins, non-statin treatments, and placebo or no treatment in deaths due to circulatory diseases other than ischaemic heart disease and stroke (OR 0.87, 95% CI 0.73 to 1.03; cancer: OR 1.06, 95% CI 0.96 to 1.16; injuries and suicide: OR 0.94, 95% CI 0.72 to 1.23; adverse events other than circulatory diseases or cancer: OR 0.88, 95% CI 0.78 to 1.01).[27] The RCT comparing clofibrate with placebo found similar adverse effect rates for treatments (23/268 [8.6%] with clofibrate *v* 28/264 [10.6%] with placebo; P value not reported).[24] The RCT comparing gemfibrozil with placebo found no significant difference

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between treatments in the rate of cancer or of death from any specific cause and no significant difference between treatments in any symptom apart from dyspepsia (40% with gemfibrozil *v* 34% with placebo; P = 0.002).[25] The RCT comparing bezafibrate with placebo found similar adverse effect rates for treatments (no further data reported).[26]

Comment: The systematic review found that, overall, statins or non-statins significantly reduced mortality and fatal coronary heart disease compared with placebo or no treatment (mortality: OR 0.85, 95% CI 0.76 to 0.93; fatal coronary heart disease: 0.79, 95% CI 0.74 to 0.85).[4] Another systematic review found that the relative risk reduction of stroke and of ischaemic heart disease events was proportional to the size of the reduction in LDL-cholesterol; for each 1.0 mmol/L reduction in LDL-cholesterol, the risk of stroke was reduced by about a fifth, with smaller reductions in the first 2 years of treatment.[27] It also found that the risk of ischaemic heart disease events was reduced by about a third with 3–5 years of treatment, with much smaller reductions in the first 2 years of treatment.[27] The largest RCT included in the review found that the relative reduction in major vascular events was similar among those people with different pretreatment concentrations of cholesterol and triglycerides, in all age groups included, and irrespective of a prior history of coronary artery disease, ischaemic stroke or TIA, ischaemic heart disease, peripheral arterial disease, or diabetes.[28] An RCT comparing atorvastatin versus placebo in 4700 people with minor stroke or TIA is in progress.[29] A planned overview of individual participant data from all RCTs of cholesterol reduction aims to summarise the effects of reducing cholesterol in different groups of people, including those with previous stroke or TIA.[30] Two observational studies have suggested that cholesterol reduction decreases thromboembolic, but not haemorrhagic, stroke.[3,27]

OPTION ANTIPLATELET TREATMENT VERSUS NO ANTIPLATELET TREATMENT

Cathie Sudlow

One systematic review found that prolonged antiplatelet treatment reduced the risk of serious vascular events, including stroke, in people with previous stroke or transient ischaemic attack compared with placebo or no antiplatelet treatment.

Benefits: We found one systematic review (search date 1997, 195 RCTs, 135 640 people at high risk of vascular disease: previous stroke or transient ischaemic attack (TIA), acute stroke, ischaemic heart disease, heart failure, cardiac valve disease, atrial fibrillation, peripheral arterial disease, diabetes, and haemodialysis), which compared antiplatelet treatment (mostly aspirin) versus placebo or no antiplatelet treatment.[7] It found that in people with previous stroke or TIA (21 RCTs, 18 270 people), antiplatelet treatment significantly reduced serious vascular events (stroke, myocardial infarction [MI], or vascular death) compared with placebo or no antiplatelet treatment after 3 years (18% with antiplatelet treatment *v* 21% with placebo or no antiplatelet treatment; OR 0.78, 95% CI 0.73 to 0.85). Antiplatelet treatment also reduced the separate outcomes of stroke, MI, vascular death, and death (see figure 1, p 30). For every 1000 people with previous stroke or TIA treated for about 3 years, antiplatelet treatment prevented 25 non-fatal strokes, six non-fatal MIs, and 15 deaths.[7]

Harms: The systematic review found that antiplatelet treatment in people with previous stroke or TIA increased major extracranial haemorrhage (haemorrhages requiring hospital admission or blood transfusion) and intracranial haemorrhage compared with no antiplatelet treatment

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Stroke prevention

(intracranial haemorrhage: AR 0.64% with antiplatelet treatment *v* 0.56% with no antiplatelet treatment; OR 1.2, CI not reported; major extracranial haemorrhage: AR 0.97% with antiplatelet treatment *v* 0.47% with no antiplatelet treatment; OR 2.0, CI not reported).[7] We found one systematic review (search date 1999, 24 RCTs), which assessed the effects of aspirin on gastrointestinal bleeding.[31] It found that aspirin increased gastrointestinal bleeding compared with placebo or no aspirin (OR 1.68, 95% CI 1.51 to 1.88). Another systematic review (search date 1997, 16 RCTs, 55 462 people) found that aspirin increased intracranial haemorrhage by about one event per 1000 people treated for 3 years.[32]

Comment: In people at high risk of vascular disease, including those with prior ischaemic stroke or TIA, the large absolute reductions in serious vascular events produced by antiplatelet treatment far outweighed any absolute hazards.

OPTION HIGH DOSE VERSUS LOW DOSE ASPIRIN

Cathie Sudlow

One systematic review and one subsequent RCT in people at high risk of vascular events found that low dose aspirin (75–150 mg/day) was as effective as higher doses for preventing serious vascular events (stroke, myocardial infarction, or vascular death). It also found no significant difference in serious vascular events between doses of 75 mg or more and doses lower than 75 mg. However, the comparison lacked power to detect a clinically important difference. Systematic reviews found no evidence of an association between aspirin dose and risk of intracranial, major extracranial, or gastrointestinal haemorrhage. RCTs found that high dose aspirin (500–1500 mg/day) increased the risk of upper gastrointestinal upset compared with medium dose aspirin (75–325 mg/day).

Benefits: We found one systematic review (search date 1997)[7] and one subsequent RCT.[33] The systematic review (7225 people at high risk of vascular disease in RCTs comparing different doses of aspirin; about 60 000 people at high risk of vascular disease, excluding those with acute stroke, in RCTs comparing different doses of aspirin versus placebo or no aspirin) compared the effects of higher versus lower dose aspirin on serious vascular events.[7] It found no significant difference between aspirin 500–1500 mg daily and 75–325 mg daily in serious vascular events (stroke, myocardial infarction, or vascular death; OR 0.97, 95% CI 0.79 to 1.19). It also found that doses of 75 mg or more did not reduce serious vascular events compared with doses lower than 75 mg (OR 1.08, 95% CI 0.90 to 1.31). However, the comparison lacked power to detect a clinically important difference. The review also found that different aspirin doses reduced serious vascular events compared with placebo or no antiplatelet treatment by similar amounts for the higher daily doses but by a smaller amount for very low doses (higher doses: 500–1500 mg/day *v* placebo or no antiplatelet treatment: OR 0.81, 95% CI 0.75 to 0.87; 160–325 mg/day *v* placebo or no antiplatelet treatment: OR 0.74, 95% CI 0.69 to 0.80; 75–150 mg/day *v* placebo or no antiplatelet treatment: OR 0.68, 95% CI 0.59 to 0.79; lower doses: < 75 mg/day *v* placebo or no antiplatelet treatment: OR 0.87, 95% CI 0.74 to 1.03). See figure 2 in secondary prevention of ischaemic cardiac events, p 00. People with acute stroke were excluded from these analyses. The results in people with previous stroke or transient ischaemic attack were not presented separately. The subsequent RCT (2849 people scheduled for carotid endarterectomy, most of whom had previous stroke or transient ischaemic attack) compared low

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dose aspirin (81 and 325 mg/day) versus high dose aspirin (650 and 1300 mg/day).[33] It found that high dose aspirin increased the combined outcome of stroke, myocardial infarction, and death after 3 months compared with low dose aspirin (AR 8.4% with high dose *v* 6.2% with low dose; RR 1.34, 95% CI 1.03 to 1.75).[33]

Harms: **Extracranial haemorrhage:** The systematic review found that the proportional increase in the risk of major extracranial haemorrhage was similar with all daily aspirin doses. In direct comparisons, 75–325 mg aspirin did not increase major extracranial haemorrhage compared with doses lower than 75 mg (AR 2.5% with 75–325 mg/day *v* 1.8% with < 75 mg/day; P > 0.05).[7] We found one systematic review (search date 1999, 24 RCTs) of the effects of aspirin on gastrointestinal bleeding.[31] Indirect comparisons in a meta-regression analysis found no association between dose of aspirin and risk of gastrointestinal bleeds. RCTs directly comparing different daily doses of aspirin have found a trend toward more gastrointestinal haemorrhage and a significant increase in upper gastrointestinal symptoms with high (500–1500 mg) than with medium (75–325 mg) doses (upper gastrointestinal symptoms: OR 1.3, 95% CI 1.1 to 1.5), but no significant difference in these outcomes between 30 mg and 283 mg daily.[33–35] We found one systematic review of observational studies (search date 2001, 5 studies) of the effects of different doses of aspirin on the risk of upper gastrointestinal complications (bleeding, perforation, or upper gastrointestinal event leading to hospital admission or a visit to a specialist).[36] It found greater risks of upper gastrointestinal complications with doses of aspirin greater than 300 mg daily. **Intracranial haemorrhage:** We found one systematic review (search date 1997, 16 RCTs, 55 462 people) of the effects of aspirin on intracranial haemorrhage.[32] It found no clear variation in risk with the dose of aspirin used. Three RCTs directly compared different daily doses of aspirin and found no significant differences in the risk of intracranial haemorrhage, but they lacked power to detect clinically important differences.[33–35]

Comment: None.

OPTION ALTERNATIVE ANTIPLATELET REGIMENS TO ASPIRIN

Cathie Sudlow

Two systematic reviews and one subsequent RCT in people at high risk of vascular events found no good evidence that thienopyridines (ticlopidine or clopidogrel) were superior to aspirin for long term prevention of serious vascular events (stroke, myocardial infarction, or vascular death), but found that clopidogrel was a safe and effective alternative to aspirin. One systematic review in people at high risk of vascular events found that dipyridamole plus aspirin reduced non-fatal stroke compared with aspirin alone, but found no significant difference between treatments in serious vascular events (stroke, myocardial infarction, or vascular death). One systematic review and two subsequent RCTs in people at high risk of stroke found no significant difference between triflusal and aspirin in serious vascular events.

Benefits: **Thienopyridines (clopidogrel and ticlopidine) versus aspirin:** We found two systematic reviews (search dates 1997[7] and 1999[37]) and one subsequent RCT[38], which compared thienopyridines versus aspirin. The first systematic review (4 RCTs, 3791 people at high risk of vascular events, mean treatment duration: 3 years) found no significant difference between ticlopidine and aspirin in serious vascular events at the end of treatment (stroke, myocardial infarction [MI], or vascular death: 21% with ticlopidine *v* 23% with aspirin; OR 0.88, 95% CI 0.75 to 1.03).[7] It also found that the risk of serious vascular events was similar

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with clopidogrel and aspirin (1 RCT, 19 185 people: 10% with clopidogrel *v* 11% with aspirin; OR 0.90, 95% CI 0.82 to 0.99). The second systematic review (4 RCTs) found that ticlopidine or clopidogrel marginally reduced vascular events after about 2 years compared with aspirin (OR 0.91, 95% CI 0.84 to 0.98; ARR 1.1%, 95% CI 0.2% to 1.9%).[37] The subsequent RCT (1809 African Americans with a recent non-cardioembolic ischaemic stroke) compared ticlopidine (500 mg daily) versus aspirin (650 mg daily) over 2 years and found no significant difference between treatments in the primary outcome of recurrent stroke, MI, or vascular death (AR: 14.7% with ticlopidine *v* 12.3% with aspirin; HR 1.22, 95% CI 0.94 to 1.57).[38] **Dipyridamole plus aspirin versus aspirin:** We found one systematic review (search date 1997, 25 relevant RCTs, 10 404 people at high risk of vascular events), which compared dipyridamole plus aspirin versus aspirin alone.[7] The review found no significant difference between treatments in serious vascular events (stroke, MI, or vascular death: 614/5198 [11.8%] with dipyridamole plus aspirin *v* 648/5206 [12.4%] with aspirin alone; OR 0.94, 95% CI 0.83 to 1.06).[7] Overall, the review found that dipyridamole plus aspirin significantly reduced non-fatal stroke compared with aspirin alone (183/4419 [4.1%] with dipyridamole plus aspirin *v* 236/4432 [5.3%] with aspirin alone; OR 0.76, 95% CI 0.62 to 0.92).[7] **Triflusal versus aspirin:** We found one systematic review [7] and two subsequent RCTs, which compared triflusal versus aspirin.[39,40] The systematic review (3 RCTs, 2675 people at high risk of vascular events, of whom 400 had a history of ischaemic stroke or transient ischaemic attack [TIA]), found no significant difference between triflusal and aspirin in vascular events (10% with triflusal *v* 10% with aspirin; OR 0.93, 95% CI 0.72 to 1.19).[7] The first subsequent RCT (2113 people with a recent ischaemic stroke or TIA) found no significant difference between triflusal and aspirin in the primary outcome of ischaemic stroke, MI, or vascular death (13.1% with triflusal *v* 12.4% with aspirin; HR 1.09, 95% CI 0.85 to 1.38).[39] However, the RCT lacked power to rule out a clinically important difference between treatments. The second subsequent RCT (431 people with a prior ischaemic stroke or TIA, treated for a mean of 586 days) found no significant difference between triflusal (600 mg daily) and aspirin (325 mg daily) in the combined incidence of ischaemic stroke, MI, or vascular death or major haemorrhage (27/213 [12.7%] with triflusal *v* 30/216 [13.9%] with aspirin; OR 0.90, 95% CI 0.51 to 1.56).[40] However, the RCT lacked power to rule out a clinically important difference between treatments.[40]

Harms:

Thienopyridines (clopidogrel and ticlopidine) versus aspirin: The first systematic review did not report on harms.[7] The second systematic review comparing thienopyridines versus aspirin found that the thienopyridines reduced gastrointestinal haemorrhage and upper gastrointestinal symptoms compared with aspirin (gastrointestinal haemorrhage: OR 0.71, 95% CI 0.59 to 0.86; indigestion, nausea, or vomiting: OR 0.84, 95% CI 0.78 to 0.90).[37] However, thienopyridines increased the incidence of skin rash and diarrhoea compared with aspirin (skin rash: clopidogrel *v* aspirin OR 1.3, 95% CI 1.2 to 1.5; ticlopidine *v* aspirin OR 2.2, 95% CI 1.7 to 2.9; diarrhoea: clopidogrel *v* aspirin OR 1.3, 95% CI 1.2 to 1.6; ticlopidine *v* aspirin OR 2.3, 95% CI 1.9 to 2.8). Ticlopidine (but not clopidogrel) increased neutropenia compared with aspirin (OR 2.7, 95% CI 1.5 to 4.8). Observational studies have found ticlopidine to be associated with thrombocytopenia and thrombotic thrombocytopenic purpura.[41,42] The subsequent RCT comparing aspirin and ticlopidine found that aspirin increased gastrointestinal tract haemorrhage compared with ticlopidine, but the increase was not statistically significant (0.9% with aspirin *v* 0.4% with ticlopidine; P = 0.39).[38] It found that ticlopidine increased diarrhoea, thrombocytopenia, and neutropenia compared with aspirin, but the difference

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was not statistically significant (diarrhoea: 0.3% with ticlopidine *v* 0.2% with aspirin; P = 0.69; thrombocytopenia: 0.3% with ticlopidine *v* 0.2% with aspirin; P = 0.69; neutropenia: 3.4% with ticlopidine *v* 2.2% with aspirin; P = 0.12). **Dipyridamole plus aspirin versus aspirin:** The systematic review found no significant difference between treatments in intracranial or major extracranial bleeds (no further data reported).[7] The largest RCT identified by the systematic review found that dipyridamole plus aspirin did not significantly increase the risk of major extracranial bleeds compared with aspirin alone (38/2110 [0.02%] with dipyridamole plus aspirin *v* 24/2094 [0.01%] with aspirin alone; OR 1.52, 95% CI 0.93 to 2.49).[43] The RCT also found that dipyridamole plus aspirin was discontinued more frequently owing to adverse effects than was aspirin alone (262/1650 [15.9%] with aspirin plus dipyridamole *v* 141/1649 [8.6%] with aspirin alone; significance not reported).[43] **Triflusal versus aspirin:** The systematic review did not report on harms.[7] The first subsequent RCT found a lower risk of haemorrhage with triflusal compared with aspirin (intracranial or major extracranial haemorrhage: 1.9% with triflusal *v* 4.0% with aspirin; HR 0.48, 95% CI 0.28 to 0.82; any haemorrhage: 16.7% with triflusal *v* 25.2% with aspirin; OR 0.76, 95% CI 0.67 to 0.86).[39] The second subsequent RCT also found that triflusal significantly lowered the risk of any haemorrhage compared with aspirin (2.8% with triflusal *v* 8.3% with aspirin; P = 0.01).[40] However, this reduction was not significant for intracranial or major extracranial haemorrhages specifically (0.5% with triflusal *v* 3.2% with aspirin; P = 0.07).[40]

Comment: **Thienopyridines (clopidogrel and ticlopidine) versus aspirin:** Two large RCTs have assessed the effects of adding clopidogrel to aspirin for up to 1 year among a total of about 15 000 high risk ischaemic heart disease patients (see benefits of antiplatelet treatments in angina , p 01).[44,45] Three further large RCTs are assessing the effects of clopidogrel plus aspirin versus aspirin alone among people at high vascular risk (including those with a prior ischaemic stroke or TIA) and among people with a very recent (< 12 hours) minor ischaemic stroke or TIA.[46–48] One ongoing RCT is comparing the effects of oral anticoagulation, aspirin plus dipyridamole, and aspirin alone among 4500 people with a prior TIA or minor ischaemic stroke.[49] One RCT, which compared aspirin plus clopidogrel versus clopidogrel alone (7599 high risk patients with a recent ischaemic stroke or TIA) found no significant difference between treatments in the combined primary outcome of ischaemic stroke, myocardial infarction, vascular death, or rehospitalisation for acute ischaemia, but found an increased risk of life threatening bleeding with aspirin plus clopidogrel compared with clopidogrel alone (combined primary outcome: 15.7% with aspirin plus clopidogrel *v* 16.7% with clopidogrel alone; RR 0.94, 95% CI 0.84 to 1.05; life threatening bleeding: 2.6% with aspirin plus clopidogrel *v* 1.3% with clopidogrel alone; ARI 1.3%, 95% CI 0.6% to 1.9%).[50] **Dipyridamole plus aspirin versus aspirin:** The systematic review[7] found that most non-fatal strokes were recorded in one large RCT (about 6000 people with a prior ischaemic stroke or TIA), which compared aspirin (50 mg daily) versus modified release dipyridamole (400 mg daily) versus both versus neither.[43] The RCT found that dipyridamole plus aspirin significantly reduced stroke compared with aspirin alone. However, dipyridamole plus aspirin did not reduce stroke compared with aspirin alone in the other trials included in the review.[7] These conflicting results may be due to chance, to the very low aspirin dose used in the large trial, or to the particular dose and preparation of dipyridamole used in the large trial.

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OPTION ANTICOAGULATION IN PEOPLE IN SINUS RHYTHM

Cathie Sudlow

Systematic reviews found no significant difference between oral anticoagulation and placebo or antiplatelet treatment for preventing recurrent stroke after presumed ischaemic stroke in people in normal sinus rhythm. Anticoagulants increased the risk of fatal intracranial and extracranial haemorrhage compared with placebo or no treatment. High intensity anticoagulation increased the risk of intracranial or major bleeding compared with antiplatelet treatment.

Benefits:

Versus placebo or no treatment: We found one systematic review (search date 2002, 11 RCTs, 2487 people in sinus rhythm with previous non-embolic presumed ischaemic stroke or transient ischaemic attack [TIA], mean duration 1.9 years).[51] It found no significant difference between oral anticoagulant treatment (coumarins, phenindione, or low dose heparin) and placebo or no treatment for death or dependency, serious vascular events (stroke, myocardial infarction, or vascular death), or all cause mortality during follow up (death or dependency: 2 RCTs; 114/169 [67.5%] with anticoagulant *v* 111/157 [71.0%] with control; ARR + 4%, 95% CI –6% to + 14%; RR 0.95, 95% CI 0.82 to 1.09; serious vascular events: 4 RCTs; 122/294 [41.5%] with anticoagulant v 118/281 [42.0%] with control; ARR + 1%, 95% CI –7% to + 8%; RR 0.98, 95% CI 0.82 to 1.18; any cause of death: 10 RCTs; 163/679 [24.0%] with anticoagulant v 161/654 [24.6%] with control; ARR + 1%, 95% CI –4% to + 5%; RR 0.97, 95% CI 0.81 to 1.16).
Versus antiplatelet treatment: We found one systematic review (search date 2001, 5 RCTs, 4015 people), which compared long term (> 6 months) treatment with oral anticoagulants (warfarin, phenprocoumarin, or acenocoumarol [nicoumalone]) versus antiplatelet treatment (aspirin or aspirin plus dipyridamole) in people with a history of TIA or minor stroke of presumed arterial (non-cardiac) origin in the past 6 months.[52] The mean duration of follow up ranged from 12.4–24 months. The RCTs identified by the review compared different intensities of anticoagulation versus antiplatelet treatment (aspirin). The review found no significant difference between high intensity (international normalised ratio [INR]G 3.0–4.5), medium intensity (INR 2.1–-3.5), and low intensity (INR 1.4–2.8) anticoagulation compared with antiplatelet treatment in preventing recurrent stroke (high intensity anticoagulation: 1 RCT; 14/651 [2.2%] with anticoagulation *v* 14/665 [2.1%] with antiplatelet treatment; RR 1.02, 95% CI 0.49 to 2.13; ARI 0%, 95% CI –2% to + 2%; medium intensity anticoagulation: 2 RCTs; 8/182 [4.4%] with anticoagulation *v* 9/194 [4.6%] with antiplatelet treatment; RR 0.96, 95% CI 0.38 to 2.42); ARR 0%, 95% CI –4% to + 4%).[52] The RCT of low intensity anticoagulation versus aspirin (2206 people) did not report effects on recurrent stroke. The review also found that high intensity anticoagulation significantly increased the risk of the composite outcome of vascular death, non-fatal stroke, non-fatal myocardial infarction, or major bleeding complication compared with aspirin (1 RCT; 81/651 [12.4%] with anticoagulation *v* 36/665 [5.4%] with aspirin; RR 2.30, 95% CI 1.58 to 3.35; see harms, below). The RCTs of medium and low intensity anticoagulation versus aspirin did not report on this outcome. The RCT of low intensity anticoagulation versus aspirin found no significant difference between treatments in the composite outcome of death or recurrent ischaemic stroke (HR 1.13, 95% CI 0.92 to 1.38).[52]

Harms:

Versus placebo or no treatment: The systematic review found that anticoagulants significantly increased the risk of fatal intracranial haemorrhage and of major extracranial haemorrhage (fatal and non-fatal)

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compared with control during follow up (fatal intracranial haemorrhage: 20/618 [3.2%] with anticoagulant *v* 7/596 [1.2%] with control; RR 2.51, 95% CI 1.12 to 5.60; ARI 2%, 95% CI 0% to 4%; all major extracranial haemorrhage: 40/604 [6.6%] with anticoagulant *v* 10/579 [1.7%] with control; RR 3.45, 95% CI 1.82 to 6.54); ARI 5%, 95% CI 3% to 7%).[51] **Versus antiplatelet treatment:** The systematic review found that high intensity anticoagulation significantly increased the risk of a major bleeding complication (intracranial or major extracranial bleeding) compared with aspirin (53/651 [8.1%] with anticoagulation *v* 6/665 [0.9%] with aspirin; RR 9.02, 95% CI 3.91 to 20.84). ARI 7%, 95% CI 5% to 9%).[52] It found no significant difference in the risk of intracranial or major extracranial bleeding between either medium intensity or low intensity anticoagulation compared with aspirin (medium intensity anticoagulation versus aspirin: 15/241 [6.2%] with anticoagulation *v* 13/252 [5.2%] with aspirin; RR 1.19, 95% CI 0.59 to 2.41; ARR 1%, 95% CI –4% to + 5%; low intensity anticoagulation versus aspirin: 38/1103 [3.4%] with anticoagulation *v* 30/1103 [2.7%] with aspirin; RR 1.27, 95% CI 0.79 to 2.03; ARI 1%, 95% CI –1% to + 2%), but the numbers of events were small and confidence intervals were wide, especially for medium intensity anticoagulation versus aspirin. The RCT of low intensity anticoagulation versus aspirin found that low intensity anticoagulation significantly increased the risk of minor haemorrhage compared with aspirin (RR 1.39, 95% CI 1.17 to 1.64; ARI 7%, 95% CI 3% to 10%).[53]

Comment: **Versus placebo or no treatment:** Most trials in the systematic review had major problems with their methods, including poor monitoring of anticoagulation.[51] Most were completed before introducing routine computerised tomography scanning, which means that people with primary haemorrhagic strokes could have been included. The systematic review could not therefore provide a reliable and precise overall estimate of the balance of risk and benefit regarding death or dependency. **Versus antiplatelet treatment:** Ongoing RCTs (including several thousand people with a non-cardioembolic ischaemic stroke or TIA) are comparing medium intensity oral anticoagulation (INR 2.0–3.0) versus antiplatelet treatment.[49,54,55]

OPTION CAROTID ENDARTERECTOMY FOR PEOPLE WITH RECENT CAROTID TERRITORY ISCHAEMIA

Peter Rothwell

Evidence from a pooled analysis of individual patient data from three RCTs in people with symptomatic carotid artery stenosis found that carotid endarterectomy did not significantly increase the risk of stroke or death owing to surgery in people with less than 30% carotid stenosis, was of no benefit in people with 30–49% stenosis, and reduced stroke and death in people with 50–69% carotid stenosis, compared with no endarterectomy. The RCTs found that carotid endarterectomy reduced the risk of stroke and death compared with no endarterectomy in people with more than 70% carotid stenosis, although no benefit was found in people with near occlusion. One systematic review and one subsequent RCT found that carotid endarterectomy reduced perioperative stroke, death, and subsequent ipsilateral stroke in people with asymptomatic but severe stenosis. However, because the absolute risk of stroke in asymptomatic people is relatively low, the benefit from surgery is small.

Benefits: **People with symptomatic stenosis:** We found one pooled analysis[56] of individual patient data from the three large RCTs (4 publications), which examined the effects of endarterectomy in people with symptomatic carotid stenosis.[57–60] The RCTs used different methods to measure the degree of carotid stenosis, studied different populations, and

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used different definitions of outcome events. However, the pooled analysis adjusted for these differences. The pooled analysis (3 RCTs, 6092 people, 35 000 person years of follow up) found that surgery increased the 5 year risk of any stroke or surgical death in people with less than 30% stenosis, had no significant effect in people with 30–49% stenosis, was of some benefit in people with 50–69% stenosis, and was highly beneficial in people with 70% or more stenosis without near occlusion (< 30% stenosis, 1746 people: RR 1.17, 95% CI 0.90 to 1.43; 30–49% stenosis, 1429 people: RR 0.90, 95% CI 0.75 to 1.04; 50–69% stenosis, 1549 people: RR 0.72, 95% CI 0.58 to 0.86; ≥ 70% stenosis without near occlusion, 1095 people: RR 0.52, 95% CI 0.40 to 0.64).[56] However, there was no evidence of benefit in people with the most severe disease (near occlusion of ipsilateral carotid artery, 262 people: RR compared with control 0.98, 95% CI 0.61 to 1.59). **People with asymptomatic stenosis:** We found one systematic review (search date 1998, 4 RCTs, 2203 people), which assessed carotid endarterectomy for asymptomatic carotid stenosis (no carotid territory transient ischaemic attack (TIA) or minor stroke within previous few months)[61] and one subsequent RCT.[62] The review found that carotid endarterectomy reduced the risk of perioperative stroke, death, or subsequent ipsilateral stroke compared with medical treatment only (for the review of 4 RCTs:[61] AR 4.9% over 3 years in the surgical group *v* 6.8% in the medical group; ARR 1.9%, 95% CI 0.1% to 3.9%; NNT 52, 95% CI 26 to 1000; see comment below). The subsequent RCT (3129 people with carotid stenosis, asymptomatic for the previous 6 months) compared carotid endarterectomy versus medical treatment (including antiplatelet, antihypertensive, and lipid lowering treatment where appropriate).[62] It found that carotid endarterectomy significantly reduced the risk of all stroke or perioperative death compared with medical treatment after 5 years (AR 6.4% with carotid endarterectomy *v* 11.8% with medical treatment; ARR 5.4%, 95% CI 3.0% to 7.8%; RR not reported). It also found that carotid endarterectomy significantly reduced the risk of disabling or fatal stroke compared with medical treatment after 5 years (AR 3.5% with carotid endarterectomy *v* 6.1% with medical treatment; ARR 2.5%, 95% CI 0.8% to 4.3%; RR not reported).[62] **Eversion carotid endarterectomy versus conventional carotid endarterectomy:** We found one systematic review (search date 1999, 5 RCTs, 2645 people, 2590 carotid arteries), which compared eversion carotid endarterectomy versus conventional carotid endarterectomy G performed either with primary closure or patch angioplasty.[63] Overall, the review found no significant differences in the rate of perioperative stroke, stroke or death, local complication rate, and rate of neurological events (for stroke or death: AR 1.7% with eversion *v* 2.6% with conventional; ARR + 0.9%, 95% CI –0.3% to + 2.1%; for stroke: AR 1.4% with eversion *v* 1.7% with conventional; ARR + 0.3%, 95% CI –0.7% to + 1.3%).

Harms:

People with symptomatic stenosis: The pooled analysis (3248 people randomised to surgery a median of 6 days after randomisation) reported 229 strokes or deaths within 30 days of surgery (7.1%, 95% CI 6.3% to 8.1%).[56] Operative risk was not related to the degree of stenosis. The risk of death within 30 days of endarterectomy was 1.1% (36/3248; 95% CI 0.8% to 1.5%), and among 209 people who had an operative stroke, 20 people died (9.6%, 95% CI 5.9% to 14.4%). One earlier systematic review (search date 1996, 36 studies) identified several risk factors for operative stroke and death from carotid endarterectomy, including female sex, occlusion of the contralateral internal carotid artery, stenosis of the ipsilateral external carotid artery, and systolic blood pressure greater than 180 mm Hg.[64] One systematic review (search date 2000, 103 studies including 6 RCTs, case series,

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and routinely collected data) examining harms of carotid endarterectomy found that the operative risk of stroke and death was highest in people with cerebral TIA or stroke and in people with re-stenosis, and lowest in people with ocular ischaemic events and asymptomatic stenosis (symptomatic stenosis *v* asymptomatic stenosis, 59 studies: OR 1.62, 95% CI 1.45 to 1.81; re-stenosis *v* primary surgery, 6 studies: OR 1.95, 95% CI 1.21 to 3.16; ocular events only *v* asymptomatic stenosis, 15 studies: OR 0.75, 95% CI 0.50 to 1.14).[65] It found that emergency surgery immediately after a TIA or stroke was associated with a major increase in operative risk compared with elective surgery performed a few days later (OR 4.9, 95% CI 3.4 to 7.1).[65] Endarterectomy is also associated with other postoperative complications, including wound infection (3%), wound haematoma (5%), and lower cranial nerve injury (5–7%).[66] **People with asymptomatic stenosis:** Given the low prevalence of severe carotid stenosis in the general population, there is concern that screening and surgical intervention in asymptomatic people may result in more strokes than it prevents.[67] The systematic review did not report on harms.[61] The subsequent RCT found that in the people receiving immediate carotid endarterectomy, the risk of perioperative stroke or death was 2.8%.[62] However, it did not report on overall harms in the medical treatment group. Among 229 people in the medical treatment group who eventually received carotid endarterectomy, the perioperative risk of stroke or death was 4.5%, which was not significantly different from the risk in the immediate carotid endarterectomy group (P value not reported).[62] The overall risk of death as a result of carotid endarterectomy at 30 days was 1.1% and the risk of stroke or death as a result of surgery at 30 days was 3.0%.[68] These figures are consistent with rates reported in case series.[68]

Comment: **People with symptomatic stenosis:** The RCTs included in the pooled analysis found different results.[57–60] However, this was because of differences in the methods of measurement of the degree of carotid stenosis on the pre-randomisation catheter angiograms (the method used in one RCT[57] produced higher values than the method used in the other trials[58,59,69]) and differences in the definitions of outcome events. Meta-analyses of the overall trial results have been reported but these took no account of the differences between the trials.[70,71] The subsequent pooled analysis of individual participant data corrected for these differences in methods, after which there were no clinically or statistically significant differences between the results of the three trials.[56] The degree of carotid stenosis was the single most important factor influencing the effects of endarterectomy.[56] Subgroup analyses of the pooled data from the three RCTs[57–60] showed that the benefits of carotid endarterectomy were greatest within 2 weeks of an ischaemic event (excluding emergency surgery and surgery in people with major disabling stroke) and that the benefits were reduced if surgery was delayed (interaction; $P = 0.009$).[72] There was also evidence of a reduced benefit in women (interaction; $P = 0.003$) and a trend towards increasing benefit with age ($P = 0.03$). These observations were consistent across the individual trials. **People with asymptomatic stenosis:** Although the risk of perioperative stroke or death from carotid surgery for people with asymptomatic stenosis seems to be lower than in people with symptomatic stenosis, the risk of stroke or death without surgery in asymptomatic people is low and so the absolute benefit from surgery is small, and for most people the balance of risk and benefit from surgery remains unclear.[61] Subgroup analysis of data from two RCTs that compared endarterectomy versus medical treatment in people with asymptomatic carotid stenosis found that the benefits of surgery on stroke may be greater in men than in women after a mean follow up of 2–3 years (stroke in men: 69/1565 [4.4%] with surgery *v* 38/1570 [2.4%] with medical treatment; OR 0.49, 95% CI 0.36 to 0.66; stroke

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in women: 46/820 [5.6%] with surgery *v* 48/824 [5.8%] with medical treatment; OR 0.96, 95% CI 0.63 to 1.45).[73] There is currently no evidence of benefit in women after 5 years.[73] **"Prophylactic" endarterectomy for people having coronary bypass surgery:** It is common practice for endarterectomy for asymptomatic stenosis to be performed as a "prophylactic" procedure either before or during coronary artery bypass surgery because of the high risk of stroke in this group (stroke after coronary artery bypass graft overall: 1.71%; risk of stroke in people with asymptomatic stenosis: 3%).[74] We found no RCTs of endarterectomy for this indication. One systematic review (search date 2002, 97 RCTs) of outcomes after staged and synchronous carotid endarterectomy and coronary artery bypass reported overall operative risks of stroke and death of 10%.[75]

OPTION CAROTID AND VERTEBRAL PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY

Peter Rothwell

RCTs provided insufficient evidence about the effects of carotid or vertebral percutaneous transluminal angioplasty or stenting compared with medical treatment or carotid endarterectomy in people with a recent carotid or vertebral territory transient ischaemic attack or non-disabling ischaemic stroke who have severe stenosis of the ipsilateral carotid or vertebral artery.

Benefits:

Carotid percutaneous transluminal angioplasty versus endarterectomy: We found one large RCT[76] and one small RCT[77], which was stopped prematurely. The larger RCT (504 people with a recent carotid territory transient ischaemic attack or non-disabling ischaemic stroke with stenosis of the ipsilateral carotid artery) compared "best medical treatment" plus carotid percutaneous transluminal angioplasty versus "best medical treatment" plus carotid endarterectomy.[76] It found no significant difference between endovascular treatment and surgery for disabling stroke or death within 30 days of first treatment (AR for disabling stroke or death: 6.4% with percutaneous transluminal angioplasty *v* 5.9% with surgery; AR for stroke lasting > 7 days or death: 10.0% with percutaneous transluminal angioplasty *v* 9.9% with surgery). The trial found no significant difference between treatments for ipsilateral stroke rate up to 3 years after randomisation (adjusted HR 1.04, 95% CI 0.63 to 1.70; P = 0.9). A small RCT of 23 people was stopped after 17 people had received allocated treatment because of a high procedural risk of stroke in the angioplasty group compared with the endarterectomy group (5/7 [71%] with angioplasty *v* 0/10 [0%] with endarterectomy; P = 0.03).[77] **Carotid angioplasty plus stenting versus endarterectomy:** We found three RCTs in symptomatic people.[78–80] The first RCT (219 people with carotid stenosis of 60–90%) found that carotid stenting significantly increased the combined outcome of ipsilateral stroke, procedure related death, or vascular death at 1 year compared with carotid endarterectomy (12.1% with stent *v* 3.6% with endarterectomy; P = 0.022).[78] The second RCT (104 people with > 70% carotid stenosis) found no significant difference between carotid angioplasty plus stenting and carotid endarterectomy for death or cerebral ischaemia (1 transient ischaemic attack with angioplasty *v* 1 death for endarterectomy; P value not reported).[79] The third RCT (334 people, either asymptomatic with > 80% stenosis or symptomatic with > 50% stenosis and considered to have a high operative risk with endarterectomy) compared carotid artery stenting (with an emboli protection device) versus endarterectomy.[80] The trial was designed to test whether carotid artery stenting was at least as effective as endarterectomy. The RCT was stopped prematurely after 1 year, owing to slow enrolment. It found no significant difference between carotid artery stenting and endarterectomy in the cumulative incidence

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of death, stroke, or myocardial infarction within 1 year (cumulative incidence: 12.2% with stent *v* 20.1 % with endarterectomy; ARR: + 7.9%, 95% CI –0.7% to + 16.4%; myocardial infarction was only included if it occurred within 30 days).[80] **Vertebral artery angioplasty:** We found one RCT (16 people), which compared vertebral angioplasty versus "best medical treatment".[76] The RCT did not provide enough data for reliable estimates of efficacy to be made.

Harms: **Carotid angioplasty versus endarterectomy:** The RCT comparing carotid angioplasty versus endarterectomy found that cranial neuropathy was more common with endarterectomy (22 [8.7%] people with endarterectomy *v* 0 [0%] people with angioplasty; $P < 0.0001$).[76] Major groin or neck haematoma occurred less often after angioplasty than after endarterectomy (3 [1.2%] people with angioplasty *v* 17 [6.7%] people with endarterectomy; $P < 0.0015$).[76] **Carotid angioplasty plus stenting versus endarterectomy:** Harms data are not yet available from the other trials, which are still to be published in full.[14,78]

Comment: The RCTs comparing angioplasty versus endarterectomy had low power, and results lacked precision.[76] Several ongoing RCTs are comparing carotid endarterectomy versus primary stenting in people with recently symptomatic severe carotid stenosis. **Carotid percutaneous transluminal angioplasty:** The two RCTs comparing angioplasty (with or without stenting) and endarterectomy suggest that angioplasty with or without stenting is associated with a higher procedural risk than endarterectomy, and a higher rate of restenosis during follow up.[78,79] However, improvements in cerebral protection devices may reduce the procedural risks,[81] and several other RCTs comparing angioplasty plus stenting with cerebral protection versus endarterectomy are currently ongoing. The use of angioplasty is likely to increase in future, but trial results will help to decide whether increased use will be confined to people in whom endarterectomy is technically difficult.

QUESTION What are the effects of preventive anticoagulant and antiplatelet treatments in people with atrial fibrillation and previous stroke or transient ischaemic attack?

Gregory YH Lip

OPTION ANTICOAGULANT AND ANTIPLATELET TREATMENT

One systematic review found that adjusted dose warfarin reduced the risk of stroke compared with control in people with previous stroke or transient ischaemic attack. The best time to begin anticoagulation after an ischaemic stroke is unclear. One systematic review provided insufficient evidence to compare warfarin versus aspirin. One RCT found no significant difference between aspirin and placebo in stroke or death in people with previous stroke or transient ischaemic attack.

Benefits: **Adjusted dose warfarin versus placebo:** We found one systematic review (search date 1999,[82], 1 RCT,[83] 439 people with previous stroke or transient ischaemic attack [TIA]), which compared adjusted dose warfarinⒼ with a control, in which people could self select to take aspirin. Target international normalised ratio (INR)Ⓖ was 2.9. The RCT found that adjusted dose warfarin significantly reduced the risk of stroke compared with control (20/225 [8.9%] with warfarin *v* 50/214 [23.4%] with control; ARR 14.5%, 95% CI 7.7% to 21.3%; NNT 7, 95% CI 5 to 13). **Conventional intensity warfarin versus low intensity or minidose warfarin:** We found one RCT (115 people with ischaemic stroke in the previous 1–6 months).[84] It found no significant difference between conventional intensity warfarin (target INR 2.2–3.5) and low

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intensity warfarin (target INR 1.5–2.1) in ischaemic stroke rate after a mean follow up of about 1 year (AR 1/55 [1.1%] with conventional intensity *v* 2/60 [1.7%] with low intensity warfarin; P > 0.99).[84] The RCT was terminated prematurely because of significantly more bleeding complications with conventional intensity warfarin (see harms and comment below). **Adjusted dose warfarin versus aspirin:** We found one systematic review (search date 1999),[82] which identified one RCT[83] comparing warfarin with aspirin. However, this comparison was not randomised, and therefore did not meet inclusion criteria for this chapter. **Conventional intensity warfarin versus other antiplatelet treatments:** We found one systematic review (search date 1999, 1 RCT,[85] 916 people within 15 days of stroke onset), which compared warfarin (target INR 2.0–3.5) versus indobufen.[82] It found no significant difference in the rate of recurrent stroke between treatments (5% with indobufen *v* 4% with warfarin; ARR + 1.0%, 95% CI −1.7% to + 3.7%).[82] **Conventional intensity warfarin versus other anticoagulants:** We found one RCT (3410 people with atrial fibrillation and at least 1 other risk factor for stroke, 24% with previous stroke or TIA), which compared open label warfarin (INR 2.0–3.0) versus the oral thrombin inhibitor, ximelagatran (fixed dose, 36 mg twice daily).[86] It found no significant difference in stroke between warfarin and ximelagatran in a subgroup (822 people) with previous stroke or TIA after mean follow up of 17 months (5.1% a year with warfarin *v* 3.8% a year with ximelagatran; P = 0.313). **Aspirin versus placebo:** We found one systematic review (search date 1999, 1 RCT, 782 people with atrial fibrillation and previous stroke or TIA).[87] The RCT found no significant difference between aspirin and placebo for stroke or death (stroke: OR 0.89, 95% CI 0.64 to 1.24; death: OR 0.95, 95% CI 0.69 to 1.31).

Harms:

The major risk associated with anticoagulants and antiplatelet agents was haemorrhage. In the overview assessing elderly people with variable risk factors for stroke, the absolute risk of major bleeding was 1.0% for placebo, 1.0% for aspirin, and 1.3% for warfarin.[88] Another systematic review found that the absolute risk of intracranial haemorrhage increased from 0.1% a year with control to 0.3% a year with warfarin, but the difference was not significant.[82] The absolute risks were three times higher in people who had bled previously. Both bleeding and haemorrhagic stroke were more common in people aged over 75 years. The risk of death after a major bleed was 13–33%, and the risk of subsequent morbidity in those who survived a major bleed was 15%. The risk of bleeding was associated with an INR greater than 3, fluctuating INRs, and uncontrolled hypertension. In a systematic review (search date not reported, 2 RCTs) major extracranial bleeding was more frequent with anticoagulation treatment than with placebo (ARI 4.9%, 95% CI 1.6% to 8.2%; RR 6.2, 95% CI 1.4 to 27.1; NNH 20, 95% CI 12 to 63).[89] The studies were too small to define the rate of intracranial haemorrhage (none occurred). In a systematic review (search date not reported) comparing anticoagulants versus antiplatelet treatment, major extracranial bleeding was more frequent with anticoagulation (ARI 4.9%, 95% CI 1.6% to 8.2%; RR 6.4, 95% CI 1.5 to 28.1; NNH 20, 95% CI 12 to 63).[90] The studies were too small to define the rate of intracranial haemorrhage (in 1 RCT, none of the people on anticoagulant and 1 person on aspirin had an intracranial bleed). In the systematic review of oral anticoagulants versus placebo in low risk people, the number of intracranial haemorrhages was small, with a non-significant increase in the treatment group (5 in the treatment group *v* 2 in the control group).[91] Likewise, in the systematic review assessing antiplatelet treatment in low risk people with atrial fibrillation, too few haemorrhages occurred to characterise the effects of aspirin.[92] One more recent systematic review found no evidence that warfarin significantly increased the risk of major haemorrhage compared with

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placebo among people with no prior TIA or stroke (5 RCTs, 2415 people: ARI for major haemorrhage warfarin *v* placebo + 0.8%, 95% CI –1.3% to + 2.9%).[87] However, if people with previous stroke or TIA were included, then warfarin significantly increased major haemorrhage (6 RCTs: ARI for warfarin *v* placebo 1.3%, 95% CI 0.4% to 2.2%; NNH 77, 95% CI 45 to 250). The systematic review found no evidence of a difference in major haemorrhage between warfarin and aspirin, warfarin and any antiplatelet agent, warfarin and low dose warfarin plus aspirin, and low molecular weight heparin and placebo. However, the review may have lacked power to detect a clinically important difference.[87] One small RCT (157 people) found that full dose anticoagulation (target INR 2.0–2.6) plus aspirin significantly increased haemorrhagic complications compared with aspirin alone (13/76 [17%] with fluindione plus aspirin *v* 2/81 [2.5%] with fluindione alone; P = 0.0021).[93] **Conventional intensity warfarin versus minidose warfarin:** One RCT (115 people) found that conventional intensity warfarin significantly increased major haemorrhagic complications compared with low intensity warfarin after about 1 year (6/55 [10.9%] with conventional intensity *v* 0/60 [0%] with low intensity; P = 0.01).[84]

Comment: **Adjusted dose warfarin versus minidose warfarin:** The RCT comparing conventional versus low intensity warfarin found no significant difference between treatments.[84] This may be because of insufficient power; premature termination of the trial because of significantly more bleeding complications in the conventional intensity anticoagulation group; the low rate of ischaemic stroke observed in both groups in this population, possibly contributed to by different ethnicity from original anticoagulation trial cohorts; or the similar anticoagulation range reached in the two groups (2.2 with conventional intensity *v* 1.9 with low intensity).[85] **Timing of anticoagulation:** The best time to start anticoagulation after an ischaemic stroke is unclear, but aspirin reduces the risk of recurrent stroke in such people with or without atrial fibrillation, suggesting that it is reasonable to use aspirin until it is considered safe to start oral anticoagulants.[94] See also comments in anticoagulant and antiplatelet treatment in people with atrial fibrillation and without previous stroke or transient ischaemic attack, p 24.

QUESTION What are the effects of preventive anticoagulant and antiplatelet treatment in people with atrial fibrillation and without previous stroke or transient ischaemic attack?

Gregory YH Lip

OPTION ANTICOAGULANT AND ANTIPLATELET TREATMENT

One systematic review found that warfarin reduced fatal and non-fatal ischaemic stroke compared with placebo in people at high risk of stroke, provided that there was a low risk of bleeding and careful monitoring. One overview in people less than 65 years old found no significant difference in the annual stroke rate between warfarin and placebo in people at low risk of stroke. One systematic review found that warfarin reduced the risk of stroke compared with aspirin in people at high risk of stroke. One RCT found no significant difference in stroke between warfarin and the anticoagulant ximelagatran. One systematic review found that aspirin reduced the risk of stroke compared with placebo. However, another review found no significant difference. These findings support the use of aspirin in people with atrial fibrillation and contraindications to anticoagulants.

Benefits: **Adjusted dose warfarin versus placebo in people at high risk of stroke:** We found two systematic reviews examining the effect of warfarin in different groups of people with atrial fibrillation at high risk of

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stroke G.[82,87] The first systematic review (search date 1999, 6 RCTs, 2900 people at high risk, 80% without previous stroke or transient ischaemic attack [TIA], 45% with hypertension) compared adjusted dose warfarin G versus placebo or control.[82] In one RCT (439 people) included in the review, people in the control group could self select to take aspirin. Target international normalised ratio (INR) G varied among RCTs (2.0–2.6 in primary prevention RCTs). The review found that adjusted dose warfarin significantly reduced the risk of stroke (ARR 4.0%, 95% CI 2.3% to 5.7%; NNT 25, 95% CI 18 to 43). For people without previous stroke or TIA (5 RCTs, 2462 people), the relative risk of stroke was reduced by 59% (ARR 2.7% a year, NNT for 1 year was 37, CI not reported). The second systematic review (search date 1999, 14 RCTs) identified the same trials of warfarin compared with placebo and found similar results.[87] **Adjusted dose warfarin versus low dose warfarin plus aspirin in people at high risk of stroke:** We found no RCTs. **Adjusted dose warfarin versus low intensity or minidose warfarin in people at high risk of stroke:** We found one systematic review (search date 2002; 4 RCTs, 2108 people with atrial fibrillation).[95] The review compared adjusted dose warfarin versus low intensity, minidose G, and low dose warfarin G (with or without low dose aspirin). It found that adjusted dose warfarin reduced the risk of ischaemic stroke compared with lower dose warfarin, although this difference was not significant (RR 0.46, 95% CI 0.20 to 1.07; see comment below).[95] **Adjusted dose warfarin versus aspirin in people at high risk of stroke:** We found one systematic review comparing warfarin versus different antiplatelet regimens in people at high risk of stroke G[82] and one subsequent individual patient meta-analysis.[96] The systematic review (search date 1999, 4 primary prevention RCTs, 7037 people) compared adjusted dose warfarin versus aspirin in high risk people (45% had hypertension).[82] Target INR varied among RCTs (2.0–4.5 in primary prevention RCTs). Adjusted dose warfarin reduced the overall risk of stroke compared with aspirin (ARR 2.9%, 95% CI 0.9% to 4.8%; NNT 34, 95% CI 21 to 111). The effect varied widely among the four RCTs, none of which were blinded. The subsequent individual patient meta-analysis (5 RCTs of primary and secondary prevention, 2633 people at high risk of ischaemic stroke, 76% without previous stroke or TIA) compared full dose oral anticoagulation (largely coumarin derivatives) versus aspirin 75–325 mg.[96] It found that anticoagulation significantly decreased strokes compared with aspirin in people at high risk of ischaemic stroke (ARR 3.3% a year). **Adjusted dose warfarin versus other antiplatelet treatment in people at high risk of stroke:** We found no systematic review or RCTs in people with atrial fibrillation and no previous stroke or TIA. **Adjusted dose warfarin versus other anticoagulants in people at high risk of stroke:** We found one RCT (3410 people with atrial fibrillation and ≥1 stroke risk factor, 76% without previous stroke or TIA), which compared open label warfarin (INR 2.0–3.0) with the oral thrombin inhibitor, ximelagatran (fixed dose, 36 mg twice daily).[86] It found no significant difference between warfarin and ximelagatran for stroke or systemic embolism in a subgroup (2588 people) without previous stroke after a mean follow up of 17 months (56/2240 person years [2.3% a year] with ximelagatran *v* 40/2446 person years [1.6% a year] with warfarin; ARR + 0.7%, 95% CI –0.1% to + 1.4%, RR 0.71, 95% CI 0.48 to 1.07). **Oral anticoagulant versus oral anticoagulant plus aspirin in people at high risk of stroke:** We found one RCT (157 people at high risk), which compared oral fluindione (active dose 5–25 mg) versus fluindione plus aspirin 100 mg.[93] It found no significant difference between fluindione alone and fluindione plus aspirin for a combined outcome of stroke, myocardial infarction (MI), systemic arterial embolism, vascular death, or haemorrhagic complications after

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a mean follow up of 8 months (2/81 [2.5%] with fluindione *v* 5/76 [6.6%] with fluindione plus aspirin; P = 0.21). The study was insufficiently powered to detect clinically important differences between treatments. **Minidose warfarin plus aspirin in people at moderate risk of stroke:** We found one RCT (668 people with persistent or permanent atrial fibrillation, low to medium risk defined as ≤ 4% risk of stroke), which compared warfarin 1.25 mg plus aspirin 75 mg daily versus no anticoagulation.[97] It found that warfarin plus aspirin reduced stroke and stroke or TIA compared with no anticoagulation after about 33 months, but the decrease was not significant (stroke: 32/334 [9.6%] with warfarin plus aspirin *v* 41/334 [12.3%] with no treatment; P = 0.28; stroke or TIA: 11.7% with warfarin plus aspirin *v* 16.5% with no anticoagulation; P = 0.09).[13] **Anticoagulants in people at low risk of stroke:** We found one systematic review[91] and one overview[88], which compared warfarin versus placebo in people with atrial fibrillation and a variety of stroke risks. Both reviews included the same five RCTs. The systematic review (search date 1999, 5 RCTs, 2313 people with no previous stroke or TIA, mean age 69 years, 20% aged > 75 years; 45% with hypertension, 15% diabetes, and 15% a prior history of MI) did not separately analyse people at low risk of stroke.[91] The overview (2461 people, 15% of whom were aged ≤ 65 years) analysed a subgroup of people younger than 65 years with atrial fibrillation (but no history of hypertension, stroke, TIA, or diabetes). It found that the annual stroke rate was the same with warfarin or placebo (subgroup analysis among 17% of people on warfarin and 15% on placebo; annual stroke rate for both groups 1%, 95% CI 0.3% to 3.0%).[88] **Antiplatelet treatment in people at low risk of stroke:** We found two systematic reviews in people with atrial fibrillation at low risk of stroke.[82,92] The first review (search date 1999, 2 RCTs, 1680 people with either paroxysmal or sustained non-valvular atrial fibrillation confirmed by electrocardiogram but without previous stroke or TIA, 30% aged > 75 years) compared aspirin versus placebo.[92] It found that aspirin did not significantly reduce ischaemic stroke; all stroke; all disabling or fatal stroke; or the composite end point of stroke, MI, or vascular death after a mean follow up of 1.3 years (ischaemic stroke: OR 0.71, 95% CI 0.46 to 1.10; ARR + 1.6%, 95% CI –0.5% to + 3.7%; all stroke: OR 0.70, 95% CI 0.45 to 1.08; ARR + 1.8%, 95% CI –0.5% to + 3.9%; all disabling or fatal stroke: OR 0.88, 95% CI 0.48 to 1.58; ARR + 0.4%, 95% CI –1.2% to + 2.0%; composite end point: OR 0.76, 95% CI 0.54 to 1.05; ARR + 2.3%, 95% CI –0.4% to + 5.0%). The second systematic review (search date 1999) included three RCTs of primary prevention.[82] The average rate of stroke among people taking placebo was 5.2% a year. Meta-analysis found that antiplatelet treatment reduced the risk of stroke compared with placebo after a mean follow up of 1.2–2.3 years (6 RCTs; RR 0.78, 95% CI 0.62 to 0.98).

Harms:

Adjusted dose warfarin versus low intensity or minidose warfarin in people at high risk of stroke: One systematic review found that adjusted dose warfarin significantly reduced the risk of any thrombosis compared with low intensity warfarin at follow up (RR 0.50, 95% CI 0.25 to 0.97). It found no significant difference between treatments in the risk of major haemorrhage (RR 1.23, 95% CI 0.67 to 2.27).[95] The additional RCT (115 people) found that conventional intensity warfarin significantly increased major haemorrhagic complications compared with low intensity warfarin after about 1 year (6/55 [10.9%] with conventional intensity *v* 0/60 [0%] with low intensity; P = 0.01).[84] **Adjusted dose warfarin versus other anticoagulants in people at high risk of stroke:** One RCT (3410 people, 76% with no previous stroke or TIA), which compared open label warfarin (INR 2.0–3.0) versus the oral thrombin inhibitor, ximelagatran (fixed dose, 36 mg twice daily), found that ximelagatran significantly reduced any haemorrhage (major

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plus minor) compared with warfarin but found no significant difference between treatments in rates of major haemorrhage (any haemorrhage: 29.8% a year with warfarin *v* 25.8% a year with ximelagatran; P = 0.007; major haemorrhage: 1.8% a year with warfarin *v* 1.3% a year with ximelagatran; P = 0.23).[86] It found that ximelagatran significantly increased the proportion of people with raised serum alanine aminotransferase (> 3 times normal) compared with warfarin (107/1704 [6%] with ximelagatran *v* 14/1703 [1%] with warfarin; P < 0.0001). **Minidose warfarin plus aspirin versus no anticoagulant in people at low to moderate risk of stroke:** One RCT (688 people) found that low dose warfarin plus aspirin significantly increased bleeding complications compared with no treatment after a mean follow up of 33 months (19/334 [5.7%] with warfarin plus aspirin *v* 4/334 [1.2%] with no treatment; P = 0.003).[97] There were no deaths from bleeding complications. See also harms of anticoagulant and antiplatelet treatment in people with atrial fibrillation in people with previous stroke or transient ischaemic attack, p 20.

Comment: The three risk strata used above have been identified based on evidence derived from one overview of five RCTs[88] and one subsequent RCT.[98] Most reviews have stratified the effects of treatment in terms of these risk categories. However, one systematic review (search date 1999), which did not stratify for perceived risk, has suggested that RCTs may be too heterogeneous to determine the effects of long term oral anticoagulation compared with placebo among people with non-rheumatic atrial fibrillation.[99] The review (5 RCTs, 3298 people) found results that conflicted with those of previous reviews. The review also questioned the methods and highlighted the heterogeneity of RCTs of oral anticoagulation in people with non-rheumatic atrial fibrillation.[100] People in the RCTs were highly selected (< 10% [range 3–40%] of eligible people were randomised); many were excluded after assessments for the absence of contraindications and physicians' refusal to enter them into the study. Many of the studies were not double blinded, and in some studies there was poor agreement between raters for "soft" neurological end points. The frequent monitoring of warfarin treatment under trial conditions and motivation of people/investigators was probably more than that seen in usual clinical practice. The review suggested that considerable uncertainty remains about the benefits of long term anticoagulation in people with non-rheumatic atrial fibrillation. The review has different inclusion and exclusion criteria than those in previously published reviews, having excluded data from two RCTs and included a trial not included in previous reviews.[98] Unlike previous reviews, the recent systematic review did not stratify people for perceived stroke risk and identified no significant difference between anticoagulant and placebo with either a fixed effects model or a random effects model, which was employed to account for heterogeneity of underlying trials (fixed effects: OR 0.74, 95% CI 0.39 to 1.40 for stroke deaths; OR 0.86, 95% CI 0.16 to 1.17 for vascular deaths; random effects: OR 0.79, 95% CI 0.61 to 1.02 for combined fatal and non-fatal events).[100] The publication of this review has led to debate and uncertainty about the clinical effectiveness of long term anticoagulation in people with non-rheumatic atrial fibrillation. Decisions to treat should be informed by considering trade offs between benefits and harms, and each person's treatment preferences.[99,101–105] We found net benefit of anticoagulation for people in atrial fibrillation who have had a TIA or stroke, or who are over 75 years of age and at a high risk of stroke. We found less clear cut evidence for those aged 65–75 years and at high risk, and for those with a moderate risk of stroke◐ (> 65 years and not in a high risk group or < 65 years with clinical risk factors) or for those at low risk (< 65 years with no other risk factors). The benefits of warfarin in the RCTs may not translate into effectiveness in clinical

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practice.[100,106,107] In the RCTs, most strokes in people randomised to warfarin occurred while they were not in fact taking warfarin, or were significantly underanticoagulated at the time of the event. Analyses of the optimal anticoagulation intensity for stroke prevention in atrial fibrillation found that stroke risk was substantially increased at INR levels below 2.[108,109] A recent systematic review (search date not reported, 410 people) identified three trials comparing the outcomes of people treated with anticoagulants in the community versus the pooled results of the RCTs.[110] The authors confirmed that people who have anticoagulation for atrial fibrillation in actual clinical practice are generally older and have more comorbid conditions than people enrolled in RCTs. However, both groups had similar rates of stroke and major bleeding. This risk of minor bleeding was higher in the community group, and it was suggested that these people may require more intensive monitoring in routine practice.

GLOSSARY

Adjusted dose warfarin Anticoagulation with warfarin, aiming for a specific target INR range.

Conventional carotid endarterectomy This is more commonly employed and involves a longitudinal arteriotomy of the carotid artery.

Conventional intensity warfarin Warfarin dose, which is adjusted to a target INR of about 2.0–3.0.

Eversion carotid endarterectomy This involves a transverse arteriotomy and reimplantation of the carotid artery.

International normalised ratio (INR) A value derived from a standardised laboratory test that measures the effect of an anticoagulant such as warfarin. 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. Therapeutic anticoagulation often aims to achieve an INR value of 2.0–3.5.

Low dose warfarin/minidose warfarin Anticoagulation with a fixed low dose of warfarin (e.g. 1.25 mg daily) without dose adjustment for INR.

Low intensity warfarin Warfarin dose which is adjusted to a target INR of (usually) < 1.5.

People at high risk of stroke People of any age with a previous transient ischaemic attack or stroke, or a history of rheumatic vascular disease, coronary artery disease, congestive heart failure, and impaired left ventricular function or echocardiography; and people aged 75 years and over with hypertension, diabetes, or both.

People at moderate risk of stroke People aged over 65 years who are not in the high risk group; and people aged under 65 years with clinical risk factors, including diabetes, hypertension, peripheral arterial disease, and ischaemic heart disease.

People at low risk of stroke All other people aged less than 65 years with no history of stroke, transient ischaemic attack, embolism, hypertension, diabetes, or other clinical risk factors.

Substantive changes

Blood pressure reduction: One systematic review added.[9] Benefits and harms data enhanced; categorisation unchanged.

Cholesterol reduction: One systematic review added;[22] benefits and harms data enhanced. Categorisation unchanged.

Alternative antiplatelet regimens to aspirin: One RCT added.[40] Benefits and harms data enhanced; categorisation unchanged.

Carotid endarterectomy for people with recent carotid territory ischaemia: One RCT added.[62] Benefits and harms data enhanced; categorisation unchanged.

Carotid and vertebral percutaneous transluminal angioplasty: Long term follow up results added.[80] Benefits data enhanced; categorisation unchanged.

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Stroke prevention

Anticoagulant and antiplatelet treatment: One systematic review added.[95] Benefits and harms data enhanced; categorisation unchanged.

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Stroke prevention

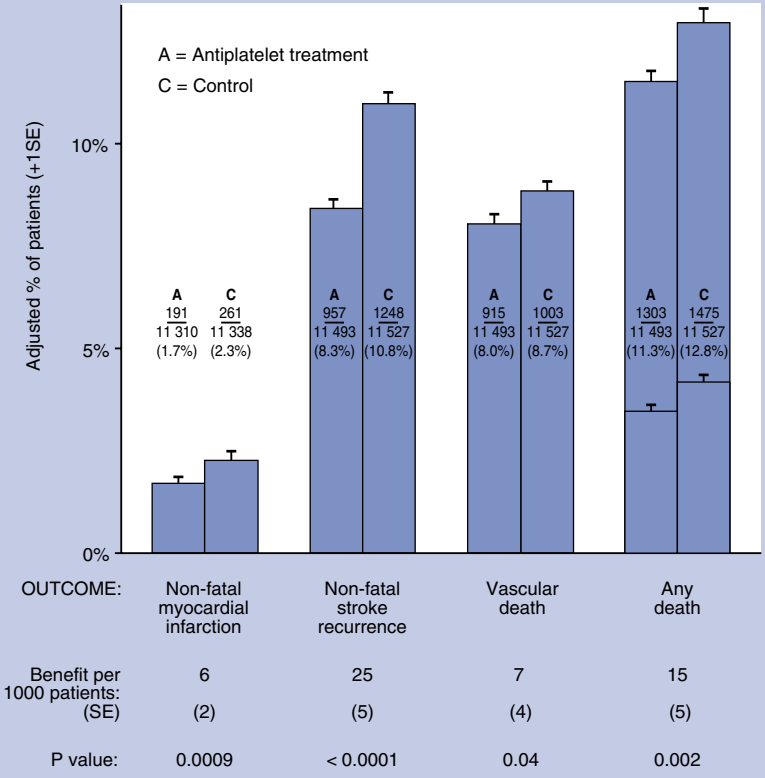

FIGURE 1 **Absolute effects of antiplatelet treatment on various outcomes in 21 trials in people with a prior (presumed ischaemic) stroke or transient ischaemic attack. The columns show the absolute risks over 3 years for each outcome. The error bars represent standard deviations. In the "any death" column, non-vascular deaths are represented by lower horizontal lines (see text, p 4). Adapted with permission.[5]**

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Thromboembolism

Search date September 2005

Richard McManus, David Fitzmaurice, and Richard Hobbs

QUESTIONS

INTERVENTIONS

*Clinical consensus based on observational data.

See glossary G

Key Messages

Proximal deep vein thrombosis

- **Compression stockings** One systematic review found that elastic compression stockings reduced the incidence of post-thrombotic syndrome after a deep vein thrombosis.

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- **Low molecular weight heparin (reduced mortality, reduced recurrence, and reduced risk of major haemorrhage compared with unfractionated heparin)** One systematic review found that low molecular weight heparin reduced recurrent thromboembolic disease in people with proximal deep vein thrombosis and decreased major haemorrhage over 3–6 months compared with unfractionated heparin. This review also found that low molecular weight heparin reduced overall mortality compared with unfractionated heparin.
- **Oral anticoagulants*** Consensus based on observational data regards oral anticoagulants as effective for people with proximal deep vein thrombosis. We found no RCTs comparing vitamin K antagonists such as acenocoumarol, flutamide, and warfarin versus placebo. One RCT found that fewer people had recurrence of proximal deep vein thrombosis within 6 months with combined intravenous unfractionated heparin plus acenocoumarol compared with acenocoumarol alone; as a result, the trial was stopped. One systematic review found no significant difference between oral anticoagulation and long term low molecular weight heparin in recurrent thromboembolism, major haemorrhage, or mortality.
- **Prolonged duration of anticoagulation** One systematic review in people with different types of venous thromboembolism found that a prolonged duration of anticoagulation reduced recurrence of venous thromboembolism, but increased major bleeding, compared with shorter durations of anticoagulation. The review found that, although the risk of recurrence drops over time, the risk of bleeding remains stable while anticoagulant treatment continues. The review found no significant difference in mortality between prolonged and shorter duration anticoagulation.
- **Venae cavae filters** One RCT in people with proximal deep vein thrombosis considered at high risk of pulmonary embolism, all receiving oral anticoagulation, found that venae cavae filters reduced rates of pulmonary embolism at 12 days compared with no filters. However, the difference in rates of pulmonary embolism was not significant at 2 years, and venae cavae filters increased rates of recurrent deep vein thrombosis at 2 years.
- **Abrupt discontinuation of oral anticoagulation** One RCT in people who had received warfarin for 3–6 months provided insufficient evidence to compare abrupt withdrawal of warfarin versus an additional month of warfarin at a fixed low dose of 1.25 mg daily.
- **Home treatment with short term low molecular weight heparin** One systematic review of weak RCTs found no significant difference in recurrence of thromboembolism between heparin treatment at home and in hospital.
- **Low molecular weight heparin versus oral anticoagulation (long term)** One systematic review found no significant difference between long term low molecular weight heparin and oral anticoagulation in recurrent thromboembolism, major haemorrhage, or mortality. One subsequent RCT found no significant difference between low molecular weight heparin and oral anticoagulation in deep venous thrombosis recurrence at 1 year.
- **Once daily versus twice daily low molecular weight heparin** Systematic reviews found no significant difference between once and twice daily low molecular weight heparin in recurrent thromboembolism or mortality at 10 days or 3 months. However, the reviews may have been underpowered to detect a clinically important difference because of low rates of recurrent thromboembolism and mortality in the trials.
- **High intensity oral anticoagulation** One RCT found that high intensity treatment with warfarin (target international normalised ratio 3.0–4.5) increased bleeding rates compared with lower intensity treatment (target international normalised ratio 2.0–3.0). However, it did not significantly reduce recurrence of thromboembolism.

Calf deep vein thrombosis

- **Warfarin (reduced rate of proximal extension compared with no further treatment in people who had received initial heparin and wore compression stockings)** One RCT, in people who had received initial intravenous unfractionated heparin (international normalised ratio > 2.5–4.2) and wore compression stockings, found that warfarin reduced rates of proximal extension compared with no further treatment.
- **Prolonged duration of anticoagulation** One open label RCT found no significant difference in recurrent thromboembolism or rates of major haemorrhage between 6 and 12 weeks of warfarin. The absolute risk of recurrent venous thromboembolism decreases with time, but the relative risk reduction with treatment remains constant. Harms of treatment, including major haemorrhage, continue during prolonged treatment. Individuals have different risk profiles and it is likely that the optimal duration of anticoagulation will vary.

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Pulmonary embolism

- **Prolonged duration of anticoagulation** In people who had received anticoagulants for 3 months after a pulmonary embolism, one RCT found no significant difference in recurrence of venous thromboembolism between a further 3 months of oral anticoagulation and longer duration treatment (up to 9 months). However, the RCT may have lacked power to detect a clinically important effect. Additional evidence for duration of treatment has been extrapolated from RCTs in people with proximal deep vein thrombosis and any venous thromboembolism, which found that longer courses of anticoagulation reduced recurrence compared with shorter courses but may increase the risk of major haemorrhage.
- **Warfarin plus heparin** We found no RCTs comparing heparin versus placebo, warfarin versus placebo, or heparin plus warfarin versus heparin alone or versus warfarin alone. One small RCT found that heparin plus warfarin reduced mortality at 1 year compared with no anticoagulation. Anticoagulants are associated with increased risk of haemorrhage.
- **Low molecular weight heparin (no clear evidence of a difference in mortality or new episodes of thromboembolism or a difference in risk of major haemorrhage compared with unfractionated heparin)** One systematic review in people with symptomatic or asymptomatic pulmonary embolism found no significant difference in recurrent venous thromboembolism or survival between low molecular weight heparin and unfractionated heparin up to 3 months after treatment. The RCTs in the systematic review found no significant difference in major haemorrhage between low molecular weight heparin and unfractionated heparin but may have been underpowered to detect a clinically important difference.
- **Thrombolysis** One systematic review found no significant difference in mortality or recurrence of pulmonary embolism between thrombolysis (plus anticoagulants) and heparin alone. It found that thrombolysis (plus anticoagulants) increased the incidence of non-major bleeding events, but not major bleeding events, compared with heparin alone. Subgroup analysis suggested a possible benefit in reducing mortality or recurrence of pulmonary embolism for people with major (haemodynamically unstable) pulmonary embolism. RCTs identified by a systematic review found no significant difference in mortality or recurrent pulmonary embolism among different thrombolytics.
- **High intensity anticoagulation** We found no direct evidence in people with pulmonary embolism about the optimum intensity of anticoagulation. Evidence for intensity of treatment has been extrapolated from RCTs in people with proximal deep vein thrombosis and any venous thromboembolism, which found that bleeding rates were increased by higher intensity anticoagulation (target international normalised ratio 3.0–4.5), but recurrence rates were not significantly different compared with a lower intensity anticoagulation (target international normalised ratio 2.0–3.0).

Computerised decision support

- **Computerised decision support in oral anticoagulation (increased time spent in target international normalised range, but effect on clinical outcomes unknown)** We found no RCTs comparing computerised decision support versus usual management of oral anticoagulation that used clinically important outcomes (major haemorrhage or death). One systematic review and six subsequent RCTs found that, compared with usual care, the use of computerised decision support in oral anticoagulation increased the time spent in the target international normalised range. Another subsequent RCT found no significant difference between computerised decision support and standard manual support in the time spent in the target international normalised ratio range.

*Clinical consensus based on observational data.

DEFINITION **Venous thromboembolism** is any thromboembolic event occurring within the venous system, including deep vein thrombosis and pulmonary embolism. **Deep vein thrombosis** is a radiologically confirmed partial or total thrombotic occlusion of the deep venous system of the legs sufficient to produce symptoms of pain or swelling. **Proximal deep vein thrombosis** affects the veins above the knee (popliteal, superficial femoral, common femoral, and iliac veins). **Isolated calf vein thrombosis** is confined to the deep veins of the calf and does not affect the veins above the knee. **Pulmonary embolism** is radiologically confirmed partial or total thromboembolic occlusion of pulmonary arteries, sufficient to cause symptoms of breathlessness, chest pain, or both. **Post-thrombotic syndrome** is oedema, ulceration, and impaired viability of the subcutaneous tissues of the leg occurring after deep vein thrombosis. **Recurrence** refers to symptomatic deterioration owing to a further (radiologically confirmed) thrombosis, after a previously confirmed thromboembolic event, where there had been an initial partial or total symptomatic improvement. **Extension** refers to a radiologically confirmed new, constant, symptomatic intraluminal filling defect extending from an existing thrombosis.

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INCIDENCE/ PREVALENCE	We found no reliable study of the incidence or prevalence of deep vein thrombosis or pulmonary embolism in the UK. A prospective Scandinavian study found an annual incidence of 1.6–1.8/1000 people in the general population.[1,2] One post mortem study estimated that 600 000 people develop pulmonary embolism each year in the USA, of whom 60 000 die as a result.[3]
AETIOLOGY/ RISK FACTORS	Risk factors for deep vein thrombosis include immobility, surgery (particularly orthopaedic), malignancy, smoking, pregnancy, older age, and inherited or acquired prothrombotic clotting disorders.[4] The oral contraceptive pill is associated with increased risk of death from venous thromboembolism (ARI with any combined oral contraception: 1–3 deaths per million women a year).[5] The principal cause of pulmonary embolism is a deep vein thrombosis.[4]
PROGNOSIS	The annual recurrence rate of symptomatic calf vein thrombosis in people without recent surgery is over 25%.[6,7] Proximal extension develops in 40–50% of people with symptomatic calf vein thrombosis.[8] Proximal deep vein thrombosis may cause fatal or non-fatal pulmonary embolism, recurrent venous thrombosis, and post-thrombotic syndrome. One case series (462 people) published in 1946 found 5.8% mortality from pulmonary emboli in people in a maternity hospital with untreated deep vein thrombosis.[9] One non-systematic review of observational studies found that, in people after recent surgery who have an asymptomatic deep calf vein thrombosis, the rate of fatal pulmonary embolism was 13–15%.[10] The incidence of other complications without treatment is not known. The risk of recurrent venous thrombosis and complications is increased by thrombotic risk factors.[11]
AIMS OF INTERVENTION	To reduce acute symptoms of deep vein thrombosis and to prevent morbidity and mortality associated with thrombus extension, post-thrombotic syndrome, and pulmonary embolisation; to reduce recurrence; to minimise any adverse effects of treatment.
OUTCOMES	Rates of symptomatic recurrence, post-thrombotic syndrome, symptomatic pulmonary embolism, and death. Proxy outcomes include radiological evidence of clot extension or pulmonary embolism. For computerised decision support©: Time spent in the target international normalised range.
METHODS	*Clinical Evidence* search and appraisal September 2005. Additional studies were identified by the authors, including an update of an existing review of prolonged duration of anticoagulation, which was updated shortly after our search date.[12] Observational studies were used for estimating incidence, prevalence, and adverse event rates. RCTs were included only if participants were included and outcomes defined on the basis of objective tests, and if the trial provided dose ranges (with adjusted dosing schedules for oral anticoagulation and unfractionated heparin) and independent, blinded outcome assessment.

QUESTION What are the effects of treatments for proximal deep vein thrombosis?

OPTION ORAL ANTICOAGULATION (VITAMIN K ANTAGONISTS SUCH AS ACENOCOUMAROL, FLUTAMIDE, WARFARIN)

Consensus based on observational data regards oral anticoagulants as effective for people with proximal deep vein thrombosis. We found no RCTs comparing vitamin K antagonists such as acenocoumarol, flutamide, and warfarin versus placebo. One RCT found that fewer people had recurrence of proximal deep vein thrombosis within 6 months with combined intravenous unfractionated heparin plus acenocoumarol compared with acenocoumarol alone; as a result, the trial was stopped. One systematic review found no significant difference between oral anticoagulation and long term low molecular weight heparin in recurrent thromboembolism, major haemorrhage, or mortality.

Benefits: **Oral anticoagulation versus placebo:** We found no systematic review or RCTs. **Acenocoumarol (nicoumalone) plus intravenous unfractionated heparin versus acenocoumarol alone:** We found no systematic review. One RCT (120 people with proximal deep vein thrombosis) found that fewer people had recurrence at interim analysis at 6 months with combined intravenous unfractionated heparin plus acenocoumarol than with acenocoumarol alone; as a result, the trial was stopped. The difference in recurrence did not quite reach significance (4/60 [7%] with combined treatment *v* 12/60 [20%] with acenocoumarol alone; P = 0.058; see comment below).[13] **Oral anticoagulation versus low molecular weight heparin:** See benefits of low molecular weight heparin, p 6.

Harms: **Coumarin derivatives (including warfarin):** We found one systematic review (search date 2003, 29 RCTs, 4 cohort studies) in 10 757 people with any type of venous thromboembolism.[14] In total, participants had received 4373 person years of coumarin

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derivatives, mainly warfarin. It found a major bleeding rate of 7.22 per 100 person years (95% CI, 7.19 per 100 person years to 7.24 per 100 person years), a fatal bleeding rate of 1.31 per 100 person years (95% CI, 1.30 per 100 person years to 1.32 per 100 person years), and intracranial bleeding rate of 1.15 per 100 person years (95% CI, 1.14 per 100 person years to 1.16 per 100 person years). The event rates for control groups were not reported. Major bleeding rates were similar for 3 months of anticoagulation treatment compared with anticoagulation for up to 1 year (major bleeding rate: 2.06 per 100 person years with 3 months of anticoagulation treatment *v* 2.74 per 100 person years with 3–12 months of anticoagulation treatment). **Acenocoumarol plus intravenous unfractionated heparin versus acenocoumarol alone:** In the RCT comparing acenocoumarol plus heparin versus acenocoumarol alone, one person in the combined treatment group committed suicide at 6 months and there were two cancer related deaths, confirmed by post mortem examination, in the group treated with warfarin alone (one in week 11 and the other in week 12).[13] **Oral anticoagulation versus low molecular weight heparin:** See harms of low molecular weight heparin, p 7.

Comment: **Acenocoumarol plus intravenous unfractionated heparin versus acenocoumarol alone for initial treatment:** It is unclear why the RCT was stopped early when it found no significant difference in recurrence between groups. The lower recurrence rates with combined intravenous unfractionated heparin plus acenocoumarol compared with acenocoumarol alone suggest that it may have been considered unethical to continue the trial.

OPTION PROLONGED DURATION OF ANTICOAGULATION

One systematic review in people with different types of venous thromboembolism found that a prolonged duration of anticoagulation reduced recurrence of venous thromboembolism, but increased major bleeding, compared with shorter durations of anticoagulation. The review found that, although the risk of recurrence drops over time, the risk of bleeding remains stable while anticoagulant treatment continues. The review found no significant difference in mortality between prolonged and shorter duration anticoagulation.

Benefits: We found one systematic review that compared longer versus shorter periods of anticoagulation with vitamin K antagonists in people with symptomatic venous thromboembolism.[12] The majority of RCTs included in the review were in people with first episode proximal deep vein thrombosis or pulmonary embolism. The exact proportion of people with proximal deep vein thrombosis was not reported. The included studies compared seven different periods of anticoagulation: the shorter time periods ranged from 4 weeks to 6 months and the longer periods from 12 weeks to 4 years. There was no significant difference between prolonged and shorter term anticoagulation in mortality (71/1498 [4.7%] with prolonged treatment *v* 75/1496 [5.0%] with shorter treatment; OR 0.93, 95% CI 0.67 to1.30). While prolonged anticoagulation was ongoing, it significantly reduced recurrent venous thromboembolism compared with shorter term treatment (search date 2005; 8 RCTs, 2994 people; 14/1499 [1%] with prolonged treatment *v* 116/1495 [8%] with shorter term treatment; OR 0.18, 95% CI 0.13 to 0.26). However, this benefit decreased after prolonged anticoagulation ceased, and there was no significant difference in recurrent venous thromboembolism between treatments during this period (6 RCTs, 2605 people; 96/1304 [7%] with prolonged treatment *v* 76/1301 [6%] with shorter term treatment; OR 1.24, 95% CI 0.91 to 1.69). The review did not quantify the pooled effect of treatment over the entire period of follow up due to heterogeneity between studies.

Harms: The review included studies with different periods of treatment, and the populations studied had different types of venous thromboembolism (see benefits above). The review found a significant increase in major haemorrhage with prolonged compared with shorter periods of anticoagulation (23/1499 [2.4%] with prolonged treatment *v* 13/1495 [0.9%] with shorter term treatment; OR 2.61, 95% CI 1.48 to 4.61). See harms of oral anticoagulation, p 4.

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Comment: The authors of the review point out that the absolute risk of recurrent venous thromboembolism decreases with time, whereas the harms associated with treatment remain constant.[12] Individuals have different risk profiles, and it is likely that the optimal duration of anticoagulation will vary.

OPTION HIGH INTENSITY ORAL ANTICOAGULATION

One RCT found that high intensity treatment with warfarin (target international normalised ratio 3.0–4.5) increased bleeding rates compared with lower intensity treatment (target international normalised ratio 2.0–3.0). However, it did not significantly reduce recurrence of thromboembolism.

Benefits: We found one RCT (96 people with a first episode of idiopathic venous thromboembolism) comparing international normalised ratio targets of 2.0–3.0 (lower intensity treatment) versus 3.0–4.5 (high intensity treatment) over 12 weeks' treatment with warfarin after an initial course of intravenous heparin.[15] It found similar recurrence rates of thromboembolism at 10 months for both international normalised ratio target ranges (1/47 [2.1%] with lower range *v* 1/49 [2.0%] with higher range; P > 0.05). However, it found significantly fewer haemorrhagic events with the lower target range (2/47 [4.3%] with lower range *v* 11/49 [22.4%] with higher range; ARR 18%, 95% CI 5% to 32%; RR 0.19, 95% CI 0.04 to 0.81; NNT 6, 95% CI 4 to 23).[15]

Harms: Two non-systematic reviews of RCTs and cohort studies found annual bleeding rates of 0–5% (fatal bleeding) and 2–8% (major bleeds) with warfarin (absolute numbers not reported).[16,17] Rates depended on how bleeding was defined and the intensity of anticoagulation. See harms of oral anticoagulation, p 4.

Comment: None.

OPTION ABRUPT DISCONTINUATION OF ORAL ANTICOAGULATION

One RCT in people who had received warfarin for 3–6 months provided insufficient evidence to compare abrupt withdrawal of warfarin versus an additional month of warfarin at a fixed low dose of 1.25 mg daily.

Benefits: One RCT (41 people with proximal deep vein thrombosis who had received intravenous heparin for 3–5 days followed by warfarin for 3–6 months) compared abrupt withdrawal of warfarin versus an additional month of warfarin at a fixed low dose of 1.25 mg daily.[18] It found similar recurrence with abrupt compared with gradual discontinuation (3 people with abrupt withdrawal *v* 1 person with gradual withdrawal; CI not reported).[18]

Harms: The RCT gave no information on adverse effects.[18]

Comment: None.

OPTION LOW MOLECULAR WEIGHT HEPARIN VERSUS UNFRACTIONATED HEPARIN

One systematic review found that low molecular weight heparin reduced recurrent thromboembolic disease in people with proximal deep vein thrombosis and decreased major haemorrhage over 3–6 months compared with unfractionated heparin. This review also found that low molecular weight heparin reduced overall mortality compared with unfractionated heparin.

Benefits: **Low molecular weight heparin (LMWH) v versus unfractionated heparin:** We found one systematic review comparing fixed dose subcutaneous LMWH versus adjusted dose intravenous or subcutaneous unfractionated heparin in people with proximal deep vein thrombosis.[19] It found that, after 3–6 months' treatment, LMWH significantly reduced overall mortality compared with unfractionated heparin (search date 2004, 8 RCTs, 4157 people; mortality: 70/2094 [3.3%] with LMWH *v* 110/2063 [5.3%] with unfractionated heparin; OR 0.62, 95% CI 0.46 to 0.84). LMWH significantly reduced overall symptomatic recurrent venous thromboembolism, as well as symptomatic recurrent deep vein thrombosis and pulmonary embolism, compared with unfractionated heparin

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(overall recurrent venous thromboembolism: 9 RCTs, 4451 people; AR 80/2192 [3.6%] with LMWH *v* 143/2259 [6.3%] with unfractionated heparin; OR 0.57, 95% CI 0.44 to 0.75; recurrent deep vein thrombosis: 6 RCTs, 2460 people; AR 37/1233 [3.0%] with LMWH *v* 58/1227 [4.7%] with unfractionated heparin; OR 0.63, 95% 0.42 to 0.95; pulmonary embolism: 6 RCTs, 2803 people; AR 18/1400 [1.3%] with LMWH *v* 44/1403 [3.1%] with unfractionated heparin; OR 0.42, 95% CI 0.26 to 0.70).[19]

Harms: **Haemorrhage:** The systematic review found that LMWH significantly reduced major haemorrhagic complications compared with unfractionated heparin (search date 2004, 8 RCTs, 3589 people; OR 0.50, 95% CI 0.29 to 0.85).[19] **Thrombocytopenia:** We found one systematic review[20] and one subsequent RCT.[21] The review (search date 1996, 3306 people treated for at least 5 days) found no significant difference between LMWH and unfractionated heparin in the risk of thrombocytopenia (RR 0.85, 95% CI 0.45 to 1.62).[20] The subsequent RCT (1137 people with symptomatic venous thromboembolism, open label) assessed the risk of thrombocytopenia with three treatments: LMWH for 5–7 days; LMWH for 26–30 days; or unadjusted dose unfractionated heparin for 5–7 days.[21] It found that short term LMWH was associated with less thrombocytopenia compared with long term LMWH or unfractionated heparin (0/388 [0%] with short term LMWH *v* 2/374 [0.53%] with long term LMWH *v* 2/375 [0.53%] with unfractionated heparin). The RCT did not assess the significance of the difference between groups.

Comment: **Studies assessing harm:** These varied in their diagnostic criteria and definitions of adverse events, making interpretation difficult.

OPTION LOW MOLECULAR WEIGHT HEPARIN VERSUS ORAL ANTICOAGULATION (LONG TERM)

One systematic review found no significant difference between long term low molecular weight heparin and oral anticoagulation in recurrent thromboembolism, major haemorrhage, or mortality. One subsequent RCT found no significant difference between low molecular weight heparin and oral anticoagulation in deep venous thrombosis recurrence at 1 year.

Benefits: We found one systematic review (search date 2001, 7 RCTs, 1137 people with proximal deep vein thrombosis treated initially with low molecular weight heparin [LMWH]G or unfractionated heparin [UFH] for 5–10 days, followed by either LMWH or vitamin k antagonists for 3–12 months) and one subsequent RCT comparing oral anticoagulation versus LMWH.[22,23] The review found no significant difference between LMWH for 3 months and oral anticoagulation for 3 months in mortality or recurrent symptomatic thromboembolism over 3–6 months (mortality: 21/568 [3.7%] with LMWH *v* 14/569 [2.5%] with oral anticoagulants; OR 1.51, 95% CI 0.77 to 2.97; recurrent symptomatic thromboembolism over 3–6 months: 27/568 [4.8%] with LMWH *v* 38/569 [6.7%] with oral anticoagulants; OR 0.70, 95% CI 0.42 to 1.16).[22] The subsequent RCT compared 6 months' treatment with intravenous unfractionated heparin followed by oral anticoagulation (requiring initial hospitalisation) versus outpatient treatment using subcutaneous LMWH.[23] It found no significant difference in recurrent deep venous thrombosis at 1 year (108 people with acute proximal deep venous thrombosis; AR for recurrence 3/50 [6%] with LMWH *v* 5/52 [9.6%] with oral anticoagulation; difference reported as not significant; figures not reported).

Harms: The review found that LMWH significantly reduced major haemorrhageG compared with long term oral anticoagulation (7 RCTs; 5/568 [0.9%] with LMWH *v* 14/569 [2.5%] with oral anticoagulation; OR 0.38, 95% CI 0.15 to 0.94). However, the review performed a separate analysis of RCTs that clearly concealed randomisation and were double blinded or where the assessor was blinded to outcome measures. When only these RCTs were included, it found no significant difference in major haemorrhage between long term LMWH and oral anticoagulation (3 RCTs; 4/236 [1.7%] with long term LMWH *v* 5/241 [2.1%] with anticoagulation; OR 0.80, 95% CI 0.21 to 3.00).[22] The subsequent RCT found no significant difference in major bleeding between subcutaneous LMWH and intravenous unfractionated heparin followed by oral anticoagulation, but was underpowered to detect a difference (108 people; 2/50 [4.0%] with LMWH *v* 4/52 [7.7%] with oral anticoagulation; reported as non-significant; figures not reported).[23]

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Thromboembolism

Comment: **Studies assessing harm:** These varied in their diagnostic criteria and definitions of adverse events, making interpretation difficult.

OPTION ONCE DAILY VERSUS TWICE DAILY LOW MOLECULAR WEIGHT HEPARIN

Systematic reviews found no significant difference between once and twice daily low molecular weight heparin in recurrent thromboembolism or mortality at 10 days or 3 months. However, the reviews may have been underpowered to detect a clinically important difference because of low rates of recurrent thromboembolism and mortality in the trials.

Benefits: We found two systematic reviews (search date 1999,[24] search date 2005,[25] 5 RCTs, 1522 adults with symptomatic proximal deep vein thrombosis) comparing once versus twice daily low molecular weight heparin (LMWH)G for 5–10 days. Both systematic reviews included the same five RCTs and found similar results. However, the first review[24] included more RCTs in its meta-analyses, so we report these results here. The reviews found no significant difference between once and twice daily LMWH in the proportion of people with symptomatic or asymptomatic venous thromboembolism at 10 days or 3 months (symptomatic venous thromboembolism at 10 days, 5 RCTs: 7/742 [0.9%] with once daily *v* 9/766 [1.2%] with twice daily; OR 0.82, 95% CI 0.26 to 2.49; at 3 months, 3 RCTs: 26/614 [4.2%] with once daily *v* 32/642 [5.1%] with twice daily; OR 0.85, 95% CI 0.48 to 1.49).[24] They also found no significant difference in mortality at 10 days or 3 months between once and twice daily LMWH, although mortality at 10 days was higher in people taking once daily LMWH (at 10 days, 5 RCTs: 7/750 [0.9%] with once daily *v* 1/772 [0.1%] with twice daily; OR 6.73, 95% CI 0.85 to 305; at 3 months, 2 RCTs: 20/614 [3.3%] with once daily *v* 20/646 [3.1%] with twice daily; OR 1.05, 95% CI 0.53 to 2.09). The reviews may have been underpowered to detect a clinically important difference between once daily and twice daily LMWH because of low rates of recurrent thromboembolism and mortality in the trials.

Harms: The first review found no significant difference in rates of major bleeding between once and twice daily LMWH (10/750 [1.3%] with once daily *v* 9/772 [1.2%] with twice daily; OR 1.16, 95% CI 0.42 to 3.24).[24]

Comment: Increased convenience but the potential for lower efficacy are elements to consider when deciding on once compared with twice daily regimens.

OPTION HOME TREATMENT WITH SHORT TERM LOW MOLECULAR WEIGHT HEPARIN

One systematic review of weak RCTs found no significant difference in recurrence of thromboembolism between heparin treatment at home and in hospital.

Benefits: We found one systematic review (search date 2004, 3 RCTs, 1104 people).[26] Two of the RCTs in the systematic review compared LMWH at home versus unfractionated heparin in hospital, and the other RCT compared LMWH both at home and in hospital. The RCTs had methodological problems, including high exclusion rates and partial hospital treatment in the home treatment arms. The systematic review found no significant difference between treatments in recurrence of thromboembolism or mortality.[26]

Harms: The systematic review found no significant difference between treatments in minor bleeding or major haemorrhageG.[26]

Comment: None.

OPTION COMPRESSION STOCKINGS

One systematic review found that elastic compression stockings reduced the incidence of post-thrombotic syndrome after a deep vein thrombosis.

Benefits: We found one systematic review (search date 2005, 3 RCTs, 421 people after deep vein thrombosis), which compared elastic compression stockings (exerting a pressure of 20–40 mm Hg at the ankle) versus no intervention or loose stockings.[27] It found that

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elastic compression stockings significantly reduced the incidence of any post-thrombotic syndrome and of severe post-thrombotic syndrome at 2 years (any post-thrombotic syndrome: AR 41/210 [20%] with compression stockings *v* 91/211 [44%] with no intervention; RR 0.46, 95% CI 0.34 to 0.62; severe post-thrombotic syndrome: AR 14/210 [7%] with compression stockings *v* 32/211 [16%] with no intervention; RR 0.44, 95% CI 0.25 to 0.80).

Harms: The systematic review and included RCTs did not report on harms.[27]

Comment: The systematic review analysed data on thigh and knee-high stockings together, because previous studies had found no difference in venous pressure measurements or foot volume between different stocking lengths.

OPTION VENAE CAVAE FILTERS

One RCT in people with proximal deep vein thrombosis considered at high risk of pulmonary embolism, all receiving oral anticoagulation, found that venae cavae filters reduced rates of pulmonary embolism at 12 days compared with no filters. However, the difference in rates of pulmonary embolism was not significant at 2 years, and venae cavae filters increased rates of recurrent deep vein thrombosis at 2 years.

Benefits: We found one open label, multicentre RCT (400 adults from 44 centres in France with venography confirmed proximal deep vein thrombosis considered at high risk of pulmonary embolism; 197/400 [49%] had concurrent pulmonary embolism diagnosed within 48 hours of admission).[28] The RCT compared four interventions in a two by two factorial design: venae cavae filters G (four different types); no filters; low molecular weight heparin (LMWH) G; and unfractionated heparin for 8–12 days. Heparin was given for 8–12 days, plus all participants received oral anticoagulation with warfarin or acenocoumarol for at least 3 months. There was no significant association between the type of heparin and use or not of filters (reported as non-significant, CI not reported); results for heparin and filters were analysed separately (see low molecular weight heparin option for comparison of LMWH v unfractionated heparin, p 6). The RCT found that venae cavae filters significantly reduced the incidence of pulmonary embolism at 12 days (2/200 [1%] with filter *v* 9/200 [5%] without filter; OR 0.22, 95% CI 0.05 to 0.90). However, it found no significant difference in pulmonary embolism at 2 years (6/200 [3%] with filters *v* 12/200 [6%] with no filters; OR 0.50, 95% CI 0.19 to 1.33), and found that venae cavae filters significantly increased rates of recurrent thromboembolism over 2 years (37/200 [19%] with filters *v* 21/200 [11%] with no filters; OR 1.87, 95% CI 1.10 to 3.20). It also found no significant difference in mortality at 2 years (43/200 [22%] with filters *v* 40/200 [20%] with no filters; OR 1.10, 95% CI 0.72 to 1.70).

Harms: The RCT found no significant difference between venae cavae filters and no filters in major bleeding (17/200 [9%] with filters *v* 22/200 [11%] with no filters; OR 0.77, 95% CI 0.41 to 1.45).[28]

Comment: None.

QUESTION What are the effects of treatment for isolated calf vein thrombosis?

OPTION ANTICOAGULATION

One RCT, in people who had received initial intravenous unfractionated heparin (international normalised ratio > 2.5–4.2) and wore compression stockings, found that warfarin reduced rates of proximal extension compared with no further treatment.

Benefits: **Warfarin or heparin versus placebo:** We found no RCTs comparing heparin versus placebo, warfarin versus placebo, or heparin plus warfarin versus placebo. **Warfarin plus heparin versus heparin alone:** We found no systematic review. We found one RCT

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Thromboembolism

(51 people), which compared intravenous unfractionated heparin (international normalised ratio 2.5–4.2) for at least 5 days with or without 3 months of warfarin.[6] All participants also wore compression stockings. It found that heparin plus warfarin significantly reduced proximal extension of clot at 1 year compared with heparin alone (1/23 [4%] people with heparin plus warfarin *v* 9/28 [32%] people with heparin alone; ARR 28%, 95% CI 9% to 47%).

Harms: **Warfarin plus heparin versus heparin alone:** The RCT found that two people taking warfarin plus heparin had clinically important bleeding.[6] No-one taking heparin alone had clinically important bleeding. See harms of anticoagulation under treatments for proximal deep vein thrombosis, p 4.

Comment: Many reported cases of isolated calf vein thrombosis are asymptomatic but detected radiologically for research purposes. We found limited evidence about the clinical importance of asymptomatic calf vein thrombosis. Similarly, studies into the incidence of pulmonary embolism associated with isolated calf vein thrombosis detected asymptomatic embolism by ventilation–perfusion scanning, and the clinical relevance of these findings is unclear.

OPTION PROLONGED DURATION OF ANTICOAGULATION

One open label RCT found no significant difference in recurrent thromboembolism or rates of major haemorrhage between 6 and 12 weeks of warfarin. The absolute risk of recurrent venous thromboembolism decreases with time, but the relative risk reduction with treatment remains constant. Harms of treatment, including major haemorrhage, continue during prolonged treatment. Individuals have different risk profiles and it is likely that the optimal duration of anticoagulation will vary.

Benefits: We found one open label RCT (736 people with proximal deep vein thrombosis, pulmonary embolism, or isolated calf vein thrombosis; 197 with isolated calf vein thrombosis) comparing 6 weeks versus 12 weeks of warfarin.[29] A pre-planned subgroup analysis in people with isolated calf vein thrombosis found no significant difference in recurrence of venous thromboembolism (AR 2/105 [1.9%] with 6 weeks *v* 3/92 [3.3%] with 12 weeks; RR 0.58, 95% CI 0.10 to 3.36). However, the study may have lacked power to exclude a clinically important effect.[29]

Harms: The RCT found no significant difference in rates of haemorrhage between 6 weeks and 12 weeks of warfarin in people with isolated calf vein thrombosis (AR 13/105 [12.4%] with 6 weeks *v* 19/92 [20.6%] with 12 weeks; RR 0.59, 95% CI 0.31 to 1.26).[29]

Comment: Many reported cases of isolated calf vein thrombosis are asymptomatic but detected radiologically for research purposes. We found limited evidence about the clinical importance of asymptomatic calf vein thrombosis. Similarly, studies into the incidence of pulmonary embolism associated with isolated calf vein thrombosis detected asymptomatic embolism by ventilation–perfusion scanning, and the clinical relevance of these findings is unclear (see also comment about prolonged duration of anticoagulation under proximal deep vein thrombosis, p 6).

QUESTION What are the effects of treatments for pulmonary embolism?

OPTION ANTICOAGULATION

We found no RCTs comparing heparin versus placebo, warfarin versus placebo, or heparin plus warfarin versus heparin alone or versus warfarin alone. One small RCT found that heparin plus warfarin reduced mortality at 1 year compared with no anticoagulation. Anticoagulants are associated with increased risk of haemorrhage.

Benefits: **Warfarin or heparin versus placebo:** We found no RCTs comparing heparin versus placebo or warfarin versus placebo. **Heparin plus warfarin versus no anticoagulation:** We found no systematic review. We found one RCT (published in

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1960; 35 people with pulmonary embolism) comparing heparin plus warfarin versus no anticoagulation.[30] It found that anticoagulation significantly reduced mortality at 1 year compared with no anticoagulation (0/16 [0%] deaths with anticoagulation *v* 5/19 [26%] deaths with no anticoagulation: NNT 4, 95% CI 2 to 16). **Warfarin plus heparin versus warfarin or heparin alone:** We found no RCTs.

Harms: **Heparin plus warfarin versus no anticoagulation:** The RCT gave no information on adverse effects.[30] See harms of anticoagulation under treatments for proximal deep vein thrombosis, p 4.

Comment: None.

OPTION PROLONGED DURATION OF ANTICOAGULATION

In people who had received anticoagulants for 3 months after a pulmonary embolism, one RCT found no significant difference in recurrence of venous thromboembolism between a further 3 months of oral anticoagulation and longer duration treatment (up to 9 months). However, the RCT may have lacked power to detect a clinically important effect. Additional evidence for duration of treatment has been extrapolated from RCTs in people with proximal deep vein thrombosis and any venous thromboembolism, which found that longer courses of anticoagulation reduced recurrence compared with shorter courses but may increase the risk of major haemorrhage.

Benefits: We found one RCT (326 people with pulmonary embolism and previous anticoagulant treatment for 3 months) comparing continued treatment with oral anticoagulant (warfarin or acenocoumarol to target international normalised ratio G 2.0–3.0) for a short duration (3 months) versus a longer duration (6 months for people with transient risk factors or 9 months for people with no identifiable risk factors). It found no significant difference in recurrence of venous thromboembolism at about 3 years (AR 15/165 [9.1%] with short duration *v* 18/161 [11.2%] with longer duration; RR 0.82, 95% CI 0.42 to 1.56).[31] However, the RCT may have lacked power to detect a clinically important effect.

Harms: The RCT found similar major bleeding rates and mortality between short duration and longer duration oral anticoagulation at about 3 years (major bleeding: AR 1/161 [0.6%] with short duration *v* 3/165 [1.8%] with longer duration; mortality: AR 7/161 [4.2%] with short duration *v* 12/165 [7.5%] with longer duration).[31]

Comment: The RCT reported only one episode of recurrent thromboembolism during anticoagulation treatment. Other than this RCT, we found no direct evidence in people with pulmonary embolism. Evidence for intensity and duration of treatment has been extrapolated from RCTs in people with proximal deep vein thrombosis and any venous thromboembolism. These trials found that longer courses of anticoagulation reduced recurrence compared with shorter courses (see benefits of anticoagulation under treatments for proximal deep vein thrombosis, p 4) but may increase the risk of major haemorrhage haemorrhage G.

OPTION HIGH INTENSITY ANTICOAGULATION

We found no direct evidence in people with pulmonary embolism about the optimum intensity of anticoagulation. Evidence for intensity of treatment has been extrapolated from RCTs in people with proximal deep vein thrombosis and any venous thromboembolism, which found that bleeding rates were increased by higher intensity anticoagulation (target international normalised ratio 3.0–4.5), but recurrence rates were not significantly different compared with a lower intensity anticoagulation (target international normalised ratio 2.0–3.0).

Benefits: We found no direct evidence (see comment below).

Harms: We found no direct evidence (see comment below).

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Thromboembolism

Comment: Evidence for intensity of treatment has been extrapolated from RCTs in people with proximal deep vein thrombosis and any venous thromboembolism. These trials found that recurrence rates were not significantly different with higher international normalised ratio G target ranges (international normalised ratio 3.0–4.5) compared with a lower range (international normalised ratio 2.0–3.0), but bleeding rates were increased by higher international normalised ratio target ranges.

OPTION LOW MOLECULAR WEIGHT HEPARIN VERSUS UNFRACTIONATED HEPARIN

One systematic review in people with symptomatic or asymptomatic pulmonary embolism found no significant difference in recurrent venous thromboembolism or survival between low molecular weight heparin and unfractionated heparin up to 3 months after treatment. The RCTs in the systematic review found no significant difference in major haemorrhage between low molecular weight heparin and unfractionated heparin but may have been underpowered to detect a clinically important difference.

Benefits: We found one systematic review (search date 2003, 12 RCTs, 1951 people with symptomatic or asymptomatic pulmonary embolism), which compared low molecular weight heparin (LMWH) G versus intravenous unfractionated heparin.[32] It found no significant difference in recurrent venous thromboembolism at the end of treatment or at 3 months after treatment (at the end of treatment: AR 14/1023 [1.4%] with LMWH *v* 22/928 [2.4%] with unfractionated heparin; OR 0.63, 95% CI 0.33 to 1.18; 3 months after treatment: AR 30/988 [3.0%] with LMWH *v* 39/895 [4.4%] with unfractionated heparin; OR 0.68, 95% CI 0.42 to 1.09). It also found no significant difference in deaths from any cause (AR 14/1023 [1.4%] with LMWH *v* 11/928 [1.2%] with unfractionated heparin; OR 1.20, 95% CI, 0.59 to 2.45).

Harms: The systematic review found no significant difference in major bleeding between LMWH or unfractionated heparin (AR 14/1023 [1.4%] with LMWH *v* 21/928 [2.3%] with unfractionated heparin; OR 0.67, 95% CI 0.36 to 1.27).[32] See harms of anticoagulation under treatments for proximal deep vein thrombosis, p 4. However, the incidence of major haemorrhage G was low and the number of people is likely to have been too small to detect a clinically important difference.

Comment: The meta-analysis may have lacked power to detect clinically important effects of LMWH.

OPTION THROMBOLYSIS

One systematic review found no significant difference in mortality or recurrence of pulmonary embolism between thrombolysis (plus anticoagulants) and heparin alone. It found that thrombolysis (plus anticoagulants) increased the incidence of non-major bleeding events, but not major bleeding events, compared with heparin alone. Subgroup analysis suggested a possible benefit in reducing mortality or recurrence of pulmonary embolism for people with major (haemodynamically unstable) pulmonary embolism. RCTs identified by a systematic review found no significant difference in mortality or recurrent pulmonary embolism among different thrombolytics.

Benefits: **Thrombolysis versus heparin:** We found one systematic review (search date 2003, 11 RCTs, 748 people with acute pulmonary embolism).[33] It found no significant difference in recurrent pulmonary embolism or death between thrombolysis (plus anticoagulation) and heparin (AR 25/374 [6.7%] with thrombolysis *v* 36/374 [9.6%] with heparin; OR 0.67, 95% CI 0.40 to 1.13).[33] However, subgroup analysis in people who were haemodynamically unstable found that thrombolysis significantly reduced recurrent pulmonary embolism or death compared with heparin alone (AR 9.4% with thrombolysis *v* 19.0% with heparin alone; OR 0.45, 95% CI 0.22 to 0.92). **Different thrombolytics:** We found one systematic review (search date 1998, 6 RCTs, 491 people) comparing different thrombolytic agents versus each other.[34] The review did not perform a meta-analysis. It found no significant difference in mortality or recurrent pulmonary embolism among different thrombolytics in the individual RCTs.

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Harms: **Thrombolysis plus anticoagulants versus heparin alone:** The systematic review found no significant difference in major bleeding between thrombolysis (plus anticoagulants) and heparin (AR 32/373 [9.1%] with thrombolysis *v* 23/374 [6.1%] with heparin; OR 1.42, 95% CI 0.81 to 2.46).[33] However, it found that thrombolysis (plus anticoagulants) significantly increased non-major bleeding events compared with heparin (AR 52/233 [22.7%] with thrombolysis *v* 22/221 [10.0%] with heparin; OR 2.63, 95% CI 1.53 to 4.54).[33]

Comment: **Thrombolysis plus heparin versus heparin alone:** One additional, non-randomised trial (719 people), which excluded people with shock, found limited evidence that thrombolytics reduced overall mortality (8/169 [5%] with thrombolytics *v* 61/550 [11%] with heparin; RR 0.43, 95% CI 0.21 to 0.87) and recurrent pulmonary embolism over 30 days compared with heparin (13/169 [8%] with thrombolytics *v* 103/550 [19%] with heparin; RR 0.25, 95% CI 0.13 to 0.51).[35] However, these results should be interpreted with caution because participants were not randomised, and people receiving heparin were older and more likely to have underlying cardiac or pulmonary disease than those receiving thrombolytics.

QUESTION What are the effects of computerised decision support on oral anticoagulation management?

OPTION COMPUTERISED DECISION SUPPORT

We found no RCTs comparing computerised decision support versus usual management of oral anticoagulation that used clinically important outcomes (major haemorrhage or death). One systematic review and six subsequent RCTs found that, compared with usual care, the use of computerised decision support in oral anticoagulation increased the time spent in the target international normalised range. Another subsequent RCT found no significant difference between computerised decision support and standard manual support in the time spent in the target international normalised ratio range.

Benefits: **Clinical outcomes:** We found no systematic review and no RCTs. **Laboratory outcomes:** We found one systematic review[36] and seven subsequent RCTs.[37–43] The review (search date 1997, 9 RCTs, 1336 people) included eight RCTs using warfarin and one using heparin.[36] The computer systems advised the doses for initiation of anticoagulation (2 RCTs) and for maintenance of anticoagulation (6 RCTs). Follow up was short (15 days to 12 months). Indications for treatment included cardiac diseases and venous thrombosis. The outcome reported by seven RCTs (693 people) in the systematic review was the proportion of days within the target range of anticoagulation. The review found that computerised decision support G increased the time that the international normalised ratio G (INR) was in the target range compared with usual care (OR 1.29, 95% CI 1.12 to 1.49). Reanalysis, excluding one trial that introduced significant heterogeneity, found similar results (OR for remaining RCTs 1.25, 95% CI 1.08 to 1.45). The first subsequent RCT (285 people) compared a computerised decision support dosing system versus physician adjusted dosing in five hospitals.[37] People who were taking warfarin for at least 6 days were selected and followed for at least 3 months (results not analysed by intention to treat; results from 254 people [89%] analysed). People managed by computerised decision support spent significantly more time with their INR in the target range than people managed conventionally (63% with computerised decision support *v* 53% with conventional management; $P < 0.05$).[37] The second subsequent RCT (244 people) compared a package of care that included computerised decision support versus traditional hospital outpatient management.[38] The intervention was based in primary care: a practice nurse clinic that included near patient INR testing and computerised decision support. It found significantly more time spent in the target range after 12 months with packaged care compared with traditional outpatient management (69% with packaged care *v* 57% with traditional care; $P < 0.001$). It found no significant difference in the proportion of tests in range (61% with packaged care *v* 51% with traditional care; reported as non-significant, no further data reported) or in the point prevalence of tests in range (71% with packaged care *v* 62% with traditional care; reported as non-significant, no further data reported).[38] The third subsequent RCT (101

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Thromboembolism

people receiving oral anticoagulation after heart valve replacement) compared a computerised decision support system versus standard manual monitoring of INR over 315 days.[39] It found no significant difference in the proportion of INRs in the target range or time spent in the target range (no further data and no mean follow up time reported). It found that people had significantly fewer dose changes with computerised than with standard manual monitoring (31% with computerised *v* 47% with manual; $P = 0.02$). The fourth subsequent RCT (335 people receiving initiation, 916 people receiving maintenance anticoagulation treatment for a variety of indications) compared a computerised decision support system for both dosing and appointment scheduling versus standard manual monitoring by "expert physicians".[40] It found that significantly more people managed by computerised decision support achieved a stable INR in the first month and spent more time with their INR in the target range over 3 months than people managed by standard monitoring (achieved stable range: 39% with computerised decision support *v* 27% with standard monitoring; $P < 0.01$; remained in range: 71% with computerised decision support *v* 68% with standard monitoring; $P < 0.001$). The fifth subsequent RCT (122 people on warfarin after hip replacement) compared usual care versus computerised decision support.[41] Only initiation of warfarin was studied. It found that computerised decision support significantly reduced the mean time taken to reach therapeutic levels of anticoagulation compared with usual care (2.8 days with computerised decision support *v* 4.7 days with usual care; $P = 0.002$). The sixth subsequent RCT (crossover design, 1880 people attending an anticoagulation clinic and receiving oral anticoagulants for ≥ 4 weeks) found that computerised decision support significantly increased the percentage of time in the target INR range compared with standard monitoring over 10 weeks (AR 65.5% with computerised decision support *v* 67.3% with standard monitoring; $P < 0.002$).[42] The seventh subsequent RCT found that computerised decision support significantly increased the proportion of time spent in the target INR range compared with physician dosing in hospital inpatients (30 people in hospital who were already receiving warfarin for a variety of indications, mean length of stay 35 days, target INR 2.0–3.0; time spent in target INR range: 61.7% with computerised decision support *v* 44.1% with physician dosing; $P < 0.05$).[43] In this RCT, physicians performed worse than in many of the other studies quoted above.

Harms: One systematic review (search date 1997, 9 RCTs, 1336 people) found major haemorrhage G in 14/700 (2%) people with computerised decision support compared with 25/636 (4%) in the standard monitoring group.[36] Most of the events occurred in one study, making meta-analysis inappropriate. One RCT found no significant difference in overall mortality or serious adverse events with computerised decision support versus usual care.[37]

Comment: We found limited evidence (from small trials with short follow up of proxy outcomes) on the use of computerised decision support in oral anticoagulation management. Computerised decision support for oral anticoagulation seems to be at least as effective as human performance in terms of time spent in the target INR range. It is not clear if this will translate to improved clinical outcomes. Larger and longer trials that measure clinical outcomes (particularly harms) are needed.

GLOSSARY

Computerised decision support system A computer program that provides advice on the significance and implications of clinical findings or laboratory results.

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 regions is minimised. Normal blood has an international normalised ratio of 1.0. Therapeutic anticoagulation often aims to achieve an international normalised ratio value of 2.0–3.5.

Low molecular weight heparin (LMWH) is made from heparin using chemical or enzymatic methods. The various formulations of LMWH differ in mean molecular weight, composition, and anticoagulant activity. As a group, LMWHs have distinct properties and it is not yet clear if one LMWH will behave exactly like another. Some LMWHs given subcutaneously do not require monitoring.

Major haemorrhage Exact definitions vary between studies, but usually a major haemorrhage is one involving intracranial, retroperitoneal, joint, or muscle bleeding leading directly to death or requiring

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admission to hospital to stop the bleeding or provide a blood transfusion. All other haemorrhages are classified as minor.

Venae cavae filters Devices inserted in the inferior vena cava to prevent the migration of blood clots from the peripheral veins to the pulmonary circulation system.

Substantive changes

Prolonged duration of anticoagulation One systematic review updated;[12] categorisation unchanged (Trade off between benefits and harms).

High intensity oral anticoagulation Categorisation changed from Unknown effectiveness to Unlikely to be beneficial based on re-evaluation of the evidence.

Low molecular weight heparin One systematic review added.[19] benefits data enhanced; categorisation changed from Likely to be beneficial to Beneficial.

Low molecular weight heparin versus oral anticoagulation (long term) One RCT added;[23] categorisation unchanged (Unknown effectiveness).

Low molecular weight heparin versus unfractionated heparin Categorisation changed from Trade-off between benefits and harms to Unknown effectiveness based on re-evaluation of the evidence.

Computerised decision support in oral anticoagulation One RCT added;[43] categorisation unchanged (unknown effectiveness).

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Competing interests: DF has been reimbursed by LEO laboratories for speaking and attending symposia. DF and RH are co-authors of an RCT that is referenced in this chapter. RM has received research funding from sanofi aventis and funding to attend a research conference from MSD. THe Department of Primary care and General Practice, The University of Birmingham (where the authors work), produce and market a specific Computerised Decision Support Software package which commercially available. FDRH is a member of the European Society of Cardiology (ESC) Working Party on Heart Failure, Treasurer of the British Society for Heart Failure, and Chair of the British Primary Care Cardiovascular Society (PCCS). He has received travel sponsorship and honoraria from several multinational biotechnology and pharmaceutical companies with cardiovascular products for plenary talks and attendance at major cardiology scientific congresses and conferences.

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Varicose veins

Search date March 2005

Paul Tisi

QUESTIONS

INTERVENTIONS

TREATMENTS

Likely to be beneficial

Unknown effectiveness

To be covered in future updates

Self help (exercise, diet, elevation of legs, advice).

*Categorisation based on consensus.

See glossary

Key Messages

Treatments

- **Surgery (avulsion)*** We found no RCTs comparing avulsion versus no treatment or compression stockings. We found conflicting results from three RCTs that compared avulsion plus stripping of the long saphenous vein to the knee versus avulsion. The first RCT found that avulsion of the long saphenous vein to the knee increased clinical recurrence, and decreased participant satisfaction compared with avulsion plus stripping. The second RCT found no significant difference between avulsion and avulsion plus stripping in recurrence or participant satisfaction at 5 years. The third RCT found that avulsion decreased pain compared with avulsion plus stripping after 1 week. However, it found no significant difference between treatments in daily activity scores at 1 week. One RCT found no significant difference between avulsion and powered phlebectomy in pain at 8 days, or in participant satisfaction or cosmetic appearance at 6 weeks. It also found no significant difference between treatments in nerve injury or severe bruising after 2 weeks.
- **Surgery (stripping)*** We found no RCTs comparing stripping (partial or total, with or without avulsion) versus no treatment or compression stockings. We found conflicting results from three RCTs that compared stripping plus avulsion of the long saphenous vein to the knee versus avulsion. The first RCT found that stripping plus avulsion of the long saphenous vein decreased clinical recurrence, and increased participant satisfaction compared with avulsion alone. The second RCT found no significant difference between stripping plus avulsion and avulsion in recurrence or participant satisfaction at 5 years. The third RCT found that stripping plus avulsion increased pain and bruising compared with avulsion after 1 week. However, it found no significant difference between treatments in daily activity scores at 1 week. One RCT found similar improvements in clinician assessed clinical outcome with both partial stripping of the long saphenous vein to the knee and total stripping to the ankle. However, it found that partial stripping to the knee reduced the incidence of saphenous nerve damage compared with total stripping to the ankle. One RCT found that inversion stripping reduced pain scores compared with conventional stripping at 1 week. The RCT found no significant difference between treatments in bruising after 1 week.
- **Compression stockings** One crossover RCT found no significant difference in symptoms between compression stockings for 4 weeks and no treatment in people with varicose veins. However, the study may have lacked power to detect clinically important effects. One systematic review found that, in pregnant women with varicose veins, sodium tetradecyl sulphate sclerotherapy improved symptoms and cosmetic appearance of varicose veins compared with compression stockings after 6–24 months.
- **Injection sclerotherapy** One systematic review found no RCTs that compared injection sclerotherapy versus no treatment. One RCT identified by a systematic review found that, in pregnant women with varicose veins, sodium tetradecyl sulphate sclerotherapy improved symptoms and cosmetic appearance of varicose veins compared with compression stockings after 6–24 months. One RCT found no significant difference between sclerotherapy using polidocanol and using sodium

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Varicose veins

tetradecyl sulphate for improving the appearance of varicose veins at 16 weeks. One RCT found that polidocanol plus sodium tetradecyl improved symptoms and reduced oedema compared with polidocanol or sodium tetradecyl sulphate alone. One RCT reported a similar incidence of new varicose veins at 5 or 10 years with standard dose conventional sclerotherapy, high dose conventional sclerotherapy, and foam sclerotherapy. One systematic review found that surgery (avulsion, stripping, ligation with or without sclerotherapy) significantly reduced varicose vein recurrence and cosmetic appearance compared with injection sclerotherapy alone.

- **Surgery (powered phlebectomy)** We found no RCTs comparing powered phlebectomy versus no treatment or compression stockings. One RCT found no significant difference between powered phlebectomy and avulsion in pain at 8 days, or in participant satisfaction or cosmetic appearance at 6 weeks. It also found no significant difference between treatments in nerve injury or severe bruising after 2 weeks.

*Categorisation based on consensus.

DEFINITION

Although we found no consistent definition of varicose veins,[1] the term is commonly taken to mean veins that are enlarged, twisted, and painful. Varicose veins may appear dark blue or purple in colour and commonly occur on the back of the calves or on the inside of the legs. Any vein may become varicose, but the term "varicose veins" conventionally applies to the superficial veins of the leg. The condition is caused by poorly functioning (incompetent) valves within the veins and decreased elasticity of the vein walls, which allow de-oxygenated blood being pumped back to the heart to flow backward and pool in the superficial veins, causing them to enlarge and become varicose. This most often occurs in the saphenofemoral and saphenopopliteal junctions and the perforating veins that connect the deep and superficial venous systems along the length of the leg. The presence or absence of reflux due to venous incompetence can be determined by clinical examination, handheld Doppler, or duplex ultrasound. Symptoms of varicose veins include pain, itching, limb heaviness, cramps, and distress about cosmetic appearance. This chapter focuses on uncomplicated, symptomatic varicose veins. We have excluded treatments for chronic venous ulceration and other complications. We have also excluded studies that solely examine treatments for small, dilated veins in the skin of the leg, known as thread veins, spider veins, or superficial telangiectasia G.

INCIDENCE/ PREVALENCE

One large US cohort study found the biannual incidence of varicose veins to be 2.6% in women and 2.0% in men.[2] The prevalence of varicose veins in Western populations was estimated in one study to be about 25–30% among women and 10–20% in men.[3] A recent Scottish cohort study has, however, found a higher prevalence of varices of the saphenous trunks and their main branches in men than in women (40% men *v* 32% women).[4]

AETIOLOGY/ RISK FACTORS

One large case control study found that women with two or more pregnancies were at increased risk of varicose veins compared with women with fewer than two pregnancies (RR about 1.2–1.3 after adjustment for age, height, and weight).[2] It found that obesity was also a risk factor, although only among women (RR about 1.3). One narrative systematic review found insufficient evidence on the effects of other suggested risk factors, including genetic predisposition, prolonged sitting or standing, tight undergarments, low fibre diet, constipation, deep vein thrombosis, and smoking.[3]

PROGNOSIS

We found no reliable data on prognosis, or on the frequency of complications, which include chronic inflammation of affected veins (phlebitis), venous ulceration, and rupture of varices.

AIMS OF INTERVENTION

To reduce symptoms, improve appearance, and prevent recurrence and complications, with minimal adverse effects.

OUTCOMES

Symptoms, including pain, ache, itching, heaviness, cramps, and cosmetic distress or cosmetic appearance (self or physician rated); quality of life; recurrence rates; complications of treatment, including haematoma formation; pigmentation; ulceration; superficial thrombophlebitis; and deep venous and pulmonary thromboembolism. Retreatment rates were considered only if other outcomes were unavailable, and are described only in comments.

METHODS

Clinical Evidence search and appraisal March 2005.

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QUESTION What are the effects of treatments in adults with varicose veins?

OPTION COMPRESSION STOCKINGS

One crossover RCT found no significant difference in symptoms between compression stockings for 4 weeks and no treatment in people with varicose veins. However, the study may have lacked power to detect clinically important effects. One systematic review found that, in pregnant women with varicose veins, sodium tetradecyl sulphate sclerotherapy improved symptoms and cosmetic appearance of varicose veins compared with compression stockings after 6–24 months.

Benefits: **Compression stockings versus no treatment:** We found one crossover RCT (72 people aged < 65 years with ≥ 2 of the following symptoms: pain, heaviness, itch, night cramps, swelling, or cosmetic distress).[5] People with a history of deep vein thrombosis were excluded. The study did not specify the sites of venous incompetence. It compared four treatments: a pharmacological agent (O-[beta-hydroxyethyl]-rutoside, 1 g/day orally), placebo alone, stockings plus placebo, and stockings plus the drug. Stockings were fitted to apply a pressure of 30–40 mm Hg to each ankle. Each treatment was given for 4 weeks before crossover to another treatment. The trial found no significant difference between stockings plus placebo and placebo alone for any symptom scores after each treatment (analysis not by intention to treat; 6 people excluded from analysis; symptom scores measured on 100 point visual analogue scale [high score = more severe]; pain: mean score 35 with stockings *v* 38 with placebo; P = 0.06; heaviness: 34 with stockings *v* 36 with placebo; P = 0.39; itch: 32 with stockings *v* 31 with placebo; P = 0.56; swelling: 28 with stockings *v* 35 with placebo; P = 0.13; night cramps: 22 with stockings *v* 25 with placebo; P = 0.24; cosmetic distress: 43 with stockings *v* 41 with placebo; P = 0.43). The RCT may have lacked power to detect clinically important effects. **Versus injection sclerotherapy:** See benefits of injection sclerotherapy, p 3. **Versus surgery:** See benefits of surgery, p 6.

Harms: The RCT did not report on the harms of compression stockings.[5]

Comment: **Compression stockings versus no treatment:** The RCT did not report whether investigators were blinded to treatment allocation.[5] Reliability of results could be reduced because previous treatments might have continued to have effects, even after crossover. The study did not report the duration of any washout period, which may have reduced such an effect between treatment periods.

OPTION INJECTION SCLEROTHERAPY

One systematic review found no RCTs that compared injection sclerotherapy versus no treatment. One RCT identified by a systematic review found that, in pregnant women with varicose veins, sodium tetradecyl sulphate sclerotherapy improved symptoms and cosmetic appearance of varicose veins compared with compression stockings after 6–24 months. One RCT found no significant difference between sclerotherapy using polidocanol and using sodium tetradecyl sulphate for improving the appearance of varicose veins at 16 weeks. One RCT found that polidocanol plus sodium tetradecyl improved symptoms and reduced oedema compared with polidocanol or sodium tetradecyl sulphate alone. One RCT reported a similar incidence of new varicose veins at 5 or 10 years with standard dose conventional sclerotherapy, high dose conventional sclerotherapy, and foam sclerotherapy. One systematic review found that surgery (avulsion, stripping, ligation with or without sclerotherapy) significantly reduced varicose vein recurrence and cosmetic appearance compared with injection sclerotherapy alone.

Benefits: **Injection sclerotherapy versus no treatment:** One systematic review (search date 2002) found no RCTs.[1] **Injection sclerotherapy versus compression stockings:** One systematic review (search date 2002) found one RCT (101 pregnant women with primary or recurrent varicose veins), which compared sclerotherapy using sodium tetradecyl sulphate versus compression stockings.[1] It found that sclerotherapy significantly improved symptoms and cosmetic appearance compared with compression

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Varicose veins

stockings after 6–24 months (improved symptoms and cosmetic appearance: 43/44 [98%] with sclerotherapy *v* 17/28 [61%] with compression stockings; RR 1.61, 95% CI 1.19 to 2.18). **Injection sclerotherapy versus surgery:** We found one systematic review (search date 2004, 6 relevant RCTs) which compared sclerotherapy versus surgery.[6] The review did not conduct a meta-analysis of the results of the RCTs due to heterogeneity of the data. The first RCT identified by the review (164 people with symptomatic primary varicose veins, aged 21–65 years) compared injection sclerotherapy (polidocanol 30 mg/mL; 0.5–0.75 mL injected into each varicosity, repeated after 1–2 weeks if required) versus surgery.[7] Participants were allocated to treatments without regard to site of venous incompetence (53 legs with saphenofemoral or saphenopopliteal incompetence alone; 97 legs with saphenofemoral or saphenopopliteal incompetence combined with perforator incompetence; 17 legs with perforator incompetence only). Among people allocated to surgery, the surgical technique depended on the site of venous incompetence (see comment below). The RCT found that surgery increased the proportion of people who were free of varicose veins at 5 years compared with injection sclerotherapy (AR for freedom from varicose vein at 5 years: 3% with sclerotherapy *v* 55% with surgery; significance not reported; see comment below). The second RCT (249 people with varicose veins but no prior treatment, aged 15–64 years) compared injection sclerotherapy versus surgery.[8] The study did not specify the proportions of people with saphenofemoral, saphenopopliteal, or perforator incompetence. The extent and type of surgery depended on the site of venous incompetence (see comment below). The trial did not report on symptoms, quality of life, or recurrence (see comment below). The third RCT (82 people aged over 18 years) compared sclerotherapy (3% polidocanol; repeat treatments at 2 and/or 4 weeks as necessary) versus avulsion G under local anaesthetic.[9] People with saphenofemoral or deep venous incompetence were excluded. Sclerotherapy significantly increased recurrence at 1 and 2 years compared with avulsion (AR for recurrence at 1 year: 25% with sclerotherapy *v* 2.1% with avulsion; RR 12, 95% CI 1.62 to 88.7; AR for recurrence at 2 years: 37.5% with sclerotherapy *v* 2.1% with avulsion; RR 18, 95% CI 2.5 to 129.5). The fourth RCT (887 people with long saphenous incompetence, with or without perforator incompetence; see above) compared six treatments: standard dose conventional sclerotherapy (148 people); high dose conventional sclerotherapy (136 people); foam sclerotherapy G (150 people); ligation G (155 people); stab avulsion (144 people); and combined ligation and high dose conventional sclerotherapy (154 people).[10] Avulsion or ligation with or without sclerotherapy reduced the incidence of new varicose veins at 5 and 10 years compared with sclerotherapy alone, although it was not clear whether differences were significant (AR for new varicose veins at 5 years: 48% with standard dose sclerotherapy *v* 41% with high dose sclerotherapy *v* 44% with foam sclerotherapy *v* 34% with ligation *v* 40% with stab avulsion *v* 37% with ligation plus sclerotherapy; AR for new varicose veins at 10 years: 56% standard dose sclerotherapy *v* 49% high dose sclerotherapy *v* 51% foam sclerotherapy *v* 38% ligation *v* 41% stab avulsion *v* 37% ligation plus sclerotherapy; significance not reported for any outcome). The fifth RCT (516 people with primary varicose veins) compared three treatments: conventional long or short saphenous surgery under general anaesthetic (161 people), local anaesthetic ligation of the saphenofemoral or saphenopopliteal junctions followed by injection sclerotherapy (165 people), or injection sclerotherapy with 3% aethoxysklerol (137 people).[11] It found that conventional surgery significantly improved objective outcomes (appearance of varicose veins, as judged by the surgeon) and subjective outcomes (appearance of varicose veins, as judged by the participant) compared with ligation plus sclerotherapy at 3 years ($P < 0.0005$). It also found that ligation plus sclerotherapy significantly improved objective and subjective outcomes compared with sclerotherapy alone at 3 years ($P < 0.0005$). The sixth RCT (156 patients with primary long saphenous incompetence, 181 limbs) compared ligation plus stripping G of the long saphenous vein to the ankle (78 people, 89 limbs) versus ligation plus sclerotherapy using 1% aethoxysklerol (78 people, 92 limbs).[12] It found that ligation plus stripping significantly improved both subjective cosmetic appearance (as judged by the participant) and objective cosmetic appearance (as judged by the surgeon) compared with ligation plus sclerotherapy at 3 years (subjective improvement: 72% with surgery *v* 54% with sclerotherapy; $P < 0.05$; objective improvement: 61% with surgery *v* 39% with sclerotherapy; $P < 0.05$). **Different types of sclerosant:** See glossary G . One systematic review (search date

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2002) found no RCTs reporting clinical outcomes in people with varicose veins.[1] We found two subsequent RCTs.[13,14] The first subsequent RCT (87 people with a total of 109 varicose veins; 55 veins 1–3 mm diameter; 54 veins 3–6 mm diameter) excluded people with saphenofemoral or saphenopopliteal incompetence.[13] Each vein, rather than each person, was randomly allocated to injection sclerotherapy with either polidocanol or sodium tetradecyl sulphate. The strength of solution depended on the size of the vein being treated (veins 1–3 mm diameter: polidocanol 1% or sodium tetradecyl sulphate 0.5%; veins 3–6 mm diameter: polidocanol 3% or sodium tetradecyl sulphate 1.5%). The RCT found no significant difference between polidocanol and sodium tetradecyl sulphate in change in photographic appearance of either size group of veins 16 weeks after treatment (scale of 1–5 [1 = worse than pretreatment photograph; 5 = complete disappearance]; mean score for veins 1–3 mm diameter: 4.6 with sodium tetradecyl sulphate *v* 4.4 with polidocanol; P = 0.83; mean score for veins 3–6 mm diameter: 4.5 with sodium tetradecyl sulphate *v* 4.7 with polidocanol; P = 0.58). The second subsequent RCT (1622 people) compared three treatments: polidocanol, sodium tetradecyl sulphate, and polidocanol plus sodium tetradecyl sulphate.[14] It found that polidocanol plus sodium tetradecyl sulphate improved symptoms (night cramps, pains, fatigue, and heaviness) and reduced oedema compared with polidocanol or sodium tetradecyl sulphate alone, at 5 years (symptoms: 211/306 [69%] with polidocanol *v* 277/380 [73%] with sodium tetradecyl sulphate *v* 180/228 [79%] with polidocanol plus sodium tetradecyl sulphate; significance not reported; oedema: 185/304 [61%] with polidocanol *v* 123/152 [64%] with sodium tetradecyl sulphate *v* 27/36 [74%] with polidocanol plus sodium tetradecyl sulphate; significance not reported).**Foam sclerotherapy versus conventional sclerotherapy:** We found two RCTs.[10,15] The first RCT (887 people with uncomplicated varicose veins and long saphenous vein incompetence, with or without perforator incompetence) compared six treatment arms: standard dose conventional sclerotherapy (1–2 mL 2% or 3% sodium tetradecyl sulphate according to vein calibre, with 2–3 weeks' compression after sclerotherapy); high dose conventional sclerotherapy (3–6 mL 3% sodium tetradecyl sulphate, with 1–2 weeks' compression); foam sclerotherapy (foaming agent plus 3% sodium tetradecyl sulphate); ligation; stab avulsion; and ligation plus sclerotherapy.[10] The RCT found that the incidence of new varicose veins was similar with foam sclerotherapy, standard dose conventional sclerotherapy, and high dose conventional sclerotherapy at 5 and 10 years (AR for new veins at 5 years: 48% with standard dose sclerotherapy *v* 41% with high dose sclerotherapy *v* 44% with foam sclerotherapy; AR for new veins at 10 years: 56% with standard dose sclerotherapy *v* 49% with high dose sclerotherapy *v* 51% with foam sclerotherapy; significance not reported). The second RCT (88 people with long saphenous incompetence) compared sclerotherapy with 3% polidocanol foam versus 3% polidocanol liquid.[15] The RCT did not report on clinical outcomes other than harms (see harms below).

Harms:

Injection sclerotherapy versus no treatment: We found no RCTs. **Injection sclerotherapy versus compression stockings:** The systematic review did not report on harms.[1] **Injection sclerotherapy versus surgery:** The first RCT identified by the review reported postoperative wound infection in 6% and symptoms of sural or saphenous nerve injury in 10% of surgically treated patients (rates not reported in the sclerotherapy group).[7] Five people (proportion not reported) in the sclerotherapy group had migratory thrombophlebitis and 28% developed haematoma (rates not reported for surgical group). Duration of sick leave was greater with surgery than with sclerotherapy (mean duration 20 days with surgery *v* 1 day with sclerotherapy; significance not reported). One person in the surgical arm had a symptomatic pulmonary embolism that resolved without complications. No thromboembolic events occurred in the sclerotherapy group. The second RCT reported that one person in the surgically treated group had severe bronchospasm under anaesthetic.[8] The 5 year follow up to this study reported that during surgery one person had a myocardial infarction and one person had a pulmonary embolus.[16] The third RCT found no significant difference in phlebitis between avulsion and sclerotherapy at 2 weeks (12% with avulsion *v* 27% with sclerotherapy; P = 0.07).[9] Sclerotherapy reduced telangiectasia (thread veins) at 2 years compared with avulsion (6.2% with avulsion *v* 0% with sclerotherapy; P = 0.039). The fourth RCT did not discuss harms.[10] The fifth RCT reported one pulmonary embolus

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with conventional surgery (significance not reported).[11] There was no significant difference between treatments in minor complication rates (details of complications not reported; stated as not significant; P value not reported). The sixth RCT found saphenous nerve injury in 27 limbs (33%) with surgery compared with 0% with sclerotherapy (significance not reported).[12] **Different types of sclerosant:** The first subsequent RCT only reported local reactions.[13] It found that both treatments were associated with similar rates of ecchymosis (70% of veins treated with sodium tetradecyl sulphate *v* 58% with polidocanol), hyperpigmentation (64% with sodium tetradecyl sulphate *v* 53% with polidocanol), and thrombosis (46% with sodium tetradecyl sulphate *v* 42% with polidocanol; significance not reported for any comparison). Polidocanol reduced local urticaria and skin necrosis compared with sodium tetradecyl sulphate (skin necrosis 7% with sodium tetradecyl sulphate *v* 0% with polidocanol; urticaria 36% with sodium tetradecyl sulphate *v* 23% with polidocanol; significance not reported). The second subsequent RCT found that sodium tetradecyl sulphate caused more local necrosis, hyperpigmentation and telangiectasia compared with polidocanol or polidocanol plus sodium tetradecyl sulphate combination treatment (absolute figures and significance data for the between group comparison not reported).[14] **Foam sclerotherapy versus conventional sclerotherapy:** The first RCT did not discuss harms.[10] The second RCT found similar rates of skin inflammation with polidocanol foam and with polidocanol liquid (2/45 [4%] with foam *v* 3/43 [7%] with liquid; P value not reported).[15]

Comment: **Injection sclerotherapy versus surgery:** The effects of surgery versus injection sclerotherapy or other treatments may vary according to the sites of venous incompetence. Some RCTs included in the systematic review failed to report the relative effects with regard to sites of venous incompetence. Only two out of nine RCTs included in the systematic review were judged by the review to be of sufficient quality. In the surgical groups of the first two RCTs, varicose veins from saphenofemoral or saphenopopliteal incompetence were treated by ligation and stripping, while incompetent perforator veins were treated by avulsion.[7,8] The first RCT did not report whether the investigators were blinded to treatment allocation.[7] It was also not clear whether analysis was by intention to treat. **Different types of sclerosant:** The first subsequent RCT also included a further 42 people with telangiectasia (veins < 1 mm diameter).[13] These were excluded from the results.

OPTION SURGERY New

The effects of surgery depend on the method used. We found no RCTs comparing surgery (avulsion or stripping with or without avulsion) versus no treatment or compression stockings. One systematic review found that surgery (avulsion, stripping, ligation with or without sclerotherapy) significantly reduced varicose vein recurrence and cosmetic appearance compared with injection sclerotherapy alone. We found conflicting results from three RCTs that compared avulsion plus stripping of the long saphenous vein to the knee versus avulsion. The first RCT found that avulsion plus stripping of the long saphenous vein to the knee decreased clinical recurrence and increased participant satisfaction compared with avulsion alone. The second RCT found no significant difference between avulsion plus stripping and avulsion in recurrence or participant satisfaction at 5 years. The third RCT found that avulsion plus stripping increased pain compared with avulsion after 1 week. However, it found no significant difference between treatments in daily activity scores at 1 week. One RCT found similar improvements in clinician assessed clinical outcome with both partial stripping of the long saphenous vein to the knee and total stripping to the ankle. However, it found that partial stripping to the knee reduced the incidence of saphenous nerve damage compared with total stripping to the ankle. One RCT found that inversion stripping reduced pain scores compared with conventional stripping at 1 week. The RCT found no significant difference between treatments in bruising after 1 week. One RCT found no significant difference between powered phlebectomy and avulsion in pain at 8 days, or in participant satisfaction or cosmetic appearance at 6 weeks. It also found no significant difference between treatments in nerve injury or severe bruising after 2 weeks.

Benefits: **Surgery versus no treatment:** We found no RCTs that compared surgery (avulsion or stripping with or without avulsion) versus compression stockings. **Surgery v ersus compression stockings:** We found no RCTs that compared surgery (avulsion or

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stripping with or without avulsion) versus compression stockings. **Surgery v ersus injection sclerotherapy:** See benefits of injection sclerotherapy, p 3. **Avulsion plus stripping versus avulsion:** We found three RCTs that compared avulsion plus stripping of the long saphenous vein (LSV) to the knee following saphenofemoral ligation G versus avulsion of the LSV following ligation.[17–19] The first RCT (69 people, 89 legs randomised, followed up for a median of 21 months) found that avulsion plus stripping to the knee significantly decreased clinical recurrence and significantly increased participant satisfaction compared with avulsion (clinical recurrence: 28/43 [65%] with avulsion plus stripping *v* 8/46 [17%] with avulsion; P < 0.001; proportion of legs rated as "successfully treated": 28/43 [65%] with avulsion plus stripping *v* 17/46 [37%] with avulsion; P < 0.05).[17] The second RCT (100 people randomised, 133 legs treated) found no significant difference between treatments in recurrence or participant satisfaction at 5 years (legs free of recurrence: 32/52 [61%] with avulsion plus stripping *v* 28/58 [48%] with avulsion; RR 1.28, 95% CI 0.91 to 1.82; participants "satisfied": 35/39 [90%] with avulsion plus stripping *v* 30/39 [77%] with ligation; RR 1.17, 95% CI 0.95 to 1.42).[18] The third RCT (80 people with primary saphenofemoral varicose veins) compared stripping of the LSV to the knee plus avulsion after saphenofemoral ligation versus avulsion of the LSV after ligation.[19] It found that avulsion plus stripping significantly increased pain (assessed using a linear analogue pain scale from 0–10) compared with avulsion after 1 week (results presented graphically; P < 0.001). It also found no significant difference between treatments in daily activity scores (score range 0–7) at 1 week (results presented graphically; stated as not significant; P value not reported). **Partial stripping versus total stripping:** We found one RCT (163 people), which compared partial stripping of the LSV to the knee following saphenofemoral ligation versus total stripping to the ankle following ligation.[20] It found similar improvements in clinical outcome with both treatments (clinician assessed using the Haegers classification system, where excellent = no symptoms and no residual varices; good = no symptoms but residual varices; fair = persisting symptoms and varices; poor = no improvement in symptoms and large persistent varices; treatment rated as excellent or good: 97% with partial stripping *v* 94% with total stripping; P value not reported). **Inversion stripping versus conventional stripping:** We found one RCT (30 people with primary long saphenous varicose veins), which compared inversion stripping of the long saphenous vein following saphenofemoral ligation versus conventional stripping following ligation.[21] It found that inversion stripping significantly reduced pain scores (assessed on a visual analogue scale, where 0 = no pain and 5 = severe pain) compared with conventional stripping at 1 week (mean visual analogue scale score: 9.5 with conventional stripping *v* 5.5 with inversion stripping; P = 0.02). **Powered phlebectomy versus avulsion:** We found one RCT (141 people, 188 legs randomised), which compared powered phlebectomy G versus avulsion (conventional hook phlebectomy) following ligation.[22] It found no significant difference between treatments in pain at 8 days (assessed using a visual analogue scale, where 0 = no pain and 10 = most severe pain; results presented graphically; stated as not significant; P value not reported). It also found no significant difference between treatments in participant satisfaction or cosmetic appearance at 6 weeks (both measured on a VAS scale where 0 = "very dissatisfied" and 10 = "very satisfied"; proportion of people "satisfied": 87% with powered phlebectomy *v* 91% with avulsion; P = 0.88; mean cosmetic score: 7.44 with powered phlebectomy *v* 8.27 with avulsion; results presented graphically; P value not reported). **Radiofrequency ablation versus stripping:** We found no systematic review or RCTs comparing radiofrequency ablation G versus stripping (see comment below).

Harms:

Surgery versus no treatment: We found no RCTs. **Surgery versus compression stockings:** We found no RCTs. **Surgery versus injection sclerotherapy:** See harms of injection sclerotherapy, p 5. **Avulsion plus stripping versus avulsion:** The RCTs did not report on harms.[17–19] **Stripping versus sequential avulsion:** The RCT found that three people experienced minor sensory loss in the saphenous nerve distribution after treatment (2/40 [5.0%] with stripping *v* 1/40 [2.5%] with sequential avulsion; significance not reported).[19] It also found that stripping significantly increased bruising compared with sequential avulsion (median area of bruising: 160 cm^2 with stripping *v* 56 cm^2 with sequential avulsion; P < 0.01). **Partial stripping versus total stripping:** The RCT found that partial stripping to the knee significantly reduced the incidence of

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Varicose veins

saphenous nerve damage compared with total stripping to the ankle (5/77 [7%] with partial stripping *v* 31/80 [39%] with total stripping; P < 0.001).[20] **Inversion stripping versus conventional stripping:** The RCT found no significant difference between treatments in bruising after 1 week (median area: 137.5 cm^2 with inversion stripping *v* 195.5 cm^2 with conventional stripping; P = 0.08). **Powered phlebectomy versus conventional phlebectomy:** The RCT found no significant difference between treatments in the incidence of cellulitis, cutaneous nerve injury, or severe bruising after 2 weeks (cellulitis: 2/88 [2.3%] with powered phlebectomy *v* 3/100 [3%] with conventional phlebectomy; P = 0.33; cutaneous nerve injury: 16/88 [18%] with powered phlebectomy *v* 25/100 [25%] with conventional phlebectomy; P = 0.33; severe bruising: 8/88 [9%] with powered phlebectomy *v* 7/100 [7%] with conventional phlebectomy; P = 0.77).[22] **Radiofrequency ablation versus stripping:** We found no systematic review or RCTs comparing radiofrequency ablation versus stripping (see comment below).

Comment: **Surgery versus injection sclerotherapy:** See comment of injection sclerotherapy, p 6. **Avulsion plus stripping versus avulsion:** The second RCT found that avulsion plus stripping significantly reduced the need for repeat treatment compared with avulsion (proportion of legs needing repeat treatment: 3/52 [6%] with avulsion plus stripping *v* 12/58 [20%] with avulsion; RR 0.28, 95% CI 0.13 to 0.59).[18] There was a technical procedure failure in five people in the stripping group and two people in the sequential avulsion group.[19] **Radiofrequency ablation versus stripping:** We found one systematic review (search date 2004), which identified two RCTs comparing radiofrequency ablation versus stripping of the LSV following saphenofemoral ligation in people with complicated varicose veins.[23] The review did not meet inclusion criteria for this topic due to population definition. The review did not perform a meta-analysis and the RCTs were considered to be of poor quality: assessors were not blind to treatment, methods of randomisation were unclear, and analyses were not by intention to treat. Both RCTs found that radiofrequency ablation significantly reduced postoperative pain compared with stripping, but they found conflicting evidence about the effects of radiofrequency ablation on quality of life outcomes. **Powered phlebectomy versus avulsion:** The RCT comparing powered phlebectomy versus conventional phlebectomy found that powered phlebectomy significantly reduced the number of incisions, but this made no difference to patient satisfaction.[22]

GLOSSARY

Avulsion (phlebectomy) Used to treat multiple varicosities after saphenofemoral or saphenopopliteal ligation or in people with perforator incompetence. Small incisions are made in the skin overlying each varicosity and the affected vein interrupted or excised using either a vein hook or forceps.
Ecchymosis this is a small, rounded or irregular blue or purple patch caused by a small haemorrhage in the skin or mucous membrane.
Foam sclerotherapy A new technique in which a standard sclerosant is mixed with air to create a foam. This is then injected into the varicosities under ultrasound guidance.
Ligation Involves tying off a vein close to the site of incompetence to prevent blood flowing from the deep to the superficial system.
Powered phlebectomy Involves infiltrating subcutaneous tissues with a saline solution containing local anaesthetic (lidocaine) and dilute epinephrine (adrenaline). A mechanical device is then introduced. This has a blade that rotates at 800 to 1000 rpm destroying the varicose vein. Vein fragments are removed by suction connected to the device.
Radiofrequency ablation (Closure) A new technique involving the introduction of a catheter into the long saphenous vein under ultrasound guidance. This delivers radiofrequency energy which heats the long saphenous vein, thereby sealing the lumen.
Sclerosant An injected solution which displaces blood from the vein, causing inflammation of the vein wall and occlusion. Commonly used sclerosants include sodium tetradecyl sulphate (sotradecol) and polidocanol (also called aetoxysclerol; aethoxysclerol; aethoxyskerol, or hydroxypolyaethoxydodecan).
Stripping A wire, plastic, or metal rod is passed through the lumen of the saphenous vein and is used to strip the entire vein out of the leg. This disconnects any superficial veins from the deep venous system. Inversion stripping is a newer technique where the vein is inverted upon itself after stripping.
Telangiectasia Dilated superficial blood vessels in the skin. This is often synonymous with the term 'thread veins' or 'spider veins'.
Urticaria (hives) is the presence of itchy, raised patches of skin (wheals), which may be due to certain

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foods or drugs, as well as other factors including stress. The condition may be acute or chronic.

Substantive changes

Injection sclerotherapy One systematic review and one RCT added;[6,14] benefits and harms data enhanced. Categorisation unchanged.

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Ventricular tachyarrhythmias (out of hospital cardiac arrests)

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QUESTIONS

INTERVENTIONS

Key Messages

- Cardiac arrest associated with ventricular tachyarrhythmias/ventricular fibrillation is initially managed with rapid electrical defibrillation if available. People with cardiac arrest are also treated with a standard resuscitation package consisting of chest compressions and artificial ventilation. Adrenaline (epinephrine) is given once intravenous access is obtained or endotracheal intubation is performed.

Antiarrhythmic drug treatments

- **Amiodarone** One high quality RCT found that more people survived to hospital admission with amiodarone compared with placebo. However, it found no significant difference in survival to hospital discharge. Another RCT found that more people survived to hospital admission with amiodarone compared with lidocaine. However, it also found no significant difference in survival to hospital discharge. Amiodarone was associated with more hypotension and bradycardia than placebo.
- **Lidocaine** We found no RCTs comparing lidocaine versus placebo in an out of hospital setting. One high quality RCT suggested that lidocaine is inferior to amiodarone for the outcome of admission to the hospital intensive care unit. Two small RCTs found no difference in clinical outcomes between lidocaine and bretylium.
- **Procainamide** We found no systematic review or RCTs comparing procainamide versus placebo or the other antiarrhythmic drugs included in this chapter (lidocaine, bretylium, amiodarone) for the clinical outcomes of interest.
- **Bretylium** One small RCT comparing bretylium versus placebo in an emergency department setting found no significant difference in survival to discharge from emergency department. Two RCTs found no difference in clinical outcomes between bretylium and lidocaine. One RCT suggested an increase in the rate of hypotension and bradycardia associated with bretylium compared with placebo. We found no studies comparing bretylium with amiodarone or procainamide in this context.

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Ventricular tachyarrhythmias (out of hospital cardiac arrests)

DEFINITION	**Ventricular tachyarrhythmias** are defined as abnormal patterns of electrical activity originating within ventricular tissue. The most commonly encountered ventricular tachyarrhythmias of greatest clinical importance to clinicians and which will be the focus of this chapter are ventricular tachycardia and ventricular fibrillation. **Ventricular tachycardia** is further classified as monomorphic when occurring at a consistent rate and amplitude and polymorphic when waveforms are more variable and chaotic. **Torsades de pointes** is a specific kind of polymorphic ventricular tachycardia associated with a prolonged QT interval and a characteristic twisting pattern to the wave signal. It is often associated with drug toxicity and electrolyte disturbances and is commonly treated with intravenous magnesium. Torsades de pointes will not be specifically covered in this chapter. **Pulseless ventricular tachycardia** results in similar clinical manifestations but is diagnosed by a QRS width complex of > 120 milliseconds and electrical rhythm of 150–200 beats a minute. Waveforms in ventricular fibrillation are characterised by an irregular rate, usually exceeding 300 beats a minute as well as amplitudes generally exceeding 0.2 mV. Ventricular fibrillation usually fades to asystole (flat line) within 15 minutes. Ventricular fibrillation and ventricular tachycardia associated with cardiac arrest and sudden cardiac death (SCD) are abrupt pulseless arrhythmias. **Non-pulseless (stable) ventricular tachycardia** has the same electrical characteristics as ventricular tachycardia but without haemodynamic compromise. The treatment of stable ventricular tachycardia is not covered in this chapter. **Ventricular fibrillation** is characterised by irregular and chaotic electrical activity and ventricular contraction in which the heart immediately loses its ability to function as a pump. Pulseless ventricular tachycardia and ventricular fibrillation are the primary causes of SCD. **Population:** In this chapter we focus on drug treatments, given generally by paramedics, for ventricular tachycardia and ventricular fibrillation associated with cardiac arrest in an out of hospital setting.
INCIDENCE/ PREVALENCE	The annual incidence of SCD is believed to approach 2/1000 population but can vary depending on the prevalence of cardiovascular disease in the population.[1] It is estimated that 300 000 SCDs are recorded annually in the US, representing 50% of all cardiovascular mortality in that country.[2] Data from Holter monitor studies suggest that about 85% of SCDs are the result of ventricular tachycardia/ventricular fibrillation.[3]
AETIOLOGY/ RISK FACTORS	Ventricular arrhythmias occur as a result of structural heart disease arising primarily from myocardial ischaemia or cardiomyopathies. In developed nations, ventricular tachycardia or ventricular fibrillation associated cardiac arrest is believed to occur most typically in the context of myocardial ischaemia. As a result, major risk factors for SCD reflect those that lead to progressive coronary artery disease. Specific additional risk factors attributed to SCD include dilated cardiomyopathy (especially with ejection fractions of < 30%), age (peak incidence 45–75 years), and male sex.
PROGNOSIS	Ventricular fibrillation and ventricular tachycardia associated with cardiac arrest results in lack of oxygen delivery and major ischaemic injury to vital organs. If untreated this condition is uniformly fatal within minutes.
AIMS OF INTERVENTION	In conjunction with defibrillation, to restore sinus rhythm or a sufficiently organised electrical rhythm that will support the systemic circulation with minimal adverse effects.
OUTCOMES	Survival/mortality; functional neurological recovery; survival to hospital discharge; survival to hospital admission; adverse effects of treatment; quality of life.
METHODS	*Clinical Evidence* search and appraisal October 2004.

QUESTION **What are the effects of antiarrhythmic drug treatments for use in out of hospital cardiac arrest associated with shock resistant ventricular tachycardia or ventricular fibrillation?**

OPTION AMIODARONE New

One high quality RCT found that more people survived to hospital admission with amiodarone compared with placebo. However, it found no significant difference in survival to hospital discharge. Another RCT found that more people survived to hospital admission with amiodarone compared with lidocaine. However, it also found no significant difference in survival to hospital discharge. Amiodarone was associated with more hypotension and bradycardia than placebo.

Benefits: We found no systematic review. **Amiodarone versus placebo:** One RCT (504 people with cardiac arrest and shock resistant ventricular fibrillation or pulseless ventricular fibrillation developing at some point during resuscitation) found that there were significantly more people who survived to admission to hospital in people who were given amiodarone compared with placebo (108/246 [44%] with amiodarone *v* 89/258 [34%]

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Ventricular tachyarrhythmias (out of hospital cardiac arrests)

with placebo; P = 0.03) (see table 1, p 6).[4] However, it found no significant difference in survival to hospital discharge between amiodarone compared with placebo (33/246 [13.4%] with amiodarone *v* 34/258 [13.2%] with placebo; reported as non-significant). The RCT also reported on the number of the people who survived to discharge from hospital who returned to independent living or work (18/33 [55%] with amiodarone *v* 17/34 [50%] with placebo; significance not reported). **Amiodarone versus lidocaine:** One RCT (347 people with cardiac arrest and shock resistant ventricular tachycardia or ventricular fibrillation developing at some point during their resuscitation) found that a significantly larger proportion of people survived to hospital admission with amiodarone compared with lidocaine (41/180 [22.8%] with amiodarone *v* 20/167 [12.0%] with lidocaine; OR 2.17, 95% CI 1.21 to 3.83; P = 0.009) (see table 1, p 6). However, it found no significant difference in survival to discharge from hospital between amiodarone and lidocaine (9/180 [5%] with amiodarone *v* 5/167 [3%] with lidocaine; P = 0.34) (see table 1, p 6).[5] (Both groups also received placebo.) **Amiodarone versus bretylium:** We found no RCTs. **Amiodarone versus procainamide:** We found no RCTs. See comment under procainamide, p 4.

Harms: **Amiodarone versus placebo:** The RCT found that there was significantly more hypotension (91/153 [59%] with amiodarone *v* 69/145 [48%] with placebo; P = 0.04) and bradycardia (63/153 [41%] with amiodarone *v* 36/145 [25%] with placebo; P = 0.004) in people who took amiodarone compared with placebo and who had either a transient or a sustained return of spontaneous circulation.[4] **Amiodarone versus lidocaine:** The RCT reported that pressor drugs were needed both for people who took amiodarone and people who took lidocaine (13/180 [7%] with amiodarone *v* 6/167 [4%] with lidocaine; reported as non-significant).[5] The RCT also reported that treatment for bradycardia was required in both groups (43/180 [24%] with amiodarone *v* 38/167 [23%] with lidocaine; reported as non-significant).

Comment: As neither study[4,5] found an advantage with regards to hospital discharge or meaningful neurological recovery it is conceivable that amiodarone use might simply lead to increased consumption of hospital intensive care unit (ICU) resources without patient benefit. Although methodologically sound, the selection of admission to hospital ICU as the study's primary outcome is problematic. However, important developments in post-resuscitative care (i.e. therapeutic hypothermia) might actually allow the increased ICU admission rate associated with amiodarone to translate into a clinical benefit as it relates to neurological recovery from cardiac arrest. See comment under procainamide, p 4.

OPTION BRETYLIUM New

One small RCT comparing bretylium versus placebo in an emergency department setting found no significant difference in survival to discharge from emergency department. Two RCTs found no difference in clinical outcomes between bretylium and lidocaine. One RCT suggested an increase in the rate of hypotension and bradycardia associated with bretylium compared with placebo. We found no studies comparing bretylium with amiodarone or procainamide in this context.

Benefits: We found no systematic review. **Bretylium versus placebo:** One small RCT (59 people presenting to an emergency department, as opposed to the pre-hospital setting with cardiopulmonary arrest, 29 of whom had ventricular fibrillation) found no significant difference in survival from emergency department between bretylium compared with placebo (7/18 [39%] with bretylium *v* 1/11 [9%] with placebo; P < 0.13) (see table 1, p 6).[6] The RCT did not report on survival to discharge from hospital. **Bretylium versus lidocaine:** See benefits of lidocaine, p 4. **Bretylium versus procainamide or amiodarone:** We found no RCTs.

Harms: **Bretylium versus placebo:** One RCT found that there were significantly more adverse events in survivors with bretylium compared with survivors with placebo (reported adverse events with bretylium: tachycardia 5/8 [63%], hypotension 4/8 [50%], bradycardia 1/8 [13%], hypertension 1/8 [13%] *v* reported adverse events with placebo: hypotension 1/3 [33%]; P < 0.05).[6]

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Ventricular tachyarrhythmias (out of hospital cardiac arrests)

Comment: Although the RCT found no significant difference in survival to discharge from emergency department between bretylium and placebo in people with ventricular fibrillation, there was a significant difference when a population with either ventricular fibrillation or asystole was taken into consideration (8/23 [35%] with bretylium *v* 1/16 [6%] with placebo; $P < 0.05$).[6] **Clinical guide:** The absence of evidence showing benefit of bretylium use in clinical trials compounded with adverse effects such as refractory hypotension and the lack of availability of this compound from 1998–2000, led the American Heart Association to remove bretylium from the Advanced Cardiac Life Support (ACLS) algorithm for ventricular fibrillation/pulseless ventricular tachycardia in 2000.

OPTION LIDOCAINE New

We found no RCTs comparing lidocaine versus placebo in an out of hospital setting. One high quality RCT suggested that lidocaine is inferior to amiodarone for the outcome of admission to the hospital intensive care unit. Two small RCTs found no difference in clinical outcomes between lidocaine and bretylium.

Benefits: We found no systematic review. **Lidocaine versus placebo:** We found no RCTs. **Lidocaine versus bretylium:** We found two small RCTs.[7,8] The first RCT (100 people with out of hospital ventricular fibrillation, with persistent ventricular fibrillation after initial shock) found no significant difference between lidocaine and bretylium given after the first shock in discharge from hospital (10/44 [23%] with lidocaine *v* 12/56 [21%] with bretylium; $P > 0.1$) (see table 1, p 6).[7] The second RCT (91 people with refractory ventricular fibrillation) found no significant difference between lidocaine and bretylium in the proportion of people who survived to hospital discharge (5/48 [10%] with lidocaine *v* 2/43 [5%] with bretylium; reported as non-significant; P value not reported).[8] However, in this RCT, people were given the alternative drug if they did not respond to the first drug (see table 1, p 6). **Lidocaine versus procainamide:** We found no RCTs. **Lidocaine versus amiodarone:** See benefits of amiodarone, p 2.

Harms: **Lidocaine versus bretylium:** The first RCT reported that pressor drugs were need both for people who took lidocaine and people who took bretylium (14/43 [33%] with lidocaine *v* 16/43 [37%] with bretylium; $P > 0.1$).[7] The second RCT did not report on adverse events.[8] **Lidocaine versus amiodarone:** See harms of amiodarone, p 3.

Comment: Although methodologically sound, the selection of admission to hospital intensive care unit (ICU) as the study's primary outcome is problematic. With the effect of amiodarone as compared with lidocaine uncertain in regards to functional neurological recovery it is conceivable that use of amiodarone can simply increase resource consumption through ICU and nursing home facilities without achieving any meaningful clinical benefit. However, important developments in post-resuscitative care (i.e. therapeutic hypothermia) might actually allow the increased ICU admission rate associated with amiodarone to translate into a clinical benefit as it relates to neurological recovery from cardiac arrest.

OPTION PROCAINAMIDE New

We found no systematic review or RCTs comparing procainamide versus placebo or the other antiarrhythmic drugs included in this chapter (lidocaine, bretylium, amiodarone) for the clinical outcomes of interest.

Benefits: We found no systematic review or RCTs comparing procainamide versus placebo or the other antiarrhythmic drugs included in this chapter (lidocaine, bretylium, amiodarone) for the clinical outcomes of interest.

Harms: We found no RCTs.

Comment: One RCT (CASCADE [Cardiac Arrest in Seattle: Conventional Versus Amiodarone Drug Evaluation]) showed better results for amiodarone in comparison with procainamide for the secondary prevention of cardiac arrest.[9] **Clinical guide:** The time required to infuse procainamide is usually long (slow infusion over several minutes) and this would make it a less favourable choice in acute or unstable condition as a preferred drug. It might be considered an option for recurrent ventricular tachycardia/ventricular fibrillation.

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TABLE 1 **Resuscitation protocols as reported in the included RCTs*.[4–8]**

Intervention	Initial treatment*	Further treatment*	Inclusion/exclusion criteria	Survival to hospital discharge
Amiodarone or placebo[4]	Basic life support including shocks by automated external defibrillator; then: advanced life support measures including adrenaline 1 mg after tracheal intubation	Amiodarone 300 mg or placebo while CPR continued. Single dose only	**Included:** 504 adults with non-traumatic out of hospital cardiac arrest, with VF or VT (at any time in the resuscitation attempt) after ≥ 3 pre-cordial shocks, iv access, and paramedics present with drug/placebo	33/246 [13.4%] with amiodarone *v* 34/258 [13.2%] with placebo (P = NS)
Amiodarone or lidocaine[5]	3 shocks, 1 dose of iv adrenaline, fourth shock (further details not reported)	Amiodarone 5 mg/kg or lidocaine 1.5 mg/kg plus further shocks and advance cardiac life support. If VF persisted, **same** drug given (amiodarone 2.5 mg/kg; lidocaine 1.5 mg/kg) and attempts at resuscitation (American Heart Association guidelines for ACLS)	**Included:** 347 adults with out of hospital VF tested electrocardiographically. VF resistant to initial treatment (see left).	9/180 [5%] with amiodarone *v* 5/167 [3%] with lidocaine (P = 0.34)
Bretylium or placebo[6]	Basic cardiac life support	In emergency department: Bretylium (5–10 mg/kg) or placebo plus American Heart Association guidelines for ACLS. If person in cardiopulmonary arrest after 20 minutes, a second dose of **same** drug given	**Included:** 29 people presenting with cardiopulmonary arrest and assessed by study investigator	Survival to discharge from emergency department: 7/18 [39%] with bretylium *v* 1/11 [9%] with placebo (P < 0.13)
Lidocaine or bretylium[7]	CPR, then basic life support, 320 J defibrillatory shock, ET tube, iv catheter	10 mL bolus of bretylium 500 mg or lidocaine 100 mg. If persistent VF after second shock or fibrillation recurrence, second bolus of **same** drug plus routine resuscitation measures	**Included:** 100 adults aged ≥ 13 years whose rhythm became organised or remained in VF. **Excluded:** people converting to asystole or profound bradycardia with initial shock	10/44 [23%] with lidocaine *v* 12/56 [21%] with bretylium (P > 0.1)
Lidocaine or bretylium[8]	Countershocks people in VF twice at 200 Ws, iv line of D5W and ET tube; sodium bicarbonate 1 mEq/kg and adrenaline 0.5–1.0 mg if VF persists	Bretylium (10–30 mg/kg total) or lidocaine (2–3 mg/kg total). If failure to convert, **other** drug given. If further failure to convert procainamide given (100 mg over 5 minutes, up to 1000 mg). Countershock and resuscitation by ACLS protocols given after each intervention	**Included:** 91 adults with "refractory ventricular fibrillation" – failure to convert from VF with the initial American Heart Association protocol, or return to VF before antiarrhythmics were given. **Excluded:** drugs given out of sequence; not fulfilling definition of refractory VF	5/48 [10%] with lidocaine *v* 2/43 [5%] with bretylium (P = NS)

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Ventricular tachyarrhythmias (out of hospital cardiac arrests)

*Treatments in out of hospital settings unless otherwise specified.

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Obesity

Search date April 2004

David E Arterburn, David E DeLaet, and David R Flum

QUESTIONS

INTERVENTIONS

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Obesity

Key Messages

Drug treatments in adults with obesity

- **Diethylpropion** One systematic review found that, in people having lifestyle interventions, diethylpropion promoted modest weight loss compared with placebo in obese adults. The review provided insufficient evidence to compare diethylpropion versus other agents. We found two case reports describing pulmonary hypertension and psychosis with diethylpropion. We found insufficient evidence on weight regain and long term safety. A European Commission review concluded that a link between diethylpropion and heart and lung problems could not be excluded.
- **Fluoxetine** One systematic review found that, in people having lifestyle interventions, fluoxetine promoted modest weight loss compared with placebo in obese adults. We found insufficient evidence on weight regain and long term safety of fluoxetine in obesity. One systematic review of antidepressant treatment found an association between selective serotonin reuptake inhibitors such as fluoxetine and uncommon but serious adverse events, including bradycardia, bleeding, granulocytopenia, seizures, hyponatraemia, hepatotoxicity, serotonin syndrome, and extrapyramidal effects.
- **Mazindol** One systematic review found that, in people having lifestyle interventions, mazindol promoted modest weight loss compared with placebo in obese adults. The review provided insufficient evidence to compare mazindol versus other agents. We found one case report of pulmonary hypertension diagnosed 1 year after stopping treatment with mazindol. We found one case series of mazindol in people with stable cardiac disease that reported cardiac events such as atrial fibrillation and syncope. We found insufficient evidence on weight regain and long term safety.
- **Orlistat** Systematic reviews and subsequent RCTs found that, in people on a low calorie diet, orlistat modestly increased weight loss at 6–12 months compared with placebo in obese adults, in both those who did and who did not have diabetes, hyperlipidaemia, and hypertension. One RCT in obese people with hypercholesterolaemia found that orlistat plus fluvastatin increased weight loss compared with orlistat or fluvastatin alone. Another RCT found that orlistat was less effective than sibutramine in achieving weight loss. Adverse effects such as oily spotting from the rectum, flatulence, and faecal urgency occurred in a high proportion of people taking orlistat. We found insufficient evidence on weight regain and long term safety.
- **Phentermine** One systematic review found that, in people having lifestyle interventions, phentermine promoted modest weight loss compared with placebo in obese adults. RCTs identified by the review provided insufficient evidence to compare phentermine versus other agents. We found insufficient evidence on weight regain and long term safety with phentermine. A European Commission review concluded that a link between phentermine and heart and lung problems could not be excluded.
- **Sibutramine** Systematic reviews and subsequent RCTs found that, in people having dietary interventions with or without exercise, sibutramine promoted modest weight loss at 8 weeks, 6 months, and 1 year compared with placebo in obese adults, in both those who did and who did not have diabetes, hypertension, hyperlipidaemia, or binge eating disorder. RCTs in obese adults who had lost weight by taking sibutramine found limited evidence that sibutramine was more effective than placebo for weight maintenance. Other RCTs found that weight regain occurred when sibutramine was discontinued. One RCT found that sibutramine achieved greater weight loss than orlistat or

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metformin. RCTs provided insufficient evidence to compare sibutramine versus other agents. Sibutramine was temporarily suspended from the market in Italy for use in obesity because of concerns about severe adverse reactions, including arrhythmias, hypertension, and two deaths resulting from cardiac arrest. Two RCTs found no significant difference in the incidence of valvular heart disease between sibutramine and placebo, although these trials may have lacked power to detect a clinically important difference.

- **Sibutramine plus orlistat (insufficient evidence to compare with sibutramine alone)** One RCT provided insufficient evidence to compare sibutramine plus orlistat versus sibutramine alone.

Bariatric surgery in adults with morbid obesity

- **Gastric bypass (increased weight loss compared with gastroplasty or gastric banding)** RCTs provided moderate evidence that gastric bypass promoted greater weight loss than either gastroplasty or gastric banding. Five RCTs identified by a systematic review found that gastric bypass increased weight loss compared with horizontal gastroplasty. Two RCTs identified by the review found that gastric bypass increased weight loss at 1–3 years compared with vertical banded gastroplasty but another two RCTs found no significant difference between the procedures. One small RCT identified by the review found limited evidence of greater weight loss with gastric bypass than with gastric banding or vertical banded gastroplasty. Another small RCT identified by the review found that gastric bypass increased the proportion of people with 50% weight loss at 18 months compared with vertical banded gastroplasty or gastrogastrostomy. Perioperative mortalities were similar for these procedures. Postoperative complications were common and varied by type of procedure performed.
- **Laparoscopic bariatric surgery (reduced wound infections and risk of incisional hernias compared with open bariatric surgery, no significant difference in weight loss)** Five RCTs found no significant difference in weight loss between open and laparoscopic bariatric procedures. The RCTs found consistent evidence that laparoscopic surgery reduced the incidence of wound and incisional hernia complications compared with open surgery. They found more limited evidence that laparoscopic procedures decreased length of hospital stay compared with open procedures; but data are insufficient to draw conclusions about other complication rates.
- **Bariatric surgery (more effective for clinically important weight loss in morbidly obese adults than non-surgical treatment but operative complication rates common)** One RCT and one cohort study in morbidly obese adults identified by three systematic reviews found that bariatric surgery (horizontal gastroplasty, vertical banded gastroplasty, gastric bypass, or gastric banding) was more effective than non-surgical treatment in increasing weight loss in people with morbid obesity. The cohort study found that, on average, bariatric surgery for obesity resulted in weight losses of 25–44 kg after 1–2 years (compared with matched participants who did not have surgery) and sustained weight loss of 20 kg up to 8 years later. The risk of death from bariatric surgery is estimated to be 0–1.5%. Operative and postoperative complications are common and vary with the type of bariatric procedure performed. The reviews identified no RCTs and we found no observational studies of sufficient quality comparing biliopancreatic diversion versus non-surgical treatment.

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Obesity

- **Biliopancreatic diversion (no studies comparing biliopancreatic diversion versus other bariatric techniques)** Three systematic reviews identified no RCTs and we found no observational studies of sufficient quality comparing biliopancreatic diversion versus other bariatric procedures.
- **Gastric banding (less effective in reducing weight than gastric bypass; insufficient evidence to assess benefits and harms compared with gastroplasty)** One small RCT identified by a systematic review found limited evidence that gastric banding was less effective than gastric bypass in reducing weight. Two RCTs found inconclusive results regarding weight loss with gastric banding compared with vertical banded gastroplasty. There were no postoperative deaths in either RCT. Postoperative complications were common and varied by type of procedure performed. There is insufficient evidence to recommend one procedure over the other.
- **Gastroplasty (less effective in reducing weight than gastric bypass; insufficient evidence to assess benefits and harms compared with gastric banding)** Two RCTs found inconclusive results regarding weight loss with vertical banded gastroplasty compared with gastric banding. Five RCTs identified by a systematic review found that horizontal gastroplasty was less effective than gastric bypass for increasing weight loss. Four RCTs identified by the review found that vertical banded gastroplasty was less effective than gastric bypass in increasing weight loss at 1–3 years but another two RCTs found no significant difference between the procedures. Perioperative mortalities were similar for these procedures. Postoperative complications were common and varied by type of procedure performed. There is insufficient evidence to recommend one procedure over another.

DEFINITION Obesity is a chronic condition characterised by an excess of body fat. It is most often defined by the body mass index (see glossary, p 20) (BMI), a mathematical formula that is highly correlated with body fat. BMI is weight in kilograms divided by height in metres squared (kg/m^2). Worldwide, adults with BMIs between 25–30 kg/m^2 are categorised as overweight, and those with BMIs above 30 kg/m^2 are categorised as obese.[1,2] Nearly 5 million US adults used prescription weight loss medication between 1996 and 1998. A quarter of users were not overweight. Inappropriate use of prescription medication is more common among women, white people, and Hispanic people.[3] The National Institutes of Health in the USA has issued guidelines for obesity treatment, which indicate that all obese adults (BMI > 30 kg/m^2) and all adults with a BMI of 27 kg/m^2 or more and concomitant risk factors or diseases are candidates for drug treatment.[1] Morbidly obese adults (BMI > 40 kg/m^2) and all adults with a BMI of 35 kg/m^2 or more and concomitant risk factors are candidates for bariatric surgery.

INCIDENCE/ PREVALENCE Obesity has increased steadily in many countries since 1900. In the UK in 2001, it was estimated that 21% of men and 24% of women were obese.[4] In the past decade alone, the prevalence of obesity in the USA has increased from 22.9% between 1988 and 1994, to 30.5% between 1999 and 2000.[5]

AETIOLOGY/ RISK FACTORS Obesity is the result of long term mismatches in energy balance where daily energy intake exceeds daily energy expenditure.[6] Energy balance is modulated by a myriad of factors, including metabolic rate, appetite, diet, and physical activity.[7] Although these factors are influenced by genetic traits, the increase in obesity prevalence

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in the past few decades cannot be explained by changes in the human gene pool, and is more often attributed to environmental changes that promote excessive food intake and discourage physical activity.[7,8] Less commonly, obesity may also be induced by drugs (e.g. high dose glucocorticoids), or be secondary to a variety of neuroendocrine disorders such as Cushing's syndrome and polycystic ovary syndrome.[9]

PROGNOSIS Obesity is a risk factor for several chronic diseases, including hypertension, dyslipidaemia, diabetes, cardiovascular disease, sleep apnoea, osteoarthritis, and some cancers.[1] The relationship between increasing body weight and mortality is curvilinear, where mortality is highest among adults with very low body weight (BMI < 18.5 kg/m^2) and among adults with the highest body weight (BMI > 35 kg/m^2).[2] Results from five prospective cohort studies and 1991 national statistics suggest that the number of annual deaths attributable to obesity among US adults is about 280 000.[10] Obese adults also have more annual admissions to hospitals, more outpatient visits, higher prescription drug costs, and worse health related quality of life than normal weight adults.[11,12]

AIMS OF INTERVENTION To achieve realistic gradual weight loss, and prevent the morbidity and mortality associated with obesity, without undue adverse effects.

OUTCOMES Reduction in mortality; adverse effects of treatment. We found no studies that assessed the primary outcome of reduction in mortality associated with obesity. Proxy measures assessed in studies included mean weight loss (kg), proportion of people losing 5% or more of baseline body weight, and proportion of people maintaining weight loss.

METHODS *Clinical Evidence* search and appraisal April 2004. We did not perform a search for observational studies of bariatric surgery. However, we have included all observational studies of bariatric surgery identified by systematic reviews. We have excluded RCTs with greater than 30% loss to follow up unless they performed an intention to treat analysis. However, such RCTs may be included in the meta-analyses of systematic reviews. Two systematic reviews[13,14] and two cohort studies[15,16] of bariatric surgery were published after the search date of our review. They are mentioned in the comments and will be reported in full in the next issue of *Clinical Evidence*.

QUESTION What are the effects of drug treatments in adults with obesity?

OPTION SIBUTRAMINE

Systematic reviews and subsequent RCTs found that, in people having dietary interventions with or without exercise, sibutramine promoted modest weight loss at 8 weeks, 6 months, and 1 year compared with placebo in obese adults, in both those who did and who did not have diabetes, hypertension, hyperlipidaemia, or binge eating disorder. RCTs in obese adults who had lost weight by taking sibutramine found limited evidence that sibutramine was more effective than placebo for weight

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Obesity

maintenance. Other RCTs found that weight regain occurred when sibutramine was discontinued. One RCT found that sibutramine achieved greater weight loss than orlistat or metformin. RCTs provided insufficient evidence to compare sibutramine versus other agents or sibutramine plus orlistat versus sibutramine alone. Sibutramine was temporarily suspended from the market in Italy for use in obesity because of concerns about severe adverse reactions, including arrhythmias, hypertension, and two deaths resulting from cardiac arrest. Two RCTs found no significant difference in the incidence of valvular heart disease between sibutramine and placebo, although these trials may have lacked power to detect a clinically important difference.

Benefits:

Sibutramine versus placebo: We found one systematic review (search date 2002, 29 RCTs in people with body mass index (see glossary, p 20) 25–40 kg/m^2, some with diabetes, hypertension, hyperlipidaemia, or binge eating disorder)[17] and one subsequent RCT.[18] The review meta-analyzed data for groups of RCTs with similar study duration, method of analysis, and duration of follow up.[17] All of the meta-analyses found that sibutramine significantly increased weight loss compared with placebo. The review found that sibutramine 10–15 mg daily significantly increased weight loss at 8–12 weeks compared with placebo (7 RCTs, 546 people; WMD –2.78 kg, 95% CI –3.29 kg to –2.26 kg). Trials of 16–24 weeks' duration, all comparing sibutramine 10–15 mg daily versus placebo, were meta-analyzed in three subgroups because of significant heterogeneity among the trials in methods of analysis. The weighted mean difference in weight loss between sibutramine and placebo ranged from –3.43 kg, 95% CI –4.50 to –2.36 to –6.03 kg, 95% CI –7.36 to –4.70 kg; people who completed the trial had the greatest weight loss. The review also found that sibutramine 10–15 mg daily significantly increased weight loss at 45–54 weeks compared with placebo (5 RCTs, 2188 people; WMD –4.45 kg, 95% CI –5.29 to –3.62 kg). The review found similar rates of weight loss in trials that specifically recruited obese adults with type 2 diabetes mellitus, hypertension, or hyperlipidaemia and trials in obese adults who did not have co-morbidities.[17] The subsequent RCT (60 obese adults with binge eating disorder) compared sibutramine 15 mg daily versus placebo for 12 weeks.[18] It found that sibutramine significantly increased weight loss at 12 weeks compared with placebo (7.4 kg weight loss with sibutramine *v* 1.4 kg weight gain with placebo; $P < 0.001$). One RCT identified by the review assessed sibutramine for weight maintenance.[17] Participants with greater than 5% weight loss at the completion of 6 months' treatment with sibutramine 10 mg daily were randomised to continue to receive sibutramine 10–20 mg daily or placebo for 18 months (467 people). The RCT was limited by only 56% follow up at 2 years. It found that sibutramine maintained significantly more weight loss at 2 years compared with placebo (WMD –4.0 kg, 95% CI –5.6 kg to –2.4). Two RCTs identified by the review assessed weight regain after discontinuation of treatment in people who had successful weight loss after 6 months' treatment with sibutramine. People regained 43% of lost body weight at 6 months (40 people) and 55% of lost body weight at 18 months (115 people).[17]

Sibutramine versus orlistat or metformin: We found no systematic review but found one RCT (150 obese women) comparing three

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treatments: sibutramine 20 mg daily; orlistat (120 mg 3 times daily); and metformin (850 mg twice daily) for 6 months.[19] All people were also instructed to follow a reduced calorie diet of 25 kcal/kg of ideal body weight. The RCT found that sibutramine achieved greater weight loss than either orlistat or metformin (–13.0 kg with sibutramine *v* –8.0 kg with orlistat *v* –9.0 kg with metformin; sibutramine *v* orlistat and sibutramine *v* metformin $P < 0.0001$). **Sibutramine versus other agents:** We found one systematic review (search date 1999), which identified no RCTs comparing sibutramine versus diethylpropion, fluoxetine, mazindol, orlistat, or phentermine.[20] **Sibutramine plus orlistat:** We found no systematic review but found one RCT (34 women who had completed 1 year of sibutramine plus lifestyle modification), which compared sibutramine 10–15 mg daily plus orlistat (120 mg 3 times daily) versus sibutramine plus placebo for weight maintenance.[21] Only 76% of the women completed the study. Mean body weight did not change significantly in either group over a 16 week period (+0.1 kg with sibutramine plus orlistat *v* +0.5 kg with sibutramine plus placebo).

Harms:

Sibutramine versus placebo: We found one systematic review[17] and two additional RCTs[22,23] that assessed adverse effects of sibutramine. The review found that sibutramine increased blood pressure (mean increase: systolic blood pressure: –0.2 mm Hg at 8–12 weeks, range from –1.6 to +5.6 mm Hg at 16–24 weeks in several RCTs, and range from +4.6 mm Hg at 44–54 weeks; diastolic blood pressure: range from +1.6 mm Hg at 8–12 weeks, –0.8 to +1.7 mmHg at 16–24 weeks, and +2.8 mm Hg at 44–54 weeks in several RCTs).[17] It also found that sibutramine significantly increased heart rate compared with placebo (increase in heart rate: 1.3 beats/minute at 8–12 weeks, 0.75–5.9 beats/minute at 16–24 weeks, and 5.9 beats/minute at 44–54 weeks).[17] Sibutramine was also associated with increased levels in total and low density lipoprotein cholesterol levels at 16–24 weeks compared with placebo (increase in total cholesterol: –1.9 to +1.8 mg/dL; increase in low density lipoprotein cholesterol 0.6 to 2.6 mg/dL); but no increase at 44–54 weeks.[17] Common adverse effects were headache, nausea, constipation, insomnia, and dry mouth, occurring in 20.4% of people taking sibutramine compared with 3.4% of people on placebo ($P < 0.01$).[17] We found two RCTs that assessed the effects of sibutramine on heart valve function.[22,23] Both of these RCTs may have been too small to detect clinically important adverse effects. The first RCT (210 obese people) compared sibutramine versus placebo for 12 months.[22] It found no significant difference in the incidence of valvular disease between sibutramine and placebo (3/133 [2.3%] with sibutramine 15–20 mg/day v 2/77 [2.6%] with placebo; OR 0.87, 90% CI 0.19 to 3.97). The trial did not report on efficacy. The second RCT (184 obese people) compared sibutramine 10 or 20 mg daily versus placebo.[23] It reported no change in valvular appearance on echocardiogram in any group (no statistical comparisons between or within groups reported).[23] We found no evidence about adverse effects after more than 1 year of treatment. Sibutramine was temporarily suspended from the market in Italy in March 2002 in response to 50 reported adverse reactions, including seven severe adverse reactions (tachycardia,

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hypertension, and arrhythmia) and two deaths resulting from cardiac arrest. The Central European Committee for Proprietary Medicinal Products (CPMP) completed a review of sibutramine in June 2002, and concluded that the risk benefit profile of sibutramine remains in favour of benefit; it therefore lifted the suspension in August 2002.[24] To date, searches of the websites of other regulatory authorities, including the Medicines Control Agency, UK; the Food and Drug Administration, USA; Health, Canada; and the Therapeutics Goods Administration, Australia, found that no other countries have taken any regulatory actions against the drug. **Sibutramine versus orlistat or metformin:** The RCT reported dry mouth, insomnia, constipation, and hypertension with sibutramine, and abdominal discomfort with orlistat and metformin.[19] **Sibutramine versus other agents:** The systematic review gave no information on adverse effects.[20] **Sibutramine plus orlistat:** The RCT found that people who received sibutramine plus orlistat experienced more soft stools, bowel movements, oily evacuation, and more faecal urge than sibutramine alone (soft stools: 50.0% with sibutramine plus orlistat *v* 9.1% with sibutramine alone; increased frequency of bowel movements: 50.0% with sibutramine plus orlistat *v* 9.1% with sibutramine alone; oily evacuation: 42.9% with sibutramine plus orlistat *v* 0% with sibutramine alone; more faecal urgency: 42.9% with sibutramine plus orlistat *v* 9.1% with sibutramine alone).[21]

Comment: Most of the people treated with sibutramine received additional dietary interventions, and many also have received an exercise intervention. The review suggested that weight loss with sibutramine is associated with both positive and negative changes in cardiovascular and metabolic risk factors.[17] Sibutramine has been associated with increases in systolic and diastolic blood pressure, heart rate, and total as well as low density lipoprotein cholesterol; it has conversely been associated with modest decreases in triglyceride levels, fasting serum glucose levels, glycosylated haemoglobin levels, and modest increases in high density lipoprotein cholesterol levels.[17]

OPTION PHENTERMINE

One systematic review found that, in people having lifestyle interventions, phentermine promoted modest weight loss compared with placebo in obese adults. RCTs identified by the review provided insufficient evidence to compare phentermine versus other agents. We found insufficient evidence on weight regain and long term safety with phentermine. A European Commission review concluded that a link between phentermine and heart and lung problems could not be excluded.

Benefits: **Phentermine versus placebo:** We found one systematic review (search date 1999, 6 RCTs, 368 people) comparing phentermine 15–30 mg daily versus placebo in obese adults, with mean follow up of 13.2 weeks (range 2–24 weeks).[20] The review found that phentermine produced significantly more weight loss than placebo (effect size: < 0.6 [information presented graphically]; mean difference in weight loss between phentermine and placebo in the six

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RCTs ranged from 0.6–6.0 kg). **Phentermine versus diethylpropion:** The review also found that phentermine significantly increased weight loss compared with diethylpropion (1 RCT, 99 people: mean weight loss 8.3 kg with phentermine *v* 6.3 kg with diethylpropion; effect size: 0.57, CI not reported).[20] **Phentermine versus mazindol:** See benefits of mazindol, p 9. **Phentermine versus other drugs:** The review found no RCTs comparing phentermine versus diethylpropion, fluoxetine, orlistat, or sibutramine.[20]

Harms: The systematic review gave no information on adverse effects.[20] Phentermine given alone has not been associated with valvular heart disease.[25] A European Commission review reported that, although no new safety problems were identified with phentermine, a link between phentermine and heart and lung problems could not be totally excluded.[26]

Comment: Most of the people treated with phentermine received additional lifestyle interventions.[20] High withdrawal rates have been reported for phentermine.

OPTION MAZINDOL

One systematic review found that, in people having lifestyle interventions, mazindol promoted modest weight loss compared with placebo in obese adults. The review provided insufficient evidence to compare mazindol versus other agents. We found one case report of pulmonary hypertension diagnosed 1 year after stopping treatment with mazindol. We found one case series of mazindol in people with stable cardiac disease that reported cardiac events such as atrial fibrillation and syncope. We found insufficient evidence on weight regain and long term safety.

Benefits: **Mazindol versus placebo:** We found one systematic review (search date 1999, 22 RCTs, 906 people) comparing mazindol 1–3 mg daily versus placebo in obese adults with mean follow up of 11 weeks (range 2–20 weeks).[20] The review found that mazindol significantly increased weight loss compared with placebo (effect size: < 0.5; absolute data presented graphically; mean difference in weight loss between mazindol and placebo in the 22 RCTs ranged from 0.1–7.3 kg). **Mazindol versus other drugs:** The review also compared mazindol versus other agents.[20] Three RCTs identified by the review found no significant difference in weight loss between mazindol and diethylpropion (mean 6.7 kg with mazindol *v* 5.1 with diethylpropion; effect size: +0.31, 95% CI –0.07 to +0.69). One RCT identified by the review found that mazindol significantly increased weight loss compared with phentermine (mean 6.7 kg *v* 5.5 kg; effect size: 0.12, CI not reported). The review found no RCTs comparing mazindol versus diethylpropion, fluoxetine, orlistat, or sibutramine.

Harms: The systematic review gave no information on adverse effects.[20] We found a single case report of pulmonary hypertension diagnosed 12 months after stopping mazindol that had been taken for 10

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weeks.[27] One case series of mazindol in people with stable cardiac disease reported several cardiac events (3 episodes of atrial fibrillation and 2 of syncope in 15 people receiving mazindol for 12 weeks).[28] The frequency of serious adverse events with this agent remains unclear.

Comment: Most of the people treated with mazindol received additional lifestyle interventions.[20]

OPTION DIETHYLPROPION

One systematic review found that, in people having lifestyle interventions, diethylpropion promoted modest weight loss compared with placebo in obese adults. The review provided insufficient evidence to compare diethylpropion versus other agents. We found two case reports describing pulmonary hypertension and psychosis with diethylpropion. We found insufficient evidence on weight regain and long term safety. A European Commission review concluded that a link between diethylpropion and heart and lung problems could not be excluded.

Benefits: **Diethylpropion versus placebo:** We found one systematic review (search date 1999, 9 RCTs, 353 people) comparing diethylpropion 75 mg daily versus placebo in obese adults with mean follow up of 17.6 weeks (range 6–52 weeks).[20] The review found that diethylpropion significantly increased weight loss compared with placebo (effect size: < 0.55 [information presented graphically]; mean difference in weight loss between diethylpropion and placebo in the 9 RCTs ranged from 1.6–11.5 kg). **Diethylpropion versus mazindol:** See benefits of mazindol, p 9. **Diethylpropion versus phentermine:** See benefits of phentermine, p 8. **Diethylpropion versus other drugs:** The review identified no RCTs comparing diethylpropion versus fluoxetine, orlistat, or sibutramine.[20]

Harms: The systematic review gave no information on adverse effects.[20] Case reports have described pulmonary hypertension and psychosis in users of diethylpropion.[29,30] The frequency of serious adverse events with diethylpropion remains unclear. A European Commission review of the risks and benefits of diethylpropion concluded that randomised trials do not adequately show efficacy for weight loss.[26] Although no new safety problems were identified with diethylpropion, the Commission commented that a link between diethylpropion and heart and lung problems could not be totally excluded.

Comment: Most of the people treated with diethylpropion received additional lifestyle interventions.[20]

OPTION FLUOXETINE

One systematic review found that, in people having lifestyle interventions, fluoxetine promoted modest weight loss compared with placebo in obese adults. We found insufficient evidence on weight regain and long term safety of fluoxetine in obesity. One systematic review of antidepressant treatment found an association between selective

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serotonin reuptake inhibitors such as fluoxetine and uncommon but serious adverse events, including bradycardia, bleeding, granulocytopenia, seizures, hyponatraemia, hepatotoxicity, serotonin syndrome, and extrapyramidal effects.

Benefits: **Fluoxetine versus placebo:** We found one systematic review (search date 1999, 11 RCTs, 1219 people) comparing fluoxetine 32.5–60.0 mg daily versus placebo in obese adults with mean follow up of 27.5 weeks (range 6–60 weeks).[20] The review found that fluoxetine produced significant weight loss compared with placebo (effect size: < 0.45 [information presented graphically]; mean difference in weight loss between fluoxetine and placebo in the 11 RCTs ranged from 0.2–7.4 kg). **Fluoxetine versus other drugs:** The review identified no RCTs comparing fluoxetine versus diethylpropion, mazindol, orlistat, phentermine, or sibutramine.[20]

Harms: The systematic review gave no information on adverse effects.[20] One older systematic review (search date 1998) of antidepressant treatment (for other indications) found that selective serotonin reuptake inhibitors were associated with a 10–15% incidence of anxiety, diarrhoea, dry mouth, headache, and nausea.[31] The review also found an association between selective serotonin reuptake inhibitors and uncommon but serious adverse events, including bradycardia, bleeding, granulocytopenia, seizures, hyponatraemia, hepatotoxicity, serotonin syndrome (see glossary, p 20), and extrapyramidal effects (see glossary, p 20).

Comment: Most of the people treated with fluoxetine received additional lifestyle interventions.[20]

OPTION ORLISTAT

Systematic reviews and subsequent RCTs found that, in people on a low calorie diet, orlistat modestly increased weight loss at 6–12 months compared with placebo in obese adults, in both those who did and who did not have diabetes, hyperlipidaemia, and hypertension. One RCT in obese people with hypercholesterolaemia found that orlistat plus fluvastatin increased weight loss compared with orlistat or fluvastatin alone. Another RCT found that orlistat was less effective than sibutramine in achieving weight loss. A third RCT provided insufficient evidence to compare adding orlistat to sibutramine versus sibutramine alone. Adverse effects such as oily spotting from the rectum, flatulence, and faecal urgency occurred in a high proportion of people taking orlistat. We found insufficient evidence on weight regain and long term safety.

Benefits: **Orlistat versus placebo:** We found one systematic review (search date 2002),[32] and one subsequent RCT[33] comparing orlistat versus placebo. The review (19 RCTs) meta-analyzed results from RCTs with similar study design, dose of orlistat, and duration of follow up.[32] All of the meta-analyses found that orlistat at all doses significantly increased modest weight loss at 6 months to 1 year compared with placebo. For example, orlistat 60 or 120 mg 3 times daily significantly increased weight loss at 1 year compared with placebo (2 RCTs, 910 people: WMD –2.44 kg, 95% CI –3.40 kg to –1.47 kg with 60 mg; 3 RCTs, 1789 people: WMD –3.19 kg (95% CI –3.98 kg to –2.40 kg with 120 mg). However, the meta-analyses

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found no significant difference in weight loss at 3 months between orlistat and placebo. For example, one meta-analysis found no significant difference between orlistat 50–60 mg 3 times daily and placebo in weight loss at 3 months (2 RCTs, 133 people: WMD −1.24 kg, 95% CI −2.65 kg to +0.16 kg). Similar beneficial results were found comparing the efficacy of orlistat at greater and lesser durations of treatment. The review performed separate meta-analyses comparing orlistat versus placebo in people with defined obesity related comorbidities such as type 2 diabetes mellitus, hyperlipidaemia, or multiple cardiovascular risk factors (impaired glucose tolerance/diabetes, dyslipidaemia, or hypertension) and found similar results. The subsequent RCT (343 obese people with non-insulin dependent diabetes) found that orlistat (120 mg 3 times daily) significantly increased weight loss compared with placebo at 6 months (mean weight loss: 4.24 kg with orlistat *v* 2.58 with placebo; P = 0.0003).[33] The review identified one RCT comparing orlistat versus placebo for weight maintenance.[32] After 6 months of diet alone, people received orlistat (30, 60, or 120 mg 3 times daily) or placebo for 1 year. The RCT found that orlistat 120 mg significantly reduced weight regain at 1 year compared with placebo. However, it found no significant difference in weight regain between orlistat at other doses and placebo (percentage of weight regained: 32.4% with orlistat 120 mg *v* 47.2% with orlistat 60 mg *v* 53.3% with orlistat 30 mg *v* 56.0% with placebo; P < 0.001 for orlistat 120 mg *v* placebo, P reported as non-significant for other doses, CI not reported).[32] **Orlistat plus fluvastatin:** We found no systematic review but found one RCT (99 obese people with hypercholesterolaemia) that compared four treatments over 1 year: orlistat (120 mg 3 times daily); fluvastatin (80 mg 4 times daily); orlistat (120 mg 3 times daily) plus fluvastatin (80 mg 4 times daily); and placebo.[34] It found that orlistat plus fluvastatin significantly increased weight loss compared orlistat alone, fluvastatin alone, or placebo (mean weight loss: 11.4 kg with orlistat plus fluvastatin *v* 8.6 kg with orlistat *v* 8.0 kg with fluvastatin *v* 7.6 kg with placebo; P < 0.05). **Orlistat plus sibutramine:** See benefits of sibutramine, p 6. **Versus other drugs:** We found one systematic review (search date 1999), which identified no RCTs comparing orlistat versus diethylpropion, fluoxetine, mazindol, phentermine or sibutramine.[20] We found one subsequent RCT comparing orlistat versus sibutramine (see benefits of sibutramine, p 6).[21]

Harms:

Versus placebo: Gastrointestinal adverse events such as loose stools, increased defaecation, abdominal pain, nausea and vomiting, oily spotting from the rectum, flatulence, and faecal urgency were more common with orlistat than placebo (48–95% with orlistat 120 mg 3 times daily *v* 18–68% with placebo).[32] The first subsequent RCT (343 people with type 2 diabetes mellitus) found that orlistat significantly increased gastrointestinal adverse effects and increased withdrawals because of adverse effects compared with placebo (gastrointestinal effects: 65% with orlistat *v* 37% with placebo; withdrawals: 4.7% with orlistat *v* 2.9% with placebo; P values not reported).[33] **Orlistat plus sibutramine:** See harms of sibutramine, p 7. **Versus sibutramine:** See harms of sibutramine, p 7.

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Comment: People treated with orlistat also undertook a low calorie diet.[32] Because of the high rates of gastrointestinal adverse effects associated with orlistat, authors have queried whether blinded evaluation is possible.[21] At the end of a double blinded 16 week trial, 22/26 [85%] people correctly identified their treatment group.

QUESTION **What are the effects of bariatric surgery in adults with morbid obesity?** New

OPTION **BARIATRIC SURGERY VERSUS NON-SURGICAL TREATMENT**

One RCT and one cohort study identified by three systematic reviews found that bariatric surgery (horizontal gastroplasty, vertical banded gastroplasty, gastric bypass, or gastric banding) was more effective than non-surgical treatment in increasing weight loss in people with morbid obesity. The cohort study found that, on average, bariatric surgery for obesity resulted in weight losses of 25–44 kg after 1–2 years (compared with matched participants who did not have surgery) and sustained weight loss of 20 kg up to 8 years later. The risk of death from bariatric surgery is estimated to be 0 to 1.5%. Operative and postoperative complications are common and vary with the type of bariatric procedure performed. The reviews identified no RCTs and we found no observational studies of sufficient quality comparing biliopancreatic diversion versus non-surgical treatment.

Benefits: We found three systematic reviews of bariatric surgery (search dates 2001,[35] 2003[36,37]), all of which identified the same single RCT and multicentre cohort study with matched controls comparing bariatric surgery (horizontal gastroplasty (see glossary, p 20), vertical banded gastroplasty, gastric bypass (see glossary, p 20), or gastric banding (see glossary, p 20)) versus non-surgical treatment. The RCT and cohort study both suggested that bariatric surgery was more effective than non-surgical treatment for weight loss in adults with morbid obesity. The RCT (57 adults ≥ 60% overweight) identified by the reviews compared horizontal gastroplasty versus a very low calorie diet (500 kcal, 34 g protein daily) for 24 months. It found that horizontal gastroplasty significantly reduced body weight at 24 months compared with a very low calorie diet (32 kg with gastroplasty *v* 9 kg with very low calorie diet; $P < 0.05$). However, it found no significant difference in the proportion of people who had a net weight loss of 10 kg at 5 years (30% with horizontal gastroplasty *v* 17% with a very low calorie diet; P value reported as non-significant, CI not reported). The multicentre cohort study (2188 people) identified by the reviews[35–37] compared bariatric surgery versus usual care.[38] Eligible participants self selected either a bariatric surgery group or a non-surgical (usual care) group. Each person who selected surgical treatment was matched on 18 clinical variables with a person from the non-surgical group. Each surgeon determined the surgical procedure offered: vertical banded gastroplasty (> 70%), gastric bypass (6%), or gastric banding (23%). Usual care was according to local practice and usually did not include pharmacotherapy. The cohort study found that people who had surgery lost significantly more weight than people receiving usual care at 1 year

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(mean weight loss: 44.0 kg with gastric bypass [68 people] *v* 30.7 kg with vertical banded gastroplasty [834 people] *v* 25.8 kg with gastric banding [255 people] *v* 1.6 kg with usual care [1031 people]; $P < 0.0001$ for all surgical groups *v* usual care). The differences in weight loss between groups remained significant at 8 years (mean percentage of body weight lost: 16.3% with surgery [232 people] *v* 0.9% weight gained with usual care [251 people]; mean difference in weight 20.7 kg; $P < 0.01$).

Harms: The RCT reported no deaths related to surgery and no-one required re-operation.[35–37] As of 31 January 2001 the cohort study reported five postoperative deaths in 2010 people (0.25%); three deaths owing to leakage, one owing to technical mistake during laparoscopic surgery, and one owing to postoperative myocardial infarction.[38] It reported that 2.2% of people required re-operation. One systematic review evaluated 38 surgical case series of bariatric surgery, which included people with both substantial comorbid conditions and mild health problems, and found that perioperative mortalities were low and similar across bariatric procedures: 0–1.5% among people who received gastric bypass, gastroplasty, or gastric banding.[37] Perioperative complications were common, including: subphrenic abscess (7%), atelectasis or pneumonia (4%), wound infection (4%), and pulmonary symptoms (6.2%).

Comment: The cohort study will not be able to report on total mortality until 2004–2006.[38] Horizontal gastroplasty is less often performed worldwide, because of evidence of greater weight loss and comparable complication rates with gastric bypass. Two systematic reviews were published after the search date of our review.[13,14] These reviews did not identify any additional RCTs comparing bariatric surgery versus non-surgical techniques. Two cohort studies were published after our search date, which compared bariatric surgery versus non-surgical treatment in morbidly obese adults.[15,16] The first study (1035 people having surgery and 5746 having non-surgical treatment) found significantly lower mortality over a mean of 5.3 years in people having surgery compared with people having non-surgical treatment (0.68% with surgery *v* 6.17% with non-surgical treatment; RR 0.11; 95% CI 0.04 to 0.27).[15] The second cohort study (3328 people having surgery and 62 781 having non-surgical interventions) also found significantly lower mortality at 15 years' follow up in people having surgery compared with non-surgical treatment (12% with surgery *v* 16% with non-surgical treatment; adjusted HR 0.67; 95% CI 0.54 to 0.85).[16] This study also found 2% mortality at 30 days in people having surgery.[16]

OPTION GASTRIC BANDING VERSUS OTHER BARIATRIC SURGICAL TECHNIQUES

One small RCT identified by a systematic review found limited evidence that gastric banding was less effective than gastric bypass in reducing weight. Two RCTs found inconclusive results regarding weight loss with gastric banding compared with vertical banded gastroplasty. There were no postoperative deaths in either RCT. Postoperative complications were common and varied by type of procedure performed. There is insufficient evidence to recommend one procedure over the other.

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Benefits: **Gastric banding versus gastric bypass:** See glossary, p 20. See benefits of gastric bypass, p 16. **Gastric banding versus vertical banded gastroplasty:** We found one systematic review (search date 2001, 1 RCT)[35] and one subsequent RCT.[39] The RCT (59 adults with body mass index (see glossary, p 20) [BMI] ≥ 40 or BMI ≥ 37 with associated comorbidity) identified by the review found that people having gastric banding (see glossary, p 20) had smaller weight loss at 1 year compared with people having vertical banded gastroplasty (see glossary, p 20) (results not reported), but at 5 years people having gastric banding had lost more weight (43 kg with gastric banding *v* 35 kg with vertical banded gastroplasty; CI not reported).[35] The subsequent RCT (200 adults with BMI 40–50) found that significantly fewer people having gastric banding had an excellent or good result (defined as residual excess weight of < 50%) at 2 years compared with people having vertical banded gastroplasty (35% with gastric banding *v* 74% with vertical banded gastroplasty; $P < 0.001$) Success rates were lower with gastric banding at 3 years, but the difference did not quite reach significance (25% with gastric banding *v* 63% with vertical banded gastroplasty; $P = 0.056$).[39]

Harms: **Gastric banding versus gastric bypass:** See harms of gastric bypass, p 16. **Gastric banding versus vertical banded gastroplasty:** The first RCT reported one death from each group during the follow up period but neither death was attributed to the surgery. Re-operations occurred in 33% of people having vertical banded gastroplasty and 10% of people having gastric banding. Gastroesophageal reflux was more common in people having vertical banded gastroplasty compared with people having gastric banding (14.8% with gastroplasty *v* 11.5% with gastric banding).[35] No deaths were reported in the second RCT.[39] It found that gastric banding significantly increased the proportion of people who required re-operation compared with vertical banded gastroplasty (25% with gastric banding *v* 0% with vertical banded gastroplasty; $P < 0.05$). It also found that gastric banding significantly increased late complications, such as pouch dilatation, pouch-to-fundus fistula, symptomatic reflux disease, and gastric bezoar compared with vertical banded gastroplasty (33% with gastric banding *v* 14% with gastroplasty; $P < 0.001$).[39]

Comment: None.

OPTION GASTRIC BYPASS VERSUS OTHER BARIATRIC SURGICAL TECHNIQUES

RCTs provided moderate evidence that gastric bypass promoted greater weight loss than either gastroplasty or gastric banding. Five RCTs identified by a systematic review found that gastric bypass increased weight loss compared with horizontal gastroplasty. Two RCTs identified by the review found that gastric bypass increased weight loss at 1–3 years compared with vertical banded gastroplasty but another two RCTs found no significant difference between the procedures. One small RCT identified by the review found limited evidence of greater weight loss with gastric bypass than with gastric banding or vertical banded gastroplasty. Another small RCT identified by the review found that gastric bypass

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increased the proportion of people with 50% weight loss at 18 months compared with vertical banded gastroplasty or gastrogastrostomy. Perioperative mortalities were similar for these procedures. Postoperative complications were common and varied by type of procedure performed.

Benefits: We found one systematic review (search date 2001, 9 RCTs, 962 people) comparing gastric bypass (see glossary, p 20) versus vertical banded or horizontal gastroplasty (see glossary, p 20).[35] **Gastric bypass versus horizontal gastroplasty:** The review identified five RCTs (384 morbidly obese people) that compared gastric bypass versus horizontal gastroplasty.[35] All of the RCTs found that gastric bypass significantly increased weight loss compared with horizontal gastroplasty. Trials reported an average of 35–42% weight loss with gastric bypass compared with 16–29% with horizontal gastroplasty at 12 months ($P < 0.05$ in all RCTs). **Gastric bypass versus vertical banded gastroplasty, gastric banding, or gastrogastrostomy:** The review identified four RCTs that compared gastric bypass versus vertical banded gastroplasty and two RCTs that compared three interventions.[35] The first RCT (42 adults with body mass index (see glossary, p 20) ≥ 40) found that gastric bypass significantly increased weight loss compared with vertical banded gastroplasty at 12 months (percentage weight loss: 78% with gastric bypass *v* 52% with vertical banded gastroplasty: $P < 0.05$). The second RCT (40 adults > 44 kg overweight) also found that gastric bypass significantly increased weight loss compared with vertical banded gastroplasty at 12 months, 2 years, and 3 years (12 months: 68% with gastric bypass *v* 43% with vertical banded gastroplasty; $P < 0.001$; 2 years: 66% with gastric bypass *v* 39% with vertical banded gastroplasty; $P < 0.001$; 3 years: 62% with gastric bypass *v* 37% with vertical banded gastroplasty; $P < 0.001$). The other two RCTs (109 adults, 32 with body mass index ≥ 40) found no significant difference in weight loss between the two procedures at 36 months, 3 years, and 5–6 years. The fifth RCT (77 adults) compared three interventions: gastric bypass, gastric banding (see glossary, p 20), or vertical banded gastroplasty. It found greater mean excess weight loss at 18 months with gastric bypass than with vertical banded gastroplasty or gastric banding (77% with gastric bypass *v* 65% with gastric banding *v* 60% with vertical banded gastroplasty; CI not reported). The sixth RCT (310 people) also compared three procedures: gastric bypass (99 adults), vertical banded gastroplasty (106 adults), or gastrogastrostomy (105 adults). It found that gastric bypass significantly increased the proportion of people who had a successful outcome (defined as 50% weight loss: 67% with gastric bypass *v* 48% with vertical banded gastroplasty *v* 17% with gastrogastrostomy; $P < 0.001$).[35]

Harms: **Gastric bypass versus vertical banded gastroplasty:** Three RCTs comparing gastric bypass versus vertical banded gastroplasty identified by the review reported no deaths.[35] One RCT comparing gastric bypass versus vertical banded gastroplasty reported no deaths in the vertical banded gastroplasty group but two deaths (10%) in the gastric bypass group, occurring after 3 days and 12 months owing to presumed arrhythmia. **Gastric bypass versus horizontal gastroplasty:** Four RCTs comparing gastric bypass versus horizontal gastroplasty identified by the review reported no

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operative mortality.[35] The fifth RCT reported two deaths: one 6 days after gastroplasty owing to anastomotic leak and cerebrovascular accident and one death within 30 days after gastric bypass owing to pulmonary embolism. The type of postoperative complications differed for these procedures. People having gastric bypass had symptomatic ulcer disease (25%), intractable vomiting and stomal stenosis (25%), marginal ulcers of jejunal side of gastrojejunostomy (5%), cholelithiasis (13%), and peptic gastroesophagitis (33%). People having vertical banded gastroplasty had superficial stomal erosions (5%), cholelithiasis (24%), and peptic gastroesophagitis (18%). One RCT found that significantly more people having gastric bypass had dumping syndrome (28% with gastric bypass *v* 0% with horizontal gastroplasty; $P < 0.05$) or heartburn (59% with gastric bypass *v* 32% with horizontal gastroplasty; $P < 0.05$). Other early and late complications varied little between procedures; however, one RCT reported that 32% of people having gastric bypass and 42% having gastroplasty had some form of postoperative complication.[35] **Gastric bypass versus gastric banding or vertical banded gastroplasty:** The RCT comparing gastric bypass, vertical banded gastroplasty, and gastric banding reported one death (group not specified).[35] One person who had vertical banded gastroplasty required re-operation (4%) for staple disruption, while 44% of people having gastric banding required re-operation for inadequate weight loss, nutritional disorder, or increased vomiting. **Gastric bypass versus vertical banded gastroplasty or gastrogastrostomy:** The RCT comparing gastric bypass, vertical banded gastroplasty, and gastrogastrostomy identified by the review reported two postoperative deaths (groups not specified), one from complications of a subsequent cholecystectomy, and one from carcinoma of the colon.[35] Early and late complication rates were similar among procedures.

Comment: Two systematic reviews were published after our search date, both of which concluded that gastric bypass results in greater weight loss than vertical banded gastroplasty.[13,14]

OPTION GASTROPLASTY VERSUS OTHER BARIATRIC SURGICAL TECHNIQUES

Two RCTs found inconclusive results regarding weight loss with vertical banded gastroplasty compared with gastric banding. Five RCTs identified by a systematic review found that horizontal gastroplasty was less effective than gastric bypass for increasing weight loss. Four RCTs identified by the review found that vertical banded gastroplasty was less effective than gastric bypass in increasing weight loss at 1–3 years but another two RCTs found no significant difference between the procedures. Perioperative mortalities were similar for these procedures. Postoperative complications were common and varied by type of procedure performed. There is insufficient evidence to recommend one procedure over another.

Benefits: **Gastroplasty versus gastric banding:** See glossary, p 20. See benefits of gastric banding, p 15. **Gastroplasty versus gastric bypass:** See benefits of gastric bypass, p 16.

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Harms: **Gastroplasty versus gastric banding:** See harms of gastric banding, p 15. **Gastroplasty versus gastric bypass:** See harms of gastric bypass, p 16.

Comment: Two systematic reviews were published after our search date, and these reviews both concluded that vertical banded gastroplasty (see glossary, p 20) results in less weight loss than gastric bypass (see glossary, p 20).[13,14]

OPTION BILIOPANCREATIC DIVERSION VERSUS OTHER BARIATRIC SURGICAL TECHNIQUES

Three systematic reviews identified no RCTs and we found no observational studies of sufficient quality comparing biliopancreatic diversion versus other bariatric procedures.

Benefits: We found three systematic reviews (search dates 2001,[35] 2003[36,37]), which identified no RCTs comparing biliopancreatic diversion (see glossary, p 19) versus other bariatric surgery techniques.

Harms: We found no RCTs.

Comment: None.

OPTION OPEN VERSUS LAPAROSCOPIC BARIATRIC SURGERY

Five RCTs found no significant difference in weight loss between open and laparoscopic bariatric procedures. The RCTs found consistent evidence that laparoscopic surgery reduced the incidence of wound and incisional hernia complications compared with open surgery. They found more limited evidence that laparoscopic procedures decreased length of hospital stay compared with open procedures; data are insufficient to draw conclusions about other complication rates.

Benefits: We found one systematic review (search date 2001, 3 RCTs, 256 people with morbid obesity)[35] and two subsequent RCTs[40,41] comparing open versus laparoscopic techniques. **Open versus laparoscopic gastric banding:** The review identified one RCT (50 adults with body mass index (see glossary, p 20) ≥ 40) that found no significant difference in weight loss between open and laparoscopic gastric banding (see glossary, p 20) at 12 months (34.4 kg with open *v* 35.0 kg with laparoscopic; P reported as non-significant).[35] **Open versus laparoscopic gastric bypass:** The review identified two RCTs and we found one subsequent RCT that found no significant difference in weight loss at 1 and 2 years between open and laparoscopic gastric bypass (see glossary, p 20).[35,40] The first RCT (155 people) identified by the review found no significant difference in weight loss at 1 year (62% with open *v* 68% with laparoscopic; P = 0.07). The second RCT (51 people) identified by the review also found no significant difference in body mass index (BMI) at 1 year (reduction in BMI: 13 kg/m^2 with open *v* 14 kg/m^2 with laparoscopic; reported as non-significant, CI not reported in review). The subsequent RCT (104 people with morbid obesity) found no significant difference in weight loss at a mean 23 months between open and laparoscopic techniques (reported as non-significant, results presented graphically).[40] **Open versus laparoscopic vertical**

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banded gastroplasty: The review identified no RCTs.[35] One subsequent RCT (30 adults with body mass index 40–50) found similar weight loss between open and laparoscopic vertical banded gastroplasty (see glossary, p 20) at 12 months (mean: 55% with open *v* 47% with laparoscopic; CI not reported).[41]

Harms: **Open versus laparoscopic gastric banding:** One of the RCTs reported no deaths.[35] The review found no significant difference in surgical complications between the two procedures (reported as non-significant, CI not reported in the review), although people having open gastric banding had more incisional hernia complications (12% with open *v* 0% with laparoscopic). Re-admissions and overall length of hospital stay were significantly higher in people having open compared with laparoscopic procedures (re-admissions: 60% with open *v* 24% with laparoscopic; hospital stay: 11.8 days with open *v* 7.8 days with laparoscopic; $P < 0.05$ for both outcomes). **Open versus laparoscopic gastric bypass:** The RCTs reported four postoperative deaths: one owing to malignant hyperthermia, one owing to possible pulmonary thromboembolism (laparoscopic), one owing to intestinal obstruction (laparoscopic), and one owing to evisceration.[35,40] The review found no significant difference between open and laparoscopic bypass in the proportion of people who had major surgical complications (9.2% of people with open *v* 7.6% of people with laparoscopic; $P = 0.78$).[35] In all three RCTs identified by the review, minor complications (including vomiting, colicky pain, and wound infection) were not significantly different between groups.[35] The subsequent RCT found that open gastric bypass was associated with a significantly higher rate of late complications (including eventrations, abscess, intestinal obstruction, and pancreatitis) compared with laparoscopic bypass (24% with open *v* 11% with laparoscopic; $P < 0.05$).[40] Operating time was longer for the laparoscopic procedure in two RCTs and longer for the open procedure in one RCT. Hospital stay was significantly shorter for the laparoscopic procedure in all three RCTs (4–8 days with open *v* 3–5 days with laparoscopic; $P < 0.05$). **Open versus laparoscopic vertical banded gastroplasty:** The RCT reported no deaths.[41] Operating time was significantly longer for the laparoscopic procedure (2.10 hours with open *v* 1.45 hours with laparoscopic; $P = 0.002$), but average hospital stay was not significantly different (4 days for both techniques). Two people, one in each group, developed a fistula at the gastric partition that required re-operation. Two people having open gastroplasty (see glossary, p 20) developed abdominal wall hernias at 12 months.

Comment: One systematic review was published after our search date, which also concluded that laparoscopic procedures result in fewer wound complications or incisional hernias than open procedures.[14]

GLOSSARY

Biliopancreatic diversion There are two different types of biliopancreatic diversion. Standard biliopancreatic diversion surgically removes the lower third of the stomach and then forms a connection with the remaining stomach pouch with a portion a small intestine beyond where the stomach was originally attached. Biliopancreatic diversion with duodenal switch divides the stomach vertically and removes the left half, leaving the connection between the stomach and the

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duodenum of the small intestine intact. A length of intestine is also removed and the duodenum is reconnected further down the small intestine. The aim is to increase weight loss by reducing calories and decreasing nutrient absorption.

Body mass index (BMI) Expressed as weight in kilograms divided by height in metres squared (kg/m^2). In the USA and UK, individuals with body mass indexes of 25–30 kg/m^2 are considered overweight; those with body mass indexes above 30 kg/m^2 are considered obese.

Extrapyramidal effects Include acute dystonia, a Parkinsonism-like syndrome, and akathisia.

Gastric banding involves placing an adjustable band around the upper portion of the stomach. The band is connected to a reservoir, which the surgeon can tighten or loosen, by the infusion of varying amounts of a saline solution. The newly created upper pouch will only allow the person to consume small amounts of food at a time.

Gastric bypass The roux-en-Y gastric bypass procedure involves dividing the stomach and creating a small pouch, which is then closed using several rows of staples. The remaining portion of the stomach is not removed but is "bypassed" and plays a diminished role in the digestive process. A Y-shaped portion of the small intestine is then attached to the pouch. The volume the new stomach pouch is capable of holding is about 25 g. The aim is to increase weight loss by reducing calories, altering gastrointestinal appetite hormones, and decreasing nutrient absorption.

Gastroplasty Vertical banded gastroplasty involves stapling the front of the stomach to the back of the stomach along a vertical plane, partitioning the stomach into two, unequal parts which connect through a small (about 0.5 cm) opening. This allows the partially digested food to move from the small stomach pouch into the rest of the stomach and then the intestines. The newly created upper pouch will only allow the person to consume small amounts of food at a time.

Serotonin syndrome Clinical features include agitation, ataxia, diaphoresis, diarrhoea, fever, hyper-reflexia, myoclonus, shivering, and changes in mental status. The occurrence and severity of syndrome does not seem to be dose related.

Substantive changes

Sibutramine One systematic review[17] and one subsequent RCT added;[18] categorisation unchanged.

Orlistat One systematic review[32] and one subsequent RCT added;[33] categorisation unchanged.

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Prevention of cardiovascular events in diabetes

Search date November 2004

Ronald Sigal, Janine Malcolm and Amel Arnaout

QUESTIONS

INTERVENTIONS

*No RCT but observational evidence suggests some benefit.
See glossary G

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Prevention of cardiovascular events in diabetes

Key Messages

Promoting smoking cessation

- **Smoking cessation*** We found no RCTs on promoting smoking cessation specifically in people with diabetes. Observational evidence and extrapolation from people without diabetes suggest that promotion of smoking cessation is likely to reduce cardiovascular events.

Blood pressure control

- **Antihypertensive treatment (compared with no antihypertensive treatment)** Systematic reviews and subsequent RCTs found that, in adults with diabetes and hypertension or previous cardiovascular disease, blood pressure lowering with antihypertensive agents (angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, or diuretics) reduced cardiovascular morbidity and mortality compared with no antihypertensive treatment. One systematic review found that beta-blockers reduced mortality in people with diabetes and congestive heart failure, but to a lesser extent than in non-diabetic people with congestive heart failure.
- **Lower target blood pressures** Large RCTs, primarily including people with hypertension, found that tighter control of blood pressure to a target diastolic blood pressure of 80 mm Hg or lower reduces the risk of major cardiovascular events. One RCT in normotensive people with diabetes found that intensive blood pressure lowering reduced cerebral vascular accidents but found no significant difference in cardiovascular death, myocardial infarction, congestive heart failure, or all cause mortality.
- **Different antihypertensive drugs** Systematic reviews and RCTs found that angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, beta-blockers, and calcium channel blockers were all effective in reducing cardiovascular morbidity and mortality in older people with diabetes and hypertension; most RCTs found no significant difference between different antihypertensive drugs. However, some RCTs found a lesser degree of protection against heart failure with calcium channel blockers compared with other antihypertensive agents and an increase in the risk of stroke or congestive heart failure with the angiotensin converting enzyme inhibitor lisinopril compared with the diuretic chlorthalidone. There was also an increase in the risk of cardiovascular morbidity and mortality with angiotensin II receptor antagonists compared with beta-blockers or diuretics. Different antihypertensive drugs were associated with different adverse effects. RCTs found that people taking atenolol gained more weight than those taking captopril, had a higher frequency of headache and constipation with diltiazem than with diuretics or beta-blockers, and had a higher rate of withdrawal from treatment because of adverse effects with atenolol than with losartan.

Treating dyslipidemia

- **Statins** One systematic review and a subsequent RCT found that statins reduced cardiovascular events compared with placebo. The RCT found that in people without high LDL cholesterol, atorvastatin 10 mg daily reduced cardiovascular events compared with placebo at 3.9 years.
- **Aggressive versus moderate lipid lowering with statins** One RCT found that, compared with usual care, treatment with atorvastatin to achieve a target low density lipoprotein concentration below 2.6 mmol/L (< 100 mg/dL) reduced cardiovascular morbidity and mortality. Another RCT found no significant difference between a lower target low density lipoprotein (1.55–2.20 mmol/L) using lovastatin, plus cholestyramine if needed, and a moderate target low density lipoprotein (3.36–3.62 mmol/L) in 4 year event rate for myocardial infarction and death.
- **Fibrates** One RCT found that gemfibrozil reduced cardiovascular events over 5 years compared with placebo. Another, smaller RCT found no significant difference. One RCT found that bezafibrate reduced cardiovascular events over 3 years compared with placebo. One RCT found no significant difference between fenofibrate and placebo in the frequency of myocardial infarction or death over 39 months.
- **Low versus standard statin dose in older people** One RCT found no significant difference in cardiovascular events between low dose pravastatin (5 mg/day) and standard dose pravastatin (10–20 mg/day) over 4 years.

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Antiplatelet drugs

- **Adding glycoprotein IIb/IIIa inhibitors to heparin in acute coronary syndromes** We found no RCTs comparing glycoprotein IIb/IIIa inhibitors versus no antiplatelet treatment. One RCT in people presenting with unstable angina or acute myocardial infarction without ST segment elevation found that adding tirofiban (a glycoprotein IIb/IIIa inhibitor) to heparin reduced the composite outcome of death, myocardial infarction, or refractory ischaemia at 180 days compared with heparin alone. This RCT found no significant difference between tirofiban plus heparin versus heparin alone in risk of bleeding in people already taking aspirin. RCTs in people undergoing percutaneous transluminal coronary angioplasty found that the combination of glycoprotein IIb/IIIa inhibitor plus stent reduced cardiovascular morbidity and mortality compared with placebo plus stent. One RCT in people with acute ST segment elevation myocardial infarction found that a combination of abciximab plus half dose reteplase reduced recurrent myocardial infarction compared with full dose reteplase alone at 7 days. It also found that abciximab plus half dose reteplase increased bleeding.
- **Clopidogrel** We found no RCTs comparing clopidogrel versus placebo. One RCT in people with diabetes and with recent ischaemic stroke, myocardial infarction, or established peripheral arterial disease found no significant difference in cardiovascular events between clopidogrel and aspirin at 28 days. This RCT also found a lower proportion of people hospitalised for a bleeding event with clopidogrel than with aspirin.
- **Aspirin** One systematic review found that, compared with controls, antiplatelet treatment mainly with aspirin did not reduce the combined risk of non-fatal myocardial infarction, non-fatal stroke, death from a vascular cause, or death from an unknown cause in people with diabetes and cardiovascular disease diagnosis. The review found that antiplatelet treatment was associated with an increase in the risk of major extracranial haemorrhage and haemorrhagic stroke, but the results for people with diabetes were not reported separately. One subsequent RCT comparing aspirin with placebo found no significant reduction in the composite endpoint of death, stroke, or acute myocardial infarction. One additional RCT found that aspirin reduced the risk of acute myocardial infarction over 5 years compared with placebo. Both of these RCTs also found that aspirin increased bleeding. One RCT in people with diabetes and with recent stroke, myocardial infarction, or established arterial disease found no significant difference in cardiovascular events between aspirin and clopidogrel at 28 days. This RCT also found that that aspirin increased hospitalisation for a bleeding event. One RCT in people presenting with unstable angina or non-Q wave myocardial infarction and also taking aspirin found no significant reduction in cardiovascular events after 12 months with the addition of clopidogrel compared with placebo. This RCT also found that adding clopidogrel increased the proportion of people who had major bleeds compared with placebo.
- **Adding clopidogrel to heparin in acute coronary syndromes** One RCT in people presenting with unstable angina or non-Q wave myocardial infarction and also taking aspirin found no significant reduction in cardiovascular events after 12 months with the addition of clopidogrel compared with placebo. This RCT also found that adding clopidogrel increased the proportion of people who had major bleeds compared with adding placebo.

Blood glucose control

- **Intensive versus conventional glycaemic control** One systematic review found that, compared with conventional glycaemic control, intensive glycaemic control for more than 2 years reduced the occurrence of a first major cardiovascular event in people with type 1 diabetes. Two RCTs found no significant difference in cardiovascular morbidity and mortality with intensive compared with conventional glycaemic control in people with type 2 diabetes. These RCTs also found an increase in weight gain and hypoglycaemic episodes with intensive compared with conventional treatment.
- **Metformin versus diet alone as initial treatment in overweight or obese people with type 2 diabetes** One RCT in overweight or obese people with type 2 diabetes found that intensive treatment with metformin compared with conventional treatment with diet alone reduced the incidence of myocardial infarction and stroke over 5 years, but this did not reach significance for stroke. One RCT suggested that metformin increased the incidence of mild and moderate hypoglycaemic events compared with diet alone.

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Multiple risk factor treatment

- **Intensive multiple risk factor treatment** We found no systematic review or RCTs comparing treating multiple risk factors versus treating a single risk factor for cardiovascular outcomes. One RCT found that, compared with conventional treatment according to clinical guidelines, intensive treatment of multiple risk factors with strict treatment goals in people with type 2 diabetes and microalbuminuria reduced cardiovascular disease over 8 years. Multiple risk factor treatment included simultaneously targeting diet, exercise, glycaemic control, blood pressure, treatment of microalbuminuria, and antiplatelet treatment.

Revascularisation procedures

- **Coronary artery bypass graft compared with percutaneous transluminal coronary angioplasty** One systematic review found that, in people with diabetes, CABG reduced all cause mortality at 4 years after initial revascularisation compared with PTCA, but found no significant difference at 6.5 years. One large RCT in people with diabetes and multivessel coronary artery disease found that CABG reduced mortality or myocardial infarction within 8 years compared with PTCA. Another, smaller RCT found a non-significant reduction in mortality with CABG compared with PTCA at 4 years.
- **Stent plus glycoprotein IIb/IIIa inhibitors in people undergoing percutaneous transluminal coronary angioplasty** RCTs in people with diabetes undergoing percutaneous transluminal coronary angioplasty found that the combination of stent and a glycoprotein IIb/IIIa inhibitor reduced cardiovascular morbidity and mortality compared with stent plus placebo.
- **Percutaneous transluminal coronary angioplasty compared with thrombolysis** One systematic review suggested that percutaneous transluminal coronary angioplasty reduced the risk of death or recurrent myocardial infarction at 30 days in diabetic people presenting with acute myocardial infarction compared with thrombolysis.
- **Coronary artery bypass graft compared with percutaneous transluminal coronary angioplasty plus stent** One RCT in people with diabetes and multivessel coronary artery disease found that CABG reduced death, myocardial infarction, and revascularisation at 1 and 3 years compared to PTCA plus stenting. However, it found an increased risk of stroke with CABG in the short term up to discharge.

*No RCT but observational evidence suggests some benefit.

DEFINITION

Diabetes mellitus: Diabetes mellitus is a group of disorders characterised by hyperglycaemia, defined as a fasting plasma glucose ≥ 7.0 mmol/L or ≥ 11.1 mmol/L 2 hours after a 75 g oral glucose load, on two or more occasions. Intensive treatment is designed to achieve blood glucose values as close to the non-diabetic range as possible. The components of such treatment are education, counselling, monitoring, self management, and pharmacological treatment with insulin or oral anti-diabetic agents to achieve specific glycaemic goals. **Cardiovascular disease:** Atherosclerotic disease of the heart and/or the coronary, cerebral, or peripheral vessels leading to clinical events such as acute myocardial infarction, congestive heart failure, sudden cardiac death, stroke, gangrene, and/or need for revascularisation procedures. **Population:** In previous versions of *Clinical Evidence*, we attempted to differentiate between primary and secondary prevention in this topic. However, in middle aged and older people with type 2 diabetes, this distinction may not be clinically important. We are not aware of any intervention that has been shown to be effective in secondary prevention but ineffective in primary prevention, or vice versa, in people with diabetes. In most cases, a large proportion of people with diabetes entered into cardiovascular disease prevention trials are middle aged and older, with additional cardiovascular risk factors, and a large portion of these actually have undiagnosed cardiovascular disease.

INCIDENCE/ PREVALENCE

Diabetes mellitus is a major risk factor for cardiovascular disease. In the USA, a survey of deaths in 1986 suggested that 60–75% of people with diabetes die from cardiovascular causes.[1] The annual incidence of cardiovascular disease is increased in people with diabetes (men: RR 2–3; women: RR 3–4, adjusted for age and other cardiovascular risk factors).[2] About 45% of middle aged and older white people with diabetes have evidence of coronary artery disease compared with about 25% of people without diabetes in the same populations. In a Finnish population based cohort study (1059 people with diabetes and 1373 people without diabetes, aged 45–64 years), the 7 year risk of acute myocardial infarction was as high in adults with diabetes without previous cardiac disease (20.2/100 person years) as it was in people without diabetes with previous cardiac disease (18.8/100 person years).[3]

AETIOLOGY/ RISK FACTORS

Diabetes mellitus increases the risk of cardiovascular disease. Cardiovascular risk factors in people with diabetes include conventional risk factors (age, prior cardiovascular disease, cigarette smoking, hypertension, dyslipidaemia, sedentary lifestyle, family history of premature cardiovascular disease) and more diabetes specific risk factors (elevated urinary protein excretion, poor glycaemic control).

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Conventional risk factors for cardiovascular disease contribute to an increase in the relative risk of cardiovascular disease in people with diabetes to about the same extent as in those without diabetes (see aetiology under primary prevention, p 00). One prospective cohort study (164 women and 235 men with diabetes [mean age 65 years] and 437 women and 1099 men without diabetes [mean age 61 years] followed for mortality for a mean of 3.7 years after acute myocardial infarction) found that significantly more people with diabetes died compared with people without diabetes (116/399 [29%] with diabetes *v* 204/1536 [13%] without diabetes; RR 2.2, 95% CI 1.8 to 2.7).[4] It also found that the mortality risk after myocardial infarction associated with diabetes was higher for women than for men (adjusted HR 2.7, 95% CI 1.8 to 4.2 for women *v* 1.3, 95% CI 1.0 to 1.8 for men). Physical inactivity is a considerable risk factor for cardiovascular events in both men and women. Another cohort study (5125 women with diabetes) found that participation in little (< 1 hour a week) or no physical activity compared with physical activity for at least 7 hours a week was associated with a doubling of the risk of a cardiovascular event.[5] A third cohort study (1263 men with diabetes, mean follow up 12 years) found that low baseline cardiorespiratory fitness increased overall mortality compared with moderate or high fitness (RR 2.9, 95% CI 2.1 to 3.6), and overall mortality was higher in those reporting no recreational exercise in the previous 3 months than in those reporting any recreational physical activity in the same period (RR 1.8, 95% CI 1.3 to 2.5).[6] The absolute risk of cardiovascular disease is almost the same in women as in men with diabetes. Diabetes specific cardiovascular risk factors include the duration of diabetes during adulthood (the years of exposure to diabetes before age 20 years add little to the risk of cardiovascular disease); raised blood glucose concentrations (reflected in fasting blood glucose or HbA1c); and any degree of microalbuminuria (albuminuria 30–299 mg/24 hours).[7] People with diabetes and microalbuminuria have a higher risk of coronary morbidity and mortality than do people with normal levels of urinary albumin and a similar duration of diabetes (RR 2–3).[8,9] Clinical proteinuria increases the risk of mortality from cardiac events in people with type 2 diabetes (RR 2.61, 95% CI 1.99 to 3.43)[10] and type 1 diabetes (RR 9)[7,11,12] compared with people with the same type of diabetes who have normal albumin excretion. An epidemiological analysis of people with diabetes enrolled in the Heart Outcomes Prevention Evaluation cohort study (3498 people with diabetes and at least 1 other cardiovascular risk factor, age > 55 years, of whom 1140 [32%] had microalbuminuria at baseline; 5 years' follow up) found a higher risk for major cardiovascular events in those with microalbuminuria (albumin-: creatinine ratio [ACR] ≥ 2.0 mg/mmol) than in those without microalbuminuria (adjusted RR 1.97, 95% CI 1.68 to 2.31), and for all cause mortality (RR 2.15, 95% CI 1.78 to 2.60).[13] It also found an association between ACR and the risk of major cardiovascular events (ACR 0.22–0.57 mg/mmol: RR 0.85, 95% CI 0.63 to 1.14; ACR 0.58–1.62 mg/mmol: RR 1.11, 95% CI 0.86 to 1.43; ACR 1.62–1.99 mg/mmol: RR 1.89, 95% CI 1.52 to 2.36).

PROGNOSIS

Diabetes mellitus increases the risk of mortality or serious morbidity after a coronary event (RR 1.5–3.0).[2,3,14,15] This excess risk is partly accounted for by increased prevalence of other cardiovascular risk factors in people with diabetes. A systematic review (search date 1998, 15 prospective cohort studies) found that, in people with diabetes admitted to hospital for acute myocardial infarction, "stress hyperglycaemia" was associated with significantly higher mortality in hospital compared with lower blood glucose levels (RR 1.7, 95% CI 1.2 to 2.4).[16] One large prospective cohort study (91 285 men aged 40–84 years) found that, compared with men with no diabetes and no coronary heart disease (CHD), there was higher all cause and CHD mortality at 5 years' follow up in men with diabetes with or without CHD, in men with coronary artery disease alone, with the highest risk in men with both risk factors, see table 1, p 23).[17] Multivariate analysis did not materially alter these associations. Diabetes mellitus alone is associated with a twofold increase in risk for all cause death, with a threefold increase in risk of death from CHD, and, in people with pre-existing CHD, with a 12-fold increase in risk of death from CHD compared with people with neither risk factor.[17]

AIMS OF INTERVENTION

To reduce mortality and morbidity from cardiovascular disease with minimum adverse effects.

OUTCOMES

Incidence of fatal or non-fatal acute myocardial infarction; congestive heart failure; sudden cardiac death; coronary revascularisation; stroke; gangrene; angiographic evidence of coronary, cerebral, vascular, or peripheral arterial stenosis; all cause mortality.

METHODS

Clinical Evidence search and appraisal November 2004. We searched for systematic reviews and RCTs with at least 10 confirmed clinical cardiovascular events among people with diabetes. Studies reporting only intermediate end points (e.g. regression of plaque on angiography, lipid changes) were not included. Most of the evidence comes from subgroup analyses of large RCTs that included people with diabetes. As with all subgroup analyses, and studies with small numbers, these results must be interpreted as suggestive rather than definitive.

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Prevention of cardiovascular events in diabetes

QUESTION **What are the effects of promoting smoking cessation in people with diabetes?**

OPTION **PROMOTING SMOKING CESSATION**

We found no RCTs on promoting smoking cessation specifically in people with diabetes. Observational evidence and extrapolation from people without diabetes suggest that promotion of smoking cessation is likely to reduce cardiovascular events.

Benefits: We found no systematic review or RCTs on promotion of smoking cessation specifically in people with diabetes.

Harms: We found no RCTs.

Comment: Observational studies have found that cigarette smoking is associated with increased cardiovascular death in people with diabetes. Smoking cessation in people without diabetes has been found to be associated with reduced risk. People with diabetes are likely to benefit from smoking cessation at least as much as people who do not have diabetes but have other risk factors for cardiovascular events (see smoking cessation under secondary prevention of ischaemic cardiac events, p 01).

QUESTION **What are the effects of controlling blood pressure in people with diabetes?**

OPTION **ANTIHYPERTENSIVE TREATMENT VERSUS NO ANTIHYPERTENSIVE TREATMENT**

Systematic reviews and subsequent RCTs found that, in adults with diabetes and hypertension or previous cardiovascular disease, blood pressure lowering with antihypertensive agents (angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, or diuretics) reduced cardiovascular morbidity and mortality compared with no antihypertensive treatment. One systematic review found that beta-blockers reduced mortality in people with diabetes and congestive heart failure, but to a lesser extent than in non-diabetic people with congestive heart failure.

Benefits: **Antihypertensives versus control:** We found four systematic reviews (search date 2000,[18] search date 2002,[19] search date 2002,[20] search date not reported [21]) and one meta-analysis of major RCTs.[22] We also found three subsequent RCTs.[23–25] Results are tabulated in web table A. All reviews and RCTs that analysed all cause mortality found that antihypertensives significantly reduced mortality in adults with diabetes with or without cardiovascular disease compared with control, and one large RCT found that antihypertensives reduced the incidence of stroke. One review analysed people with congestive heart failure with and without diabetes and found that the mortality risk reduction was not as great in people with diabetes as it was in the non-diabetic participants in the same trials (RR for non-diabetic participants: 0.72; 95% CI 0.65 to 0.79).[21] None of the reviews or RCTs found that antihypertensives reduced myocardial infarction, cardiovascular mortality, or non-fatal cardiovascular events.[18,20,23,25]

Harms: The systematic reviews and subsequent RCTs gave little information on adverse effects (see table A on web extra).[18–26]

Comment: None.

OPTION **DIFFERENT ANTIHYPERTENSIVE DRUGS**

Systematic reviews and RCTs found that angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, beta-blockers, and calcium channel blockers were all effective in reducing cardiovascular morbidity and mortality in older people with diabetes and hypertension; most RCTs found no significant difference between different antihypertensive drugs. However, some RCTs found a lesser degree of protection against heart failure with calcium channel blockers compared with other antihypertensive agents and

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Prevention of cardiovascular events in diabetes

an increase in the risk of stroke or congestive heart failure with the angiotensin converting enzyme inhibitor lisinopril compared with the diuretic chlorthalidone. There was also an increase in the risk of cardiovascular morbidity and mortality with angiotensin II receptor antagonists compared with beta-blockers or diuretics. Different antihypertensive drugs were associated with different adverse effects. RCTs found that people taking atenolol gained more weight than those taking captopril, had a higher frequency of headache and constipation with diltiazem than with diuretics or beta-blockers, and had a higher rate of withdrawal from treatment because of adverse effects with atenolol than with losartan.

Benefits: We found three systematic reviews,[19,27,28], one additional RCT,[29] and three subsequent RCTs[30–32] comparing different antihypertensive drugs (angiotensin converting enzyme [ACE] inhibitors, angiotensin II receptor antagonists, beta-blockers, calcium channel blockers) versus each other in older people with diabetes, primarily type 2, with or without a diagnosis of cardiovascular disease. The first systematic review (search date 2002) assessed any type of antihypertensive agents and did not attempt to pool the results of the RCTs identified.[19] The second review (search date 2000[27]) compared ACE inhibitors versus other antihypertensive agents, and the third review (search date 2003[28]) assessed calcium channel blockers. The second and third reviews pooled some of the same RCTs but combined data differently. We report the results of the relevant RCTs for each comparison identified by the reviews, reporting meta-analyses where possible. We also report the results of the subsequent RCTs. Most RCTs found no significant difference in mortality or cardiovascular events between different antihypertensive drugs. One RCT found that the ACE inhibitor lisinopril significantly increased stroke compared with the diuretic chlorthalidone. Two reviews suggested that calcium channel blockers offered significantly less protection against heart failure than did ACE inhibitors, angiotensin II receptor antagonists, beta-blockers, or diuretics. One RCT found that losartan significantly reduced composite cardiovascular outcomes compared with atenolol. Another RCT found that doxazosin significantly increased combined coronary events over 6 years compared with chlorthalidone and terminated treatment with doxazosin as a result. Results are tabulated in table B on web extra.

Harms: Most of the RCTs gave no information on adverse effects. One RCT identified by the second systematic review[27] found that people taking atenolol gained significantly more weight over the first 4 years of the trial than did those taking captopril. However, it found no significant difference between groups over the subsequent 4 years. One RCT found that people with and without diabetes taking verapamil had higher rates of constipation and cough than people taking atenolol, whereas people taking atenolol had higher rates of dyspnoea, light headedness, symptomatic bradycardia, and wheezing. RCTs found that people taking diltiazem had a significantly higher frequency of headaches and constipation than people taking diuretics or beta-blockers. One RCT found that discontinuation of treatment because of adverse effects was significantly more common with atenolol than with losartan. For full details see table B on web extra.

Comment: **Clinical guide:** The evidence suggests that thiazide-like diuretics, beta-blockers, ACE inhibitors, and calcium channel blockers all reduce cardiovascular events in people with diabetes. The results of the review of calcium channel blockers[28] cast doubt on the conclusions of earlier, smaller studies suggesting that ACE inhibitors are superior to calcium channel blockers. The review indicates that a calcium channel blocker is at least as effective as an ACE inhibitor as initial treatment for hypertension, in terms of prevention of major cardiovascular events. It is unclear whether ACE inhibitors and beta-blockers are equivalent. In most RCTs, combination treatment with more than one agent was required to achieve target blood pressures. One large RCT[33] identified by a systematic review[19] found that the ACE inhibitor ramipril, which reduces urinary protein excretion, also reduced cardiovascular morbidity and mortality in older diabetic people with other cardiac risk factors. The relative cardioprotective effect of the ACE inhibitor was present to the same extent in people with or without hypertension, and with or without microalbuminuria.

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Prevention of cardiovascular events in diabetes

OPTION LOWER TARGET BLOOD PRESSURE

Large RCTs, primarily including people with hypertension, found that tighter control of blood pressure to a target diastolic blood pressure of 80 mm Hg or lower reduces the risk of major cardiovascular events. One RCT in normotensive people with diabetes found that intensive blood pressure lowering reduced cerebral vascular accidents but found no significant difference in cardiovascular death, myocardial infarction, congestive heart failure, or all cause mortality.

Benefits: We found no systematic review but found three RCTs.[34–37] The first RCT (reported in two papers) found that, compared with a moderate target blood pressure (≤ 180/105 mm Hg), a tight target blood pressure (≤ 150/85 mm Hg) in people with type 2 diabetes significantly reduced fatal or non-fatal acute myocardial infarction and stroke but found no significant difference for peripheral vascular events over 8.4 years (1148 people with hypertension managed with atenolol or captopril; fatal or non-fatal acute myocardial infarction: 107/758 [14%] with tight blood pressure target *v* 83/390 [21%] with moderate blood pressure target; RR 0.66, 95% CI 0.51 to 0.86; NNT 14, 95% CI 9 to 35; stroke: 38/758 [5.0%] with tight blood pressure target *v* 34/390 [8.7%] with moderate blood pressure target; RR 0.58, 95% CI 0.37 to 0.90; NNT 27, 95% CI 18 to 116; peripheral vascular events: 8/758 [1.1%] with tight blood pressure target *v* 8/390 [2.1%] with moderate blood pressure target; RR 0.52, 95% CI 0.20 to 1.36).[34,35] The second RCT found that the risk of major cardiovascular events was reduced by 50% over 3.8 years with a target diastolic blood pressure of 80 mm Hg or lower compared with a target blood pressure of 90 mm Hg or lower (1 multicentre RCT, 3 arm study, 1501 people with hypertension managed with felodipine, ACE inhibitors, beta-blockers, or diuretics; major cardiovascular events: 22/499 [4.4%] with target blood pressure ≤ 80 mm Hg *v* 45/501 [9.0%] with target blood pressure ≤ 90 mm Hg; RR 0.5, 95% CI 0.3 to 0.8; NNT 22, 95% CI 16 to 57).[36] The third RCT found a significantly lower incidence of cerebrovascular accidents with a target diastolic blood pressure of 10 mm Hg below baseline using nisoldipine or enalapril compared with an unchanged baseline diastolic blood pressure of 80–89 mm Hg with placebo over 5.3 years (480 people with type 2 diabetes and baseline blood pressure < 140/90 mm Hg being managed with nisoldipine or enalapril; cerebrovascular accidents: 4/237 [1.7%] with a target diastolic blood pressure of 10 mm Hg below baseline *v* 13/243 [5.4%] with an unchanged baseline diastolic blood pressure of 80–89 mm Hg; OR 3.29, CI 1.06 to 10.25; NNT 27, 95% CI 14 to 255).[37] The RCT found no significant difference in cardiovascular death, myocardial infarction, congestive heart failure, or all cause mortality. The RCT also found that, in a subgroup of people with type 2 diabetes and peripheral arterial disease at baseline (ankle : brachial index < 0.90), intensive blood pressure lowering to a mean of 128/75 mm Hg compared with no blood pressure reduction significantly reduced major cardiovascular events (53 people, cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, heart failure requiring hospital admission, or pulmonary infarction: 3/22 [13.6%] with intensive blood pressure lowering *v* 12/31 [38.7%] with no blood pressure reduction; ARR 25%, 95% CI 3% to 47%; NNT 4, 95% CI 2 to 37).[38]

Harms: We found no good evidence of a threshold below which it is harmful to lower blood pressure. One RCT found that a significantly greater proportion of people gained weight with atenolol than with captopril (mean weight gain over 9 years: 3.4 kg with atenolol *v* 1.6 kg with captopril; P = 0.02) but it found no significant difference in hypoglycaemia or weight gain with tight blood pressure control (≤ 150/85 mm Hg) compared with moderate blood pressure control (≤ 180/105 mm Hg).[34,35] The second RCT comparing tight versus moderate blood pressure control reported adverse effects including dizziness, headache, leg oedema, flushing, and coughing. The study suggested an increased risk of cardiovascular death at the lowest achieved blood pressure, and aspirin was associated with a higher overall rate of major and minor bleeds (about 1.8 times higher).[36] The third RCT in normotensive people gave no information on adverse effects.[37]

Comment: Aggressive lowering of blood pressure in people with diabetes and hypertension reduces cardiovascular morbidity and mortality. In most trials, combination treatment with more than one agent was required to achieve target blood pressures.

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Prevention of cardiovascular events in diabetes

QUESTION What are the effects of treating dyslipidaemia in people with diabetes?

OPTION FIBRATES

One RCT found that gemfibrozil reduced cardiovascular events over 5 years compared with placebo. Another, smaller RCT found no significant difference. One RCT found that bezafibrate reduced cardiovascular events over 3 years compared with placebo. One RCT found no significant difference between fenofibrate and placebo in the frequency of myocardial infarction or death over 39 months.

Benefits: We found two systematic reviews (search date not reported,[39] search date 2002[40]) comparing fibrates with placebo. Neither of these systematic reviews included pooling or summary estimates across the fibrate trials. We have reported the results of individual RCTs identified by at least one of the systematic reviews. One RCT found that gemfibrozil did not significantly reduce myocardial infarction or cardiac death over 5 years compared with placebo (135 men aged 40–55 years with diabetes without a diagnosis of cardiovascular disease, with non-high density lipoprotein (HDL) cholesterol > 5.2 mM; 200 mg/dL: 2/59 [3.4%] events with gemfibrozil *v* 8/76 [10.5%] with placebo; ARR 7%, 95% CI – 1% to + 15%; RR 32%, 95% CI 7% to 146%).[41] The study reported greater changes from baseline serum lipid levels with gemfibrozil compared with placebo in men with diabetes (gemfibrozil results presented graphically; significance assessment not performed). A second RCT found that, compared with placebo, gemfibrozil 1200 mg daily significantly reduced coronary heart disease, death, stroke, or non-fatal acute myocardial infarction over 5 years (769 men aged < 74 years with diabetes and cardiovascular disease diagnosis, with high density lipoprotein cholesterol ≤ 40mg/dL, low density lipoprotein cholesterol ≤ 140mg/dL, and tricglyceride ≤ 300 mg/dL: 105/388 [27%] events with gemfibrozil *v* 141/381 [37%] events with placebo; HR 0.68, 95% CI 0.53 to 0.88).[42] A third RCT found that bezafibrate significantly reduced myocardial infarction or new ischaemic changes on electrocardiogram over 3 years compared with placebo (164 people aged 35–65 years with type 2 diabetes without a diagnosis of cardiovascular disease, with serum triglyceride 8.18–8.0 mmol/L, serum cholesterol 5.2–8.0 mmol/L, and total to HDL cholesterol ratio between ≥ 4.7 to ≥ 7.2; 5/64 [7.8%] events with bezafibrate *v* 16/64 [25%] events with placebo; ARR 17.2%, 95% CI 4.6% to 30.1%; RR 0.31, 95% CI 0.12 to 0.80; NNT 6, 95% CI 5 to 20).[43] It also found that bezafibrate significantly improved serum lipid levels at 3 years (total cholesterol median change from baseline [range: 5.60–5.77 mmol/L]: –4.8 with bezafibrate *v* + 0.20 with placebo; P = 0.004; triglyceride median change from baseline [range: 2.09–2.24 mmol/L]: – 0.80 with bezafibrate *v* –0.09 with placebo; P = 0.001; HDL cholesterol median change from baseline [range: 0.94–1.02 mmol/L]: + 0.02 with bezafibrate *v* –0.02 with placebo; P = 0.001). The reduction in median low density lipoprotein cholesterol did not reach significance (low density lipoprotein cholesterol median change from baseline [range: 3.66–3.98]: –0.35 with bezafibrate *v* –0.04 with placebo; P = 0.06). A fourth RCT found no significant difference in the proportion of people who either had myocardial infarction or died after 39 months of treatment between fenofibrate 200 mg daily and placebo (418 people with diabetes and with or without cardiovascular disease diagnosis, mean age 57 years: 15/207 [7.2%] events with fenofibrate *v* 21/211 [9.9%] events with placebo; ARR + 2.7%, 95% CI –2.8% to + 8.3%; RR 0.73, 95% CI 0.39 to 1.37). It found that, compared with placebo, fenofibrate significantly improved serum lipid levels from baseline (total plasma cholesterol reduction from baseline [range: 5.56–5.58]: data presented graphically; P < 0.001); low density lipoprotein cholesterol reduction from baseline [range: 3.38–3.43]: data presented graphically; P < 0.001; triglyceride reduction from baseline [range: 2.42–2.59]: data presented graphically; P < 0.001; HDL cholesterol increase from baseline [range: 1.01–1.05]: data presented graphically; P < 0.001).[44] This RCT was underpowered for the outcomes of myocardial infarction and death, but there were trends toward reduced risk of myocardial infarction with fenofibrate (9 with fenofibrate *v* 12 with placebo) and death (6 with fenofibrate *v* 9 with placebo). A benefit for fenofibrate in reducing myocardial infarction and death is suggested and certainly cannot be excluded.

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Prevention of cardiovascular events in diabetes

Harms: The systematic reviews did not comment on adverse effects.[39,40] The first, second, and third RCT did not comment on adverse effects.[41–43] The RCT comparing fenofibrate 200 mg daily and placebo reported no significant difference between fenofibrate and placebo in gallbladder symptoms (1/207 [0.5%] with fenofibrate *v* 3/211 [1.4%] with placebo), liver toxicity (3/207 [1.5%] with fenofibrate *v* 0/211 [0%] with placebo), muscle pain (0/207 [0%] with fenofibrate *v* 1/211 [0.5%] with placebo), joint pain (7/207 [3.4%] with fenofibrate *v* 6/211 [2.5%] with placebo), or cancer (5/207 [2.4%] with fenofibrate *v* 7/211 [3.3%] with placebo).[44]

Comment: None.

OPTION STATINS

One systematic review and one subsequent RCT found that statins reduced cardiovascular morbidity and mortality compared with placebo. The RCT found that treatment with atorvastatin to achieve a target low density lipoprotein below 2.6 mmol/L reduced cardiovascular morbidity and mortality compared with usual care. One RCT found that in people without high LDL cholesterol, atorvastatin 10 mg daily reduced cardiovascular events compared with placebo at 3.9 years. Another RCT found no significant difference between a lower target low density lipoprotein (1.55–2.20 mmol/L) using lovastatin, plus cholestyramine if needed, and a moderate target low density lipoprotein (3.36–3.62 mmol/L) in 4 year event rate for myocardial infarction and death. One RCT found no significant difference in cardiovascular events in older people between low dose pravastatin (5 mg/day) and standard dose pravastatin (10–20 mg/day) over 4 years.

Benefits: We found one systematic review,[40] two additional RCTs,[47,48] and one subsequent RCT.[45] We also found a systematic review that did not conduct a meta-analysis for RCTs evaluating statins, but provided a commentary on the quality of data on people with diabetes included in such trials (see comment below).[39] **Statins versus placebo:** We found one systematic review (search date 2002), which pooled data from RCTs comparing statins or fibrates with placebo.[40] We also found one subsequent RCT.[45] The review found that that statins and fibrates were significantly more effective in primary prevention of cardiovascular events including non-fatal acute myocardial infarction, stroke, cardiovascular mortality, and unstable angina compared with placebo (6 RCTs, 5 with statins,1 with fibrates; 7200 people with type 2 diabetes; cardiovascular events: 352/3598 [9.8%] with statins or fibrates *v* 455/3602 [12.6%] with placebo; RR 0.78, 95% CI 0.67 to 0.89; ARR 3%, 95% CI 1% to 4% in 4.3 years; NNT 35, 95% CI not reported).[40] It also found that statins and fibrates were significantly more effective in secondary prevention of cardiovascular events (8 RCTs, 7 with statins, 1 with fibrate; 4,723 people with type 2 diabetes and coronary artery disease; cardiovascular events: 667/2359 [28%] with statin or fibrate *v* 817/2364 [34.6%] with placebo; RR 0.76, 95% CI 0.5 to 0.93; ARR 7%, 95% CI 3% to 12% in 4.9 years; NNT 13.8, 95% CI not reported). Sensitivity analyses excluding the fibrate trials did not alter the estimated relative risk or absolute risk reduction for primary or secondary prevention.[40] The subsequent RCT (2838 people with type 2 diabetes, mean age 61 years, no prior history of cardiovascular disease, with at least one of hypertension, current smoking, albuminuria, or retinopathy; with low density lipoprotein (LDL) cholesterol < 4.1 mmol/L, followed for 3.9 years) found that atorvastatin significantly reduced cardiovascular events compared with placebo (cardiovascular events: 83/1428 [5.8%] with atorvastatin *v* 127/1410 [9%] with placebo; RR 0.63, 95% CI 0.48 to 0.83, P = 0.001).[45] **Aggressive versus moderate lipid lowering:** One RCT[46] included in the systematic review[40] found no significant difference between aggressive lipid lowering and moderate lipid lowering in 4 year event rate for myocardial infarction and death (116 people aged 21–74 years with type 2 diabetes and a diagnosis of cardiovascular disease; 4 year event rate for death: 6.5 with aggressive lipid lowering *v* 9.6 with moderate lipid lowering; RR 0.67, 95% CI 0.12 to 3.75; 4 year event rate for myocardial infarction: 4.8 with aggressive lipid lowering *v* 11.6 with moderate lipid lowering; RR 0.40, 95% CI 0.07 to 2.47). The RCT used lovastatin and cholestyramine as necessary to achieve the targets for aggressive lipid lowering (LDL cholesterol 1.55–2.20 mmol/L [60–85 mg/dL]) and moderate lipid lowering (LDL cholesterol 3.36–3.62 mmol/L [130–140 mg/dL]). This RCT had limited power because of the small number of people enrolled who had

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diabetes.[46] The first additional RCT found that, compared with usual care, treatment with atorvastatin to achieve a target LDL of below 2.6 mmol/L (< 100 mg/dL) significantly reduced the risk of all cause mortality, non-fatal myocardial infarction, unstable angina, congestive heart failure, revascularisation, and stroke over 3 years (313 people with a diagnosis of cardiovascular disease, mean age 58 years: RRR 0.42%; P = 0.0001; results presented graphically). The atorvastatin dose was titrated from 10 mg daily to a maximum of 80 mg daily to achieve a target LDL cholesterol of below 2.6 mmol/L. Usual care consisted of treatment by the family practitioner, which could include diet, exercise, weight loss, and/or drug treatment including lipid lowering agents; 14% of people in the usual care group received any lipid lowering agents.[47] **Low versus standard statin dose in older people:** The second additional RCT found no significant difference in cardiovascular events in older people between low dose pravastatin 5 mg daily and standard dose pravastatin 10–20 mg daily over 4 years (199 people aged > 60 years with diabetes: 17/104 [16.3%] events with low dose pravastatin *v* 15/95 [15.8%] events with standard dose pravastatin; ARR + 0.6%, 95% CI –9.7% to + 10.8%).[48]

Harms:

Statins versus placebo: The systematic review (search date 2002) reported similar levels of discontinuation for statins and placebo (reported as > 15% in many cases), and no significant difference in rates of elevated liver muscles enzymes in the larger scale studies (1 RCT[49], 3983 people with type 2 diabetes; rates of alanine aminotransferase > twice normal upper limit: 1.8% with simvastatin *v* 1.6% with placebo; reported as non-significant; rates of elevated creatine kinase: 0.3% with simvastatin *v* 0.2% with placebo; reported as non-significant).[40] **Aggressive versus moderate lipid lowering:** The RCT included in the review did not report on adverse events.[46] The additional RCT found no significant difference between atorvastatin and usual care in the proportion of people withdrawn from the study because of adverse effects (withdrawals because of adverse effects: 6/800 [0.75%] with atorvastatin *v* 3/800 [0.4%] with usual care; P reported as non-significant; withdrawals because of elevated liver enzymes: 4/800 [0.5%] with atorvastatin *v* 3/800 [0.4%] with usual care; significance not assessed).[47] **Low versus standard statin dose in older people:** In the additional RCT comparing low versus standard pravastatin dose, adverse effects included gastrointestinal symptoms and elevated creatine kinase and were higher in the standard dose group (proportion of adverse events: 19/334 [5.7%] with low dose pravastatin *v* 26/331 [7.9%] with standard dose pravastatin; P value not reported).[48]

Comment:

One RCT[49] included in the systematic review[40] is of major importance. The RCT is interesting because it was not necessary to have an abnormal lipid profile or prior vascular disease to be enrolled, and it provides the first clear evidence that statin treatment is effective for primary prevention of cardiovascular disease.[49] The relative risk reductions for major cardiovascular events were similar with or without previous coronary heart disease, and with lower and higher initial LDL cholesterol. The results of this RCT suggest that treatment with a statin is likely to be beneficial in most diabetic people who are at significant risk of coronary heart disease, regardless of initial LDL level and regardless of whether they have had previous cardiovascular disease. Furthermore, this and other studies provided stronger evidence for the value of treatment with statins *per se*, rather than for targeting any specific LDL cholesterol level. Besides this RCT,[49] most published RCTs with sufficient power to detect effects on cardiovascular events have enrolled comparatively few people with diabetes or have excluded them altogether. The available evidence is, therefore, based almost entirely on subgroup analyses of larger trials, in which there was generally little information regarding the type and duration of diabetes, severity of complications, and metabolic control.[39] The statin versus placebo trial published after both systematic reviews was terminated early due to the high efficacy of atorvastatin in the overall study population (HR for cardiovascular death plus non-fatal myocardial infarction 0.64, 95% CI 0.50 to 0.83).[50] Although the difference was not significant in the diabetic subgroup, the confidence intervals for diabetic and non-diabetic subgroups overlapped one another. Several large ongoing trials are evaluating the effects of fibrates in people with diabetes.

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Prevention of cardiovascular events in diabetes

QUESTION What are the effects of antiplatelet drugs in people with diabetes?

OPTION ASPIRIN

One systematic review found that, compared with controls, antiplatelet treatment mainly with aspirin did not reduce the combined risk of non-fatal myocardial infarction, non-fatal stroke, death from a vascular cause, or death from an unknown cause in people with diabetes and cardiovascular disease diagnosis. The review found that antiplatelet treatment was associated with an increase in the risk of major extracranial haemorrhage and haemorrhagic stroke, but the results for people with diabetes were not reported separately. One subsequent RCT comparing aspirin with placebo found no significant reduction in the composite endpoint of death, stroke, or acute myocardial infarction. One additional RCT found that aspirin reduced the risk of acute myocardial infarction over 5 years compared with placebo. Both of these RCTs also found that aspirin increased bleeding. One RCT in people with diabetes and with recent stroke, myocardial infarction, or established arterial disease found no significant difference in cardiovascular events between aspirin and clopidogrel at 28 days. This RCT also found that that aspirin increased hospitalisation for a bleeding event. One RCT in people presenting with unstable angina or non-Q wave myocardial infarction and also taking aspirin found no significant reduction in cardiovascular events after 12 months with the addition of clopidogrel compared with placebo. This RCT also found that adding clopidogrel increased the proportion of people who had major bleeds compared with placebo.

Benefits:

Aspirin versus placebo or control: We found one systematic review (search date 1997),[51] one additional RCT,[52] and one subsequent RCT.[53] The review found that, compared with controls, antiplatelet treatment mainly with aspirin did not significantly reduce the combined risk of non-fatal myocardial infarction, non-fatal stroke, death from a vascular cause, or death from an unknown cause (9 RCTs, 4961 people with unspecified diabetes and cardiovascular disease diagnosis; 403/2568 [15.7%] with antiplatelet treatment *v* 426/2558 [16.7%] with control; RR 0.94, 95% CI 0.83 to 1.07). This non-significant 6% relative risk reduction contrasted with a significant 25% relative risk reduction for the same outcomes in the full meta-analysis (people with or without diabetes combined).[51] The largest RCT included in the systematic review found no significant difference in reduction of fatal or non-fatal myocardial infarction or stroke at 5 years between aspirin 650 mg daily compared with placebo (3711 people with type 1 and 2 diabetes aged 18–70 years; fatal or non-fatal myocardial infarction at 5 years: 9.1% with aspirin *v* 12.3% with placebo; RR 0.83, 99% CI 0.66 to 1.04; fatal or non-fatal stroke: 4.5% with aspirin *v* 3.8% with placebo; RR 1.17, 95% CI 0.79 to 1.28).[54] The additional RCT found that aspirin significantly reduced the risk of acute myocardial infarction G over 5 years compared with placebo (533 male physicians with diabetes but no diagnosis of cardiovascular disease: 11/275 [4.0%] with aspirin *v* 26/258 [10.1%] with placebo; RR 0.39, 95% CI 0.20 to 0.79; NNT 16, 95% CI 12 to 47).[52] One subsequent open label RCT (1031 people, mean age 64 years with type 2 diabetes and no history of a major cardiovascular event) found that aspirin did not significantly reduce cardiovascular death, stroke, or myocardial infarction compared with no treatment (total cardiovascular events: 53/519 [10.2%] with aspirin *v* 59/512 [11.5%] with no treatment; RR 0.89% 95% CI 0.62% to 1.26%).[53] **Aspirin versus clopidogrel:** See benefits of clopidogrel, p 13. **Aspirin plus clopidogrel:** See benefits of clopidogrel, p 13.

Harms:

In the systematic review, doses of aspirin ranged from 75–1500 mg daily. Most RCTs used aspirin 75–325 mg daily.[51] Doses higher than 325 mg daily increased the risk of haemorrhagic adverse effects without improving preventive efficacy. No difference in efficacy or adverse effects was found in the dose range 75–325 mg daily. The systematic review found that antiplatelet treatment with aspirin was associated with a 50% relative increase in the odds of major extracranial haemorrhage (OR 1.6, 95% CI 1.4 to 1.8) and a relative increase in the risk of haemorrhagic stroke (RR 22%, 95% CI 3% to 44%, $P < 0.01$). These results were for the overall meta-analysis; results were not reported separately for the people with diabetes.[51] The largest RCT in people with diabetes included in the systematic review did not report on harms.[54] The additional RCT found

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that aspirin significantly increased the risk of bleeding compared with placebo (22 071 physicians, of which 533 had diabetes; proportion with bleeding: 2979/22 071 [13.5%] with aspirin *v* 2248/22 071 [10.1%] with placebo; RR 1.32; 95% CI 1.25 to 1.40; P < 0.00001).[52] It found no significant differences for other frequent adverse effects. These results were for the overall analysis; results were not reported separately for the people with diabetes.[52] The subsequent open label RCT found that aspirin significantly increased bleeding complications (1.9% with aspirin *v* 0.2% with no treatment; P = 0.007, absolute data not reported).[53]

Comment: We found insufficient evidence to define precisely which people with diabetes should be treated with aspirin. The risk of cardiovascular disease is low before 30 years of age; most white adults with diabetes aged over 30 years are at increased risk of cardiovascular disease. Widely accepted contraindications to aspirin treatment include aspirin allergy, bleeding tendency, anticoagulant treatment, recent gastrointestinal bleeding, and clinically active liver disease.[55]

OPTION CLOPIDOGREL

We found no RCTs comparing clopidogrel with placebo. One RCT in people with diabetes and with recent ischaemic stroke, myocardial infarction, or established peripheral arterial disease found no significant difference in cardiovascular events between clopidogrel and aspirin at 28 days. This RCT also found a lower proportion of people hospitalised for a bleeding event with clopidogrel than with aspirin. One RCT in people presenting with unstable angina or non-Q wave myocardial infarction and also taking aspirin found no significant reduction in cardiovascular events after 12 months with added clopidogrel compared with added placebo. This RCT also found that adding clopidogrel increased the proportion of people who had major bleeds compared with placebo.

Benefits: We found no systematic reviews. **Clopidogrel versus placebo:** We found no RCTs comparing clopidogrel versus placebo. **Clopidogrel versus aspirin:** One RCT in people in people with type 1 and type 2 diabetes and with recent ischaemic stroke, acute myocardial infarction, or established peripheral arterial disease found no significant difference in cardiovascular events between clopidogrel and aspirin at 28 days (3866 people, mean age 64 years; angina, vascular death, myocardial infarction, all cause stroke, and readmission to hospital for ischaemic events: 299/1914 [15.6%] with clopidogrel *v* 345/1952 [17.7%] with aspirin; ARR 2.1%, 95% CI –0.3% to + 4.4%; RR 0.88, 95% CI 0.77 to 1.02).[56] **Adding clopidogrel to aspirin:** One RCT in people presenting with unstable angina or non-Q wave myocardial infarction and also taking aspirin found no significant reduction in cardiovascular events after 12 months with added clopidogrel compared with added placebo (2840 people with unspecified diabetes, mean age 64 years; cardiovascular death, non-fatal myocardial infarction, or stroke at 12 months: 200/1405 [14.2%] with clopidogrel *v* 240/1435 [16.7%] with placebo; RR 0.85, 95% CI 0.71 to 1.01).[57] People were randomised within 24 hours of an acute event and were given either clopidogrel 300 mg bolus and then 75 mg daily plus aspirin 75–325 mg daily or placebo plus aspirin.[57]

Harms: **Clopidogrel versus placebo:** One RCT found that a significantly lower proportion of people with type 1 and type 2 diabetes were hospitalised for a bleeding event with clopidogrel than with aspirin at 28 days (3866 people, mean age 64 years; hospital admission for a bleeding event: 34/1914 [1.8%] with clopidogrel *v* 55/1952 [2.8%] with aspirin; RRR 37.0%, 95% CI 3.8% to 58.7%; P = 0.031).[56] **Adding clopidogrel to aspirin:** One RCT in people presenting with unstable angina or non-Q wave myocardial infarction and also taking aspirin found a significantly higher proportion of major bleeds with clopidogrel than with placebo (major bleeds: 3.7% with clopidogrel *v* 2.7% with placebo; RR 1.38, 95% CI 1.13 to 1.67; P = 0.001).[57]

Comment: None.

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Prevention of cardiovascular events in diabetes

OPTION GLYCOPROTEIN IIB/IIIA INHIBITORS

We found no RCTs comparing glycoprotein IIb/IIIa inhibitors versus no antiplatelet treatment. One RCT in people presenting with unstable angina or acute myocardial infarction without ST segment elevation found that adding tirofiban (a glycoprotein IIb/IIIa inhibitor) to heparin reduced the composite outcome of death, myocardial infarction, or refractory ischaemia at 180 days compared with heparin alone. This RCT found no significant difference between tirofiban plus heparin versus heparin alone in risk of bleeding in people already taking aspirin. RCTs in people undergoing percutaneous transluminal coronary angioplasty found that the combination of glycoprotein IIb/IIIa inhibitor plus stent reduced cardiovascular morbidity and mortality compared with placebo plus stent. One RCT in people with acute ST segment elevation myocardial infarction found that a combination of abciximab plus half dose reteplase reduced recurrent myocardial infarction compared with full dose reteplase alone at 7 days. It also found that abciximab plus half dose reteplase increased bleeding.

Benefits: We found no systematic reviews. **Glycoprotein IIb/IIIa inhibitors versus no antiplatelet treatment:** We found no RCTs comparing glycoprotein IIb/IIIa inhibitors versus no antiplatelet treatment. **Adding glycoprotein IIb/IIIa inhibitors to heparin:** One RCT, in people with type 1 and type 2 diabetes presenting with unstable angina or acute myocardial infarction G without ST segment elevation, found that adding tirofiban (a glycoprotein IIb/IIIa inhibitor) to heparin compared with heparin alone significantly reduced the composite outcome of death, myocardial infarction, or refractory ischaemia at 180 days (362 people already taking aspirin, mean age 65 years: 19/169 [11.2%] with tirofiban plus heparin *v* 37/193 [19.2%] with heparin alone; ARR 8.0%, 95% CI 0.7% to 15.3%; RR 59%, 95% CI 35% to 98%; P = 0.03; NNT 13, 95% CI 7 to 146).[58] **Glycoprotein IIb/IIIa inhibitors as an adjunct to percutaneous coronary revascularisation:** See benefits of intracoronary stenting plus glycoprotein IIb/IIIa inhibitors, p 19. **Adding glycoprotein IIb/IIIa inhibitors to fibrinolytic therapy:** One RCT in people presenting with acute ST segment elevation myocardial infarction found that combination of abciximab plus half dose reteplase significantly reduced recurrent myocardial infarction compared with full dose reteplase alone at 7 days (2633 people with type 1 and type 2 diabetes, mean age 64 years: rate of recurrent myocardial infarction at 7 days: 33/1334 [2.5%] with abciximab plus reteplase *v* 56/1299 [4.3%] with retiplase alone; ARR 1.8%, 95% CI 0.4% to 3.2%; NNT 54, 95% CI 31 to 221).[59] Abciximab plus half dose reteplase also significantly reduced the composite outcome of death, recurrent myocardial infarction, recurrent angina, ischaemia, and revascularisation compared with full dose reteplase alone at 7 days (540/1334 [40.5%] with abciximab plus reteplase *v* 584/1299 [45%] with retiplase alone; P = 0.021; ARR 4.5%, 95% CI 0.7% to 8.3%; NNT 22, 95% CI 12 to 142).[59]

Harms: **Adding glycoprotein IIb/IIIa inhibitors to heparin:** One RCT found no significant difference between tirofiban plus heparin and heparin alone in the risk of bleeding in people already taking aspirin (9.5% with tirofiban plus heparin *v* 8.3% with heparin alone; RR 1.16, 95% CI 0.56 to 2.39).[58] **Adding glycoprotein IIb/IIIa inhibitors to fibrinolytic therapy:** The RCT in people presenting with acute ST segment elevation myocardial infarction found a significant increase in bleeding with abciximab plus half dose reteplase compared with reteplase alone (rate of bleeding: 356/1334 [26.7%] with abciximab plus reteplase *v* 184/1299 [14.2%] with reteplase alone; P < 0.001).[59]

Comment: None.

QUESTION What are the effects of blood glucose control in prevention of cardiovascular disease in people with diabetes?

OPTION BLOOD GLUCOSE CONTROL

One systematic review found that, compared with conventional glycaemic control, intensive glycaemic control for more than 2 years reduced the occurrence of a first major cardiovascular event in people with type 1 diabetes. Two RCTs found no significant difference in cardiovascular morbidity and mortality with intensive compared with

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conventional glycaemic control in people with type 2 diabetes. These RCTs also found an increase in weight gain and hypoglycaemic episodes with intensive compared with conventional treatment. One RCT in overweight or obese people with type 2 diabetes found that intensive treatment with metformin compared with conventional treatment with diet alone reduced the incidence of myocardial infarction and stroke over 5 years, but this did not reach significance for stroke. One RCT suggested that metformin increased the incidence of mild and moderate hypoglycaemic events compared with diet alone.

Benefits:

We found one systematic review (search date 1996)[60] and three subsequent RCTs.[61–63] **Intensive versus conventional glycaemic control in type 1 diabetes:** The systematic review found that, compared with conventional glycaemic control, intensive glycaemic control for more than 2 years significantly reduced the occurrence of a first major cardiovascular event in people with type 1 diabetes (6 RCTs, 1731 people aged 30–42 years with type 1 diabetes; number of first major cardiovascular events: 27/961 [2.8%] with intensive control *v* 55/970 [5.7%] with conventional glycaemic control; OR 0.55, 95% CI 0.35 to 0.88).[60] Major macrovascular events were defined as fatal or non-fatal myocardial infarction, sudden cardiac death, revascularisation procedure, angina with confirmed coronary artery disease, stroke, lower limb amputation, peripheral arterial events, and peripheral vascular disease. Conventional glycaemic control consisted of one or two daily injections of insulin without self adjustment of insulin dosage according to blood or urine glucose monitoring results. Intensive glycaemic control consisted of three or more injections of insulin with the dosage adjusted according to self monitoring of blood glucose levels.[60] **Intensive versus conventional glycaemic control in type 2 diabetes:** The first subsequent in people with type 2 diabetes found no significant difference between intensive and conventional glycaemic control in myocardial infarction or stroke over 5 years (1138 people with type 2 diabetes but without a diagnosis of cardiovascular disease, mean age 54 years; myocardial infarction: 387/2729 [14.2%] with intensive control *v* 186/1138 [16.3%] with conventional control; RR 0.84, 95% CI 0.71 to 1.00; P = 0.052; stroke: 148/2729 [5.4%] with intensive control *v* 55/1138 [4.8%] with conventional control; RR 1.11, 95% CI 0.81 to 1.51).[62] The second subsequent RCT in people with type 2 diabetes found no significant difference between intensive insulin treatment with a stepped plan designed to achieve near normal blood sugar levels and standard once daily insulin injection in the rate of new cardiovascular events over 27 months (153 men with type 2 diabetes, mean age 60 years, many of whom had previous cardiovascular events; new cardiovascular events: 24/75 [32%] with intensive treatment *v* 16/80 [20%] with standard treatment; RR 1.60, 95% CI 0.92 to 2.50).[63] **Metformin versus diet alone in overweight or obese people with type 2 diabetes:** The third subsequent RCT in overweight or obese people with type 2 diabetes found that intensive treatment with metformin compared with conventional treatment with diet alone reduced myocardial infarction and stroke over 5 years, but this reduction did not reach significance for stroke (753 people without a diagnosis of cardiovascular disease, mean age 53 years; myocardial infarction: 39/342 [11%] with metformin *v* 73/411 [18%] with diet alone; RR 0.61, 95% CI 0.41 to 0.89; stroke: 12/342 [3.5%] with metformin *v* 23/411 [5.6%] with diet alone; RR 0.59, 95% CI 0.29 to 1.18).[61]

Harms:

Intensive versus conventional glycaemic control in type 1 diabetes: The systematic review did not comment on harms.[60] The largest RCT included in the review found that weight gain and waist to hip ratio were significantly increased in the intensive treatment group compared with conventional treatment (weight gain: P ≤ 0.001; waist to hip ratio: P = 0.02).[64] **Intensive versus conventional glycaemic control in type 2 diabetes:** The first subsequent RCT found that intensive treatment significantly increased weight gain and hypoglycaemic episodes compared with conventional treatment (weight gain: data presented graphically; P < 0.0001; hypoglycaemic episodes: data presented graphically; P < 0.0001).[62] The second subsequent RCT found significantly higher mild and moderate hypoglycaemic events with intensive treatment compared with conventional treatment (proportion of hypoglycaemic events per patient per year: 16.5 with intensive treatment *v* 1.5 with conventional treatment; P < 0.01).[63] However, it was noted that some hypoglycaemic episodes may not have been detected in the conventional treatment group because of less frequent measurement of blood

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glucose levels.[63] **Metformin versus diet alone in overweight or obese people with type 2 diabetes:** In the third subsequent RCT, metformin was associated with a similar proportion of major hypoglycaemic events to diet alone (ITT analysis; proportion of people with major hypoglycaemic events: 0.6% with metformin *v* 0.7% with diet alone; P value not reported).[61]

Comment: The role of intensive glucose lowering in primary prevention of cardiovascular events remains unclear. However, such treatment clearly reduces the risk of microvascular disease and does not increase the risk of cardiovascular disease. The potential of the largest RCT in people with type 2 diabetes to show an effect of tighter glycaemic control was limited by the small difference achieved in median HbA1c between intensive and conventional treatment and the relatively low risk of cardiovascular disease.[61,62] By contrast, in another primary prevention trial, a larger difference (1.9%) in median HbA1c was achieved between groups (mean HbA1c levels: 7.2% with intensive treatment *v* 9.1% with conventional treatment; $P < 0.001$),[64] but the young age of the participants and consequent low incidence of cardiovascular events limited the power of the study to detect an effect of treatment on the incidence of cardiovascular disease.[64,65] The RCT of insulin in type 2 diabetes included men with a high baseline risk of cardiovascular events and achieved a 2.1% absolute difference in HbA1c (mean HbA1c levels at 6 months: 7.1% with intensive treatment *v* 9.2% with conventional treatment; $P < 0.001$).[63] The RCT was small and the observed difference between groups could have arisen by chance.

QUESTION What are the effects of treating multiple risk factors in prevention of cardiovascular disease in people with diabetes?

OPTION INTENSIVE MULTIPLE RISK FACTOR TREATMENT

We found no systematic review or RCTs comparing treating multiple risk factors versus treating a single risk factor for cardiovascular outcomes. One RCT found that, compared with conventional treatment according to clinical guidelines, intensive treatment of multiple risk factors with strict treatment goals in people with type 2 diabetes and microalbuminuria reduced cardiovascular disease over 8 years. Multiple risk factor treatment included simultaneously targeting diet, exercise, glycaemic control, blood pressure, treatment of microalbuminuria, and antiplatelet treatment.

Benefits: We found no systematic review or RCTs comparing treating multiple risk factors with treating a single risk factor for cardiovascular outcomes. **Intensive versus conventional treatment:** We found one RCT comparing intensive treatment of multiple risk factors versus conventional treatment of multiple risk factors.[66] The RCT found that, compared with conventional treatment, intensive treatment of multiple risk factors in people with type 2 diabetes and microalbuminuria significantly reduced cardiovascular disease over 8 years (160 people including 39 with cardiovascular disease diagnosis, mean age 55 years; combined outcome of death from cardiovascular disease, non-fatal myocardial infarction, non-fatal stroke, revascularisation, or amputation: HR 0.47, 95% CI 0.24 to 0.73; ARR 20.0%, 95% CI 5.7% to 34.0%; NNT 5, 95% CI 3 to 18). The intensive treatment group received a stepwise treatment plan with strict treatment goals, and included behaviour modification (diet, exercise, and smoking cessation); drug treatment for aggressive management of blood glucose, blood pressure, dyslipidaemia, and microalbuminuria; and aspirin treatment for people with ischaemic cardiovascular disease. The conventional treatment group received treatment for multiple risk factors according to clinical guidelines from their general practitioner.

Harms: **Intensive versus conventional treatment:** The RCT did not specifically evaluate adverse events.[66] It found no significant difference in the incidence of minor episodes of hypoglycaemia between intensive and conventional treatment of multiple risk factors (42/80 [53%] with intensive treatment *v* 39/80 [49%] with conventional treatment; $P = 0.5$). A higher proportion of people had at least one major hypoglycaemic event

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requiring assistance from another person in the conventional group compared with the intensive group, but this difference was not significant (major hypoglycaemic events: 5/80 [6.3%] with intensive treatment *v* 12/80 [15%] with conventional treatment; P = 0.12). One person in the intensive treatment group was hospitalised for a bleeding ulcer.[66]

Comment: **Intensive versus conventional treatment:** All people in the RCT had microalbuminuria at baseline, so their cardiovascular risk would have been higher than in people with diabetes without microalbuminuria. However, the conventional treatment group received high quality care, based on guidelines, and the risk reductions from the intensive treatment might have been greater if the comparison had been with "usual care" in the community.[66]

QUESTION What are the effects of revascularisation procedures in people with diabetes?

OPTION CORONARY ARTERY BYPASS VERSUS PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY

One systematic review found that, in people with diabetes, coronary artery bypass graft (CABG) reduced all cause mortality at 4 years after initial revascularisation compared with percutaneous transluminal coronary angioplasty (PTCA) but found no significant difference at 6.5 years. One large RCT in people with diabetes and multivessel coronary artery disease found that CABG reduced mortality or myocardial infarction within 8 years compared with PTCA. A smaller RCT found a non-significant reduction in mortality with CABG compared with PTCA at 4 years. One RCT in people with diabetes and multivessel coronary artery disease found that CABG reduced death, myocardial infarction, and revascularisation at 1 and 3 years compared to PTCA plus stenting. However, it found an increased risk of stroke with CABG in the short term up to discharge.

Benefits: **Coronary artery bypass graft compared with percutaneous transluminal coronary angioplasty without stenting:** One systematic review (search date 2001) found that in people with diabetes, coronary artery bypass graft (CABG) significantly reduced all cause mortality at 4.0 years after initial revascularisation compared with percutaneous transluminal coronary angioplasty (PTCA) but it found no significant difference at 6.5 years (3 RCTs: 537 people with diabetes; all cause mortality at 4.0 years: ARR 8.6%, 95% CI 2.2% to 15.0%; P < 0.01; all cause mortality at 6.5 years; ARR 3.9%, 95% CI −17.0% to + 25.0%; P = 0.71).[67] The systematic review identified four RCTs. Two RCTS reported results at both 4.0 and 6.5 years, one at only 4.0 years, and one at only 6.5 years.[67] Two RCTs identified by the systematic review compared CABG versus PTCA, without stenting or a glycoprotein IIb/IIIa inhibitor.[68,69] The first RCT found that CABG significantly reduced the proportion of people who died or suffered Q wave myocardial infarction over a mean of 7.7 years compared with PTCA (353 people with type 1 or type 2 diabetes and 2 or 3 vessel coronary disease, mean age 62 years: 60/173 [34.7%] with CABG *v* 85/170 [50%] with PTCA; ARR 15%, 95% CI 5% to 26%; RR 0.69, 95% CI 0.54 to 0.89; NNT 7, 95% CI 4 to 20).[68] This survival benefit was confined to those receiving at least one internal mammary graft. The second RCT found no significant difference between CABG or PTCA in mortality at 4 years (125 people with type 1 or type 2 diabetes, mean age 61 years; mortality: 8/63 [12.5%] with CABG *v* 14/62 [22.6%] with PTCA; RR 0.56, 95% CI 0.25 to 1.25; ARR 9.9%, 95% CI −3.4% to + 23.1%).[69] **Coronary artery bypass graft compared with percutaneous transluminal coronary angioplasty plus stenting:** One RCT compared the effectiveness of PTCA plus stenting versus CABG in people with type 1 or type 2 diabetes. It found that at 1 year and at 3 years CABG was significantly more effective than PTCA plus stenting in preventing death, myocardial infarction, or repeat revascularisation (208 people, 15.6% with type 1 diabetes, 84.4% with type 2 diabetes, all with 2 or 3 vessel coronary disease; proportion of people event free at 1 year: 81/96 [84.4%] with CABG *v* 71/112 [63.4%] with PTCA plus stenting; P < 0.001; proportion of people event free

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at 3 years: 78/96 [81.3%] with CABG *v* 59/112 [52.7%] with PTCA plus stenting; $P < 0.0001$).[70] Revascularisation within 3 years was required more frequently after PTCA plus stenting than after CABG (revascularisation rates: 8/96 [9.3%] with CABG *v* 46/112 [41%] with PTCA plus stenting; significance not assessed).[70]

Harms: **Coronary artery bypass graft compared with percutaneous transluminal coronary angioplasty without stenting:** The systematic review[67] and the two RCTs it identified did not report on adverse effects.[68,69] **Coronary artery bypass graft compared with percutaneous transluminal coronary angioplasty plus stenting:** Initial findings from the RCT comparing PTCA plus stenting versus CABG[70] were published in an earlier paper.[71] It found a significant increase in stroke with CABG compared with PTCA in the short term up to discharge (208 people with type 1 and type 2 diabetes and 2 or 3 vessel coronary disease; short term risk of stroke: 4/96 [4.2%] with CABG *v* 0/112 [0%] with PTCA plus stent; $P = 0.04$).[71] It found no significant difference between CABG and PTCA in short term risk (up to discharge) of a composite end point of death, myocardial infarction, repeat CABG, and repeat PTCA (composite outcome of death, myocardial infarction, repeat CABG, and repeat PTCA: 9/96 [9.4%] with CABG *v* 11/112 [9.8%] with PTCA; RR 1.05, 95% CI 0.45 to 2.42).[71]

Comment: None.

OPTION PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY COMPARED WITH THROMBOLYSIS

One systematic review suggested that percutaneous transluminal coronary angioplasty reduced the risk of death or recurrent myocardial infarction at 30 days in diabetic people presenting with acute myocardial infarction compared with thrombolysis.

Benefits: **Percutaneous transluminal coronary angioplasty versus thrombolysis in people with acute myocardial infarction:** We found one systematic review (search date not reported)[72] and one subsequent RCT.[73] The systematic review pooled individual patient data from 11 RCTs comparing percutaneous transluminal coronary angioplasty (PTCA) versus thrombolysis in people with acute myocardial infarction⊖.[72] It found that the rate of combined death or non-fatal recurrent myocardial infarction was significantly lower with PTCA compared with thrombolysis at 30 days (11 RCTs, 367 people with unspecified diabetes and acute myocardial infarction; combined rate of death or non-fatal recurrent myocardial infarction:18/196 [9.2%] with PTCA *v* 33/171 [19.3%] with thrombolysis; $P < 0.05$).[72] Treating 10 diabetic individuals with primary PTCA rather than thrombolysis prevented one case of death or non-fatal recurrent myocardial infarction. The subsequent RCT (395 people with ST segment elevation myocardial infarction; subgroup of 74 people with type 1 and 2 diabetes) found limited evidence of reduced mortality at median follow up of 7.5 years with PTCA compared with thrombolysis (absolute numbers not reported; HR 2.1; $P = 0.04$).[73] Most study comparisons were between people with diabetes versus people without diabetes, and the study failed to report statistics comparing baseline characteristics and outcome results for the treatment subgroups, making it difficult to draw conclusions from the results.

Harms: **Percutaneous transluminal coronary angioplasty versus thrombolysis in people with acute myocardial infarction:** The systematic review[72] and subsequent RCT[73] did not report on adverse effects.

Comment: None.

OPTION INTRACORONARY STENTING PLUS GLYCOPROTEIN IIB/IIIA INHIBITORS

RCTs in people with diabetes undergoing percutaneous transluminal coronary angioplasty found that the combination of stent and a glycoprotein IIb/IIIa inhibitor reduced cardiovascular morbidity and mortality compared with stent plus placebo.

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Prevention of cardiovascular events in diabetes

Benefits: We found one non-systematic review of individual patient data from three RCTs[74] and two subsequent RCTS.[75,76] **Intracoronary stenting plus glycoprotein IIb/IIIa inhibitors versus placebo:** The non-systematic review[74] pooled data from three placebo controlled trials of percutaneous coronary intervention: EPILOG,[77] EPISTENT,[78–80] and EPIC.[81] The non-systematic review found that, compared with placebo, abciximab (a glycoprotein IIb/IIIa inhibitor) plus intracoronary stent significantly reduced overall mortality at 1 year (1462 people with type 1 and type 2 diabetes, mean age 60.9 years; mortality: 22/888 [2.5%] with abciximab *v* 26/574 [4.5%] with placebo; P = 0.03).[74] The first subsequent RCT found that, compared with placebo, eptifibatide (a glycoprotein IIb/IIIa inhibitor) significantly reduced the composite outcome of death or myocardial infarction but found no significant difference for the single outcome of death at 1 year (466 people with type 1 and type 2 diabetes undergoing non-urgent coronary stent implantation, mean age 62 years; composite outcome of death or myocardial infarction: 18/232 [7.8%] with eptifibatide *v* 31/234 [13.4%] with placebo; HR 0.57, 95% CI 0.32 to 1.02; P = 0.001; single outcome of mortality: 3/232 [1.3%] with eptifibatide *v* 8/234 [3.5%] with placebo; HR 0.37, 95% CI 0.10 to 1.41; P = 0.28).[76] **Comparison of glycoprotein IIb/IIIa inhibitors in people undergoing intracoronary stenting:** The second subsequent RCT found no significant difference between tirofiban and abciximab in composite outcomes of death or myocardial infarction at 30 days and 6 months, or overall mortality at 1 year (1117 people, 503/1117 [45%] with type 1 diabetes, 614/1117 [55%] with type 2 diabetes, all having percutaneous coronary interventions, mean age 62 years; composite outcomes of death or myocardial infarction; at 30 days: 33/560 [5.9%] with tirofiban *v* 29/557 [5.2%] with abciximab; HR 1.14, 95% CI 0.69 to 1.87; P = 0.6; at 6 months: 46/560 [8.2%] with tirofiban *v* 42/557 [7.5%] with abciximab; HR 1.09, 95% CI 0.72 to 1.65; P = 0.7; overall mortality at 1 year: 2.9% with tirofiban *v* 2.1% with abciximab; P = 0.4, absolute numbers not reported).[75]

Harms: **Intracoronary stenting plus glycoprotein IIb/IIIa inhibitors versus placebo:** The non-systematic review of individual patient data found that there was slightly greater bleeding in people given abciximab than in those given placebo, but none of these differences were significant (major bleeding: 4.3% with abciximab *v* 3.0% with placebo, P = 0.21; minor bleeding: 6.9% with abciximab *v* 6.3% with placebo, P = 0.66; intracranial haemorrhage: 0% with abciximab *v* 0.17% with placebo, P = 0.39).[74] The first subsequent RCT did not report on any adverse events associated with eptifibatide.[76] **Comparison of glycoprotein IIb/IIIa inhibitors in people undergoing intracoronary stenting:** The second subsequent RCT found no significant difference between abciximab and tirofiban in major bleeding events (major bleeding events: 0.5% with tirofiban *v* 0.7% with abciximab; P = 0.725; absolute figures not reported).[75]

Comment: For people with diabetes undergoing percutaneous procedures, the combination of stent and glycoprotein IIb/IIIa inhibitor reduces restenosis rates and serious morbidity. It is unclear whether these adjunctive treatments would reduce the morbidity, mortality, and restenosis associated with percutaneous revascularisation procedures to the levels seen with coronary artery bypass grafting. The study comparing abciximab versus tirofiban and the study comparing eptifibatide versus placebo were both insufficiently powered to detect reductions in major cardiovascular events in the subgroups of people with diabetes.

GLOSSARY

Acute myocardial infarction is infarction that occurs when circulation to a region of the heart is obstructed and necrosis is occurring; clinical symptoms include severe pain, pallor, perspiration, nausea, dyspnoea, and dizziness. Myocardial infarction is gross necrosis of the myocardium as a result of interruption of the blood supply, usually caused by atherosclerosis of the coronary arteries; myocardial infarction without pain or other symptoms (silent infarction) is common in people with diabetes.

HbA1c The haemoglobin A1c test is the most common laboratory test of glycated haemoglobin (haemoglobin that has glucose irreversibly bound to it). HbA1c provides an indication of the "average" blood glucose over the preceding 3 months. The HbA1c is a weighted average over time of the blood glucose level; many different glucose profiles can produce the same level of HbA1c

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Prevention of cardiovascular events in diabetes

Substantive changes

Antihypertensive treatment versus no antihypertensive treatment Two systematic reviews[20,21] and three subsequent RCTs[23–25] added, conclusions confirmed; categorisation remains unchanged (beneficial).

Different antihypertensive drugs One systematic review[28] and two subsequent RCTs[31,32] added; categorisation remains unchanged (trade off between benefits and harms).

Aspirin One RCT added;[53] categorisation remains unchanged (trade off between benefits and harms).

Glycoprotein IIb/IIIa inhibitors One RCT added;[59] categorisation remains unchanged (likely to be beneficial).

Coronary artery bypass versus percutaneous transluminal angioplasty One RCT added;[70] categorisation remains unchanged (beneficial).

Percutaneous transluminal coronary angioplasty compared with thrombolysis One systematic review[72] and one RCT[73] added; recategorised as Likely to be beneficial.

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TABLE 1 **Diabetes and all cause mortality and coronary heart disease mortality in US physicians**

Age adjusted RR	Healthy men	Men with diabetes	Men with coronary heart disease	Mean with diabetes and coronary heart disease
All cause mortality	RR 1.00 (referent)	RR 2.3, 95% CI 2.0 to 2.6	RR 2.2, 95% CI 2.0 to 2.4	RR 4.7, 95% CI 4.0 to 5.4
CHD mortality	RR 1.00 (referent)	RR 3.3, 95% CI 2.6 to 4.1	RR 5.6, 95% CI 4.9 to 6.3	12.0, 95% CI 9.9 to 14.6

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