Unstable angina: the first 48 hours and later in-hospital management

David E Newby and **Keith A A Fox**

Department of Cardiology, Edinburgh Royal Infirmary, Edinburgh, UK
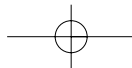
Unstable angina is a common cardiovascular condition associated with major adverse clinical events. Over the last 15 years, therapeutic advances have dramatically reduced the complication and mortality rates of this serious condition. The standard of therapy in patients with unstable angina now incorporates the combined use of potent antithrombotic (aspirin, clopidogrel, heparin and glycoprotein IIb/IIIa receptor antagonists) and anti-anginal (β-blockade and intravenous nitrates) regimens complemented by the selective and judicious application of coronary revascularisation strategies. Increasingly, these invasive and non-invasive therapeutic interventions are being guided not only by the clinical risk profile but also by the determination of serum cardiac and inflammatory markers. Moreover, rapid and intensive management of associated risk factors, such as hypercholesterolaemia, would appear to have potentially substantial benefits even within the acute in-hospital phase of unstable angina.

Unstable angina can be ascribed to a range of patients with different clinical presentations and characteristics. Moreover, it should be recognised that much of the trial evidence, upon which this article is based, includes patients with non-Q-wave or non-ST elevation myocardial infarction. This reflects the common pattern of clinical presentation and the inevitable delay in obtaining cardiac enzyme estimations that ultimately determine the diagnostic category of the acute coronary syndrome.

Each year, unstable angina accounts for over 115,000 acute hospital admissions in the UK (~200 per 100,000 population) with a significant male preponderance. Throughout Europe, hospital admission rates for unstable angina exceed those of ST elevation myocardial infarction[1]. Ten years ago, before the advent of modern therapeutic interventions, 15% of patients with unstable angina progressed to sustain an acute myocardial infarction and the overall in-hospital mortality was up to 5%. The PRAIS-UK study[2] recently estimated the contemporary impact of unstable angina in the UK by collecting data on 20 consecutive admissions to 56 representative hospital centres. This observational

Correspondence to:
Dr David E Newby,
Department of Cardiology,
The Royal Infirmary,
*Lauriston Place,*
Edinburgh EH3 9YW, UK
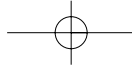
Table 1 Classification of unstable angina[3]

	CLINICAL PRESENTATION
Class I	New onset, severe, or accelerated angina.
	Patients with angina of less than 2 months' duration, severe or occurring three or more times per day, or angina that is distinctly more frequent and precipitated by distinctly less exertion. No rest pain in the last 2 months.
Class II	Angina at rest – subacute.
	Patients with one or more episodes of angina at rest during the preceding month but not within the preceding 48 h.
Class III	Angina at rest – acute.
	Patients with one or more episodes of angina at rest during the preceding 48 h.
	CLINICAL CONTEXT
Class A	Secondary unstable angina.
	A clearly defined condition extrinsic to the coronary vascular bed that has intensified myocardial ischaemia, *e.g.* anaemia, infection, fever, hypotension, tachyarrhythmia, thyrotoxicosis, hypoxaemia.
Class B	Primary unstable angina.
Class C	Post-infarction unstable angina.
	Within 2 weeks of documented myocardial infarction.
	THERAPEUTIC INTERVENTION
1	Absence of, or minimal treatment.
2	Occurring in the presence of standard therapy for chronic stable angina.
3	Occurring despite maximally tolerated doses of all three categories of oral therapy, including intravenous nitrates.

Class IIIB has been further sub-divided into IIIB-T_{pos} and IIIB-T_{neg} to reflect the marked differences in prognostic risk conferred by the presence or absence of an elevation in troponin I or T concentrations.[3]

study reported that the in-hospital event rates for unstable angina included a 2% mortality rate, 4% progression to myocardial infarction and 3% recurrence of refractory ischaemia. By 6 months this had risen to 7% mortality, 7% myocardial infarction and 17% recurrent myocardial ischaemia. One year after the index episode of unstable angina, the cardiovascular event rate had returned to that of patients with stable angina and a similar risk factor profile.

Clinical presentation

Patients with unstable angina present with prolonged anginal chest pain that may occur at rest or be precipitated by progressively less exertion. This may present on a background of chronic stable angina or as a *de novo* phenomenon. Although this is a heterogeneous group of patients, the Braunwald classification attempts to provide an objective description of the clinical presentation and context as well as the response to therapy (Table 1).
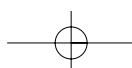
Physical examination is directed towards the identification of potential precipitants such as anaemia, confounding cardiac conditions such as critical aortic stenosis and complications of cardiac ischaemia such as hypotension or heart failure. This may also reveal the extent of co-existent vascular disease such as the presence of vascular bruits or absence of peripheral pulses.

Preliminary investigations

Electrocardiogram

The electrocardiogram will often, but not always, show evidence of ischaemia that classically takes the form of ST segment depression, T wave inversion and new bundle branch block. Frequent repeated recordings should be made, particularly in the early acute phase and/or in the presence of ongoing chest pain. Ischaemic electrocardiographic changes provide important markers of an adverse prognosis[2] with the presence, and degree, of ST segment depression being independent predictors of mortality[4,5]. They also identify those patients with the most to gain from therapeutic interventions such as percutaneous coronary intervention[6].
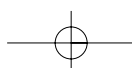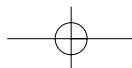
Cardiac and inflammatory markers

The measurement of cardiac enzymes in the first 24 h provides not only diagnostic but also prognostic information in patients with unstable angina[5,7]. As with the electrocardiogram, an elevation in the cardiac troponin identifies those patients who benefit most from interventions such as glycoprotein IIb/IIIa receptor antagonism[8,9] and percutaneous coronary intervention[6].

C-reactive protein, a marker of inflammation, provides further prognostic information in patients presenting with unstable angina[10] that is independent of the presence of myocardial damage. Recent evidence has also suggested that the combined measure of C-reactive protein and troponin provides additive information and that together they are powerful predictors of long-term outcome in patients with unstable angina[5].
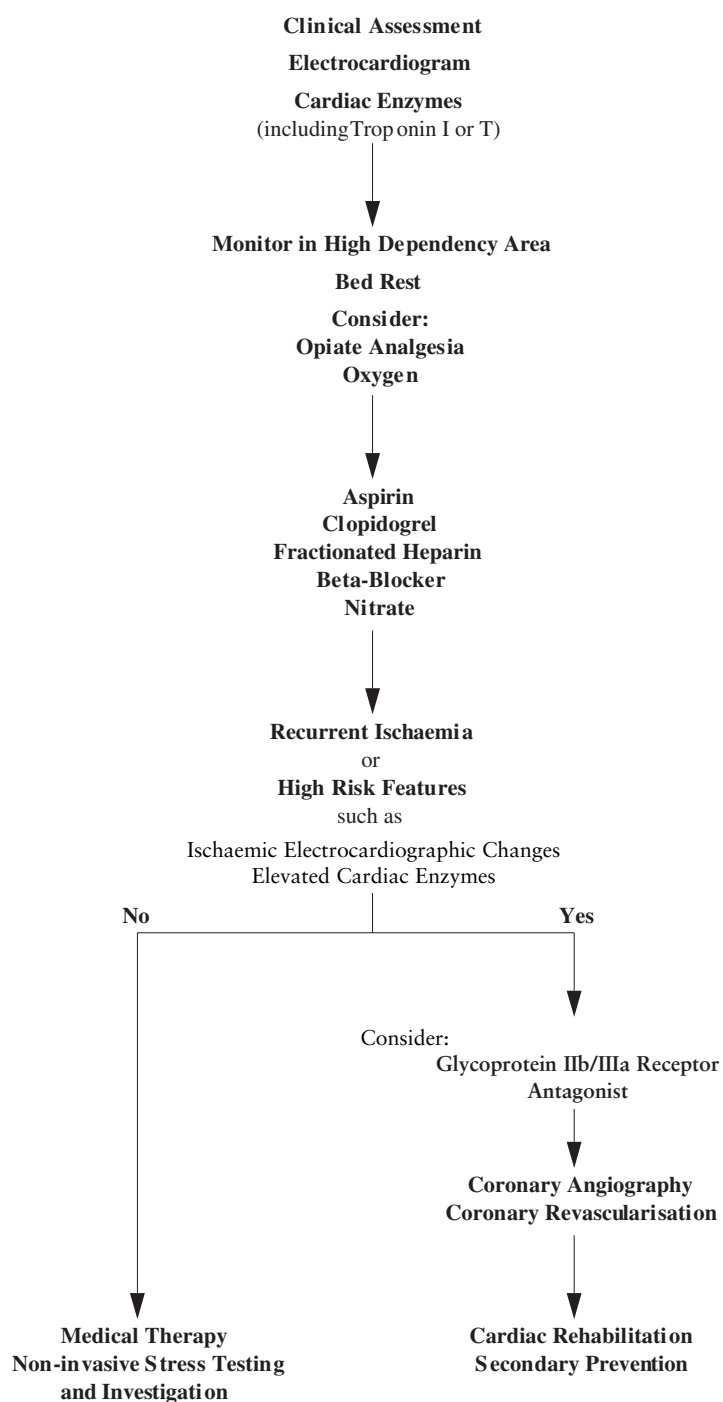
Secondary causes of unstable angina

Occasionally, unstable angina may be precipitated, or exacerbated, by an intercurrent illness (Braunwald class A). Therefore, guided investigation of potential precipitants should be undertaken, but as a
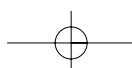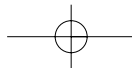
Ischaemic heart disease: therapeutic issues

Clinical Assessment

Electrocardiogram

Cardiac Enzymes
(including Troponin I or T)

↓

Monitor in High Dependency Area

Bed Rest

Consider:
Opiate Analgesia
Oxygen

↓

Aspirin
Clopidogrel
Fractionated Heparin
Beta-Blocker
Nitrate

↓

Recurrent Ischaemia
or
High Risk Features
such as
Ischaemic Electrocardiographic Changes
Elevated Cardiac Enzymes

No   **Yes**

Consider:
Glycoprotein IIb/IIIa Receptor
Antagonist

↓

Coronary Angiography
Coronary Revascularisation

↓

Medical Therapy   **Cardiac Rehabilitation**
Non-invasive Stress Testing   **Secondary Prevention**
and Investigation

Fig. 1 Simplified scheme for the in-hospital management of patients with unstable angina.

minimum haemoglobin concentration, oxygen saturation, and thyroid function should be assessed. In patients presenting within 24 h of pain onset, serum total cholesterol concentration may be determined although the full serum lipid profile will need to be re-assessed following complete recovery.

Immediate management – the first 48 h

Patients should be transferred to a high dependency area with the provision of haemodynamic and cardiac monitoring, and ready access to resuscitation facilities. The patient should be restricted to bed rest, and opiate analgesia and oxygen therapy given as appropriate. Complications of severe myocardial ischaemia, such as haemodynamic compromise or arrhythmias, should be treated as appropriate (see elsewhere in this volume).

Initial specific therapeutic interventions are targeted at the prevention of thrombotic vessel occlusion, the reduction in myocardial oxygen demand and the enhancement of coronary blood flow (Fig. 1).

Antithrombotic therapy

Antiplatelet therapy

Aspirin

Aspirin has a relatively short plasma half-life of 1–2 h, but is able to inhibit long-term platelet activity by irreversible acetylation of the platelet cyclooxygenase enzyme, thereby preventing thromboxane A_2 formation. Although a weak inhibitor of platelet aggregation, aspirin is associated with major clinical benefits[11] that may, in part, relate to its additional anti-inflammatory action[12].

The efficacy of aspirin therapy in patients with unstable angina was first described nearly 20 years ago. The Veterans Administration Cooperative Study[13] of 1266 men with unstable angina demonstrated a 50% reduction in the risk of death or myocardial infarction. The more recent meta-analysis by the Antiplatelet Trialists Collaboration incontrovertibly confirmed the benefits of aspirin therapy in patients with unstable angina[11]. Because of this marked reduction in the risk of cardiovascular death, MI and stroke, all patients with unstable angina pectoris should be commenced on aspirin therapy.

Aspirin has been used at various dosages (80–325 mg) but a reasonable dosage regimen is an initial 300 mg stat followed by a maintenance dose of 75 mg daily. The initial 300 mg dose is sufficient to achieve maximal anti-platelet effects and maintenance inhibition is achieved by 75 mg daily. This attempts to achieve maximum efficacy whilst minimising the dose related gastrointestinal side effects of aspirin.
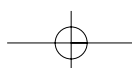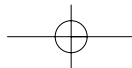
Thienopyridines

Thienopyridines inhibit platelet aggregation through blockade of the platelet adenosine diphosphate receptor. Ticlopidine was the first licensed thienopyridine to achieve widespread clinical use. In the STAI trial, administration of ticlopidine (250 mg bd) was associated with a halving of event rates in patients with unstable angina[14]. However, this trial was conducted in the absence of aspirin therapy and it is unclear whether combination therapy would achieve additional benefits.

Ticlopidine has been largely superceded by a closely related analogue, clopidogrel, since the latter is better tolerated and, unlike ticlopidine, does not cause significant bone marrow toxicity. In the CAPRIE trial[15], long-term clopidogrel treatment (75 mg daily) was at least as efficacious as aspirin in preventing ischaemic stroke, myocardial infarction or cardiovascular death in patients with atherosclerotic vascular disease. Although the overall secondary preventative benefits of clopidogrel statistically exceeded that of aspirin, the relative benefits were modest (relative risk reduction, 8.7%; $P = 0.04$). Recently, the preliminary results from the CURE study have been reported[16]. This trial was a comparison of aspirin with the combination of aspirin and clopidogrel in 12,562 patients with unstable angina. At a mean follow-up of 9 months, there was a 20% relative risk reduction in the composite primary end point of cardiovascular death, myocardial infarction or stroke (odds ratio of 0.80, 95% confidence intervals of 0.72–0.89; $P < 0.001$). The benefits of therapy were apparent within the first 24 h and were predominantly seen within the first 90 days. As expected, there was a modest increase in the risk of bleeding, but this was predominantly confined to minor bleeding events.

Glycoprotein IIb/IIIa receptor antagonists

The evidence for the use of glycoprotein IIb/IIIa receptor antagonists in the treatment of patients with unstable angina is confusing and, at times, contradictory. This, in part, results from the diversity of compounds (peptidic, non-peptidic and oral agents), receptor binding avidity (short and long receptor dissociation half lives) and pharmacokinetic profiles. Although glycoprotein IIb/IIIa receptor antagonists effectively prevent platelet aggregation, they do not inhibit platelet activation, secretion or adhesion. Indeed, this class of compounds may paradoxically cause platelet activation.

Clinical trials have demonstrated that certain agents appear to be most appropriate under specific circumstances. In patients with unstable angina, intravenous tirofiban or eptifibatide administration is associated with a significant reduction in the composite end-point of death, myocardial infarction or refractory ischaemia out to 6 months of follow-up[17,18]. This benefit was independent of percutaneous coronary
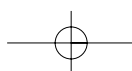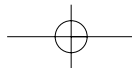
intervention. In contrast, intravenous abciximab has been shown to be of benefit in the context of percutaneous coronary intervention[19,20] and has superior efficacy in comparison to tirofiban in this setting[21]. However, abciximab administration does not appear to be beneficial in patients with unstable angina outwith the context of percutaneous coronary intervention[23].

A meta-analysis of 16 randomized controlled trials incorporating 32,135 patients confirmed glycoprotein IIb/IIIa receptor antagonists have modest beneficial effects (relative risk reduction of 14%) in patients during percutaneous coronary intervention or acute coronary syndromes[24].

Summary of antiplatelet therapy

All patients with unstable angina should be given oral aspirin and clopidogrel therapy (300 mg stat and 75 mg maintenance for both). The use of intravenous glycoprotein IIb/IIIa receptor antagonists should be reserved for patients with severe refractory ischaemia or, in particular, those undergoing urgent percutaneous coronary intervention.

Anti-coagulant therapy
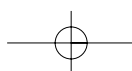
Unfractionated heparin

Heparin is composed of a range of different sized glycosaminoglycans that bind to antithrombin III and accentuate the inhibition of thrombin and factor Xa. The benefits of heparin therapy in patients with unstable angina are well established and widely accepted. A meta-analysis of six randomised controlled trials demonstrated that, in addition to aspirin, intravenous heparin conferred a relative risk reduction of 33% in the risk of death or myocardial infarction[25].

The use of unfractionated heparin is hindered by its unpredictable efficacy that necessitates monitoring of its anticoagulant effects and dose adjustments. Moreover, idiosyncratic reactions, such as heparin-induced thrombocytopaenia, do occur and can cause serious clinical problems.

Fractionated heparin

Fractionated or low molecular weight heparins have several advantages over unfractionated heparin. They have a greater selectivity for factor Xa inhibition, have less non-specific protein binding properties and produce more potent inhibition of thrombin generation. In particular, their ease of administration, the reduced incidence of idiosyncratic reactions, and the more predictable pharmacokinetics and pharmacodynamics makes their clinical use especially attractive.

There have been four major randomised controlled trials that have compared fractionated and unfractionated heparin in patients with unstable angina – the FRIC[26], ESSENCE[27], TIMI-11B[28] and FRAXIS[29] trials. Fractionated heparins appear to have equivalent benefits to
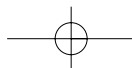
unfractionated heparin[30] and, particularly in the case of enoxaparin, may have superior efficacy in the prevention of death, myocardial infarction or recurrent angina: relative risk reduction of 15–18%[27,28]. These potential additional benefits are modest, but are predominantly seen in high-risk patients during the early acute phase and are sustained at 1-year follow-up[31]. There is little evidence to suggest that the continuation of fractionated heparin therapy beyond 7 days confers any additional benefit[30,55].

Antithrombin therapy

Hirudin is a peptidic and direct thrombin inhibitor that, in comparison to heparin, may possess additional and more complete anticoagulant actions. However, in the GUSTO IIb trial[32] of patients with unstable angina, hirudin (desirudin) had only modest benefits in comparison to unfractionated heparin. These benefits principally consisted of an early reduction in the rate of myocardial infarction at 24 h, but this was not sustained at 30 days (relative risk reduction 11%, $P = 0.06$). The subsequent OASIS-1[33] and OASIS-2[34] trials of hirudin (lepirudin) again showed a small benefit above unfractionated heparin at 30 days (relative risk reduction 14%, $P = 0.04$)[35]. Other direct thrombin inhibitors, such as inogatran and hirulog, are also under clinical evaluation and development, but again have yet to demonstrate clinically meaningful superior efficacy in comparison to heparin. Given the potential additional benefits of fractionated heparin, the routine use of direct antithrombins has not been widely accepted or implemented.

Summary of anticoagulant therapy

The major clinical benefits of anticoagulant therapy in patients with unstable angina are clear. In a recent meta-analysis, the use of fractionated or unfractionated heparin is associated with a relative risk reduction of 47% ($P <0.001$) in comparison to placebo or control[30]. Although the superiority of a specific anticoagulant therapeutic approach has yet to be definitively established, the use of fractionated heparin has the advantage of ease of administration without the requirement for therapeutic monitoring. Moreover, enoxaparin may confer a sustained small reduction in clinical events with evidence to suggest a reduction in health care costs[36].
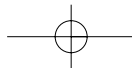
Reduction in myocardial oxygen demand and enhancement of coronary blood flow

Beta-blockers

β-Blockers inhibit the β_1-adrenergic receptors of the myocardium to produce negative chronotropism and negative inotropism of the heart. The attenuation of the heart rate response to exercise and stress reduces
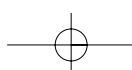
the myocardial oxygen demand and severity of ischaemia. The impact is also to prolong diastole, a major determinant of myocardial perfusion time. Randomised controlled trials in chronic stable angina have demonstrated that β-blocker therapy is efficacious in reducing symptoms of angina, episodes of ischaemia and improving exercise capacity[37,38]. Moreover, a meta-analysis of post-myocardial infarction trials has demonstrated a 23% relative risk reduction in mortality in patients maintained on long-term β-blocker therapy[39].

The direct evidence for unstable angina is limited but, in a meta-analysis of trials incorporating nearly 5000 patients with unstable angina, β-blocker therapy reduced the risk of myocardial infarction by 13% (1–23 %; P <0.04)[40]. Because of the inferred benefit from post-myocardial infarction trials, β-blocker therapy has become established as the first line medication in unstable angina. Intravenous preparations should be considered particularly in the presence of on-going pain or tachycardia, and titrated to reduce the resting heart rate below 70 beats per minute. Caution should be exercised in patients with acute pulmonary oedema, bradycardia and bronchospasm.

Nitrates

Nitrates were the first form of anti-anginal drug therapy to be discovered and utilized. Their mechanism of action is exerted through the direct or indirect release of nitric oxide causing vaso- and venodilatation. This results in a reduction in cardiac preload and afterload as well as causing epicardial vasodilatation to increase coronary blood flow.
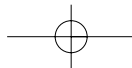
Nitrates are an effective method of alleviating acute anginal chest pain and, in order to produce rapid control of symptoms, should be administered intravenously to all patients with unstable angina, particularly where it is complicated by pulmonary oedema[41]. Randomised controlled trials in patients with chronic stable angina have demonstrated that nitrates are also effective in reducing the long-term frequency of anginal symptoms and improving exercise capacity[42,43]. However, there is no trial evidence to show that acute or chronic nitrate use has any prognostic or long-term benefits in patients with unstable or stable angina.

One of the main limitations of nitrate use is the development of tolerance that can occur from 24 h after the initiation of continuous parenteral administration. The development of nitrate tolerance appears, at least in part, to be due to the depletion of sulphydryl groups and can be rectified by the provision of a nitrate-free period.

Calcium channel blockers

Dihydropyridine calcium channel blockers, such as nifedipine and amlodipine, cause coronary and systemic vasodilatation thereby
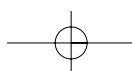
improving coronary blood flow and reducing cardiac afterload. Reflex tachycardia may, however, limit their use in the absence of rate limiting medication, such as β-blockers. Non-dihydropyridine calcium channel blockers, such as verapamil and diltiazem, have additional negative chronotropic and more pronounced negative inotropic actions that also serve to reduce myocardial oxygen demand.

Although there is a suggestion that dihydropyridines, especially nifedipine, are associated with an adverse outcome in patients with unstable angina[44], overall calcium antagonists appear to have a neutral effect on outcome[40]. Moreover, post-myocardial infarction trials suggest that rate limiting non-dihydropyridine calcium channel antagonist, such as verapamil[45] and diltiazem[46], may have modest prognostic benefits in the absence of heart failure. Therefore, rate-limiting non-dihydropyridine calcium antagonists should be reserved as second line agents in patients with contra-indications to β-blocker therapy or those with resistant anginal symptoms.

Potassium channel openers

This is a novel class of anti-anginal therapy that has vasodilator and potential cardioprotective actions. Potassium channel openers act on the ion channels of the vascular smooth muscle cell and cardiac myocyte. Consequently, they may have a role in enhancing ischaemic precon-ditioning and improving the myocardial response to an ischaemic insult.

Currently, nicorandil is the only preparation of this class in clinical use. It is effective in the treatment of angina and has both nitrate and potassium channel opening properties. In the first small randomised controlled trial of patients with unstable angina[47], nicorandil use was associated with a reduction in myocardial ischaemia and arrhythmias. However, whether this translates into reductions in major clinical events has yet to be established.

Intra-aortic balloon pump

Intra-aortic balloon counterpulsation has two main beneficial haemo-dynamic effects in the setting of unstable angina: the augmentation of diastolic aortic and coronary perfusion pressure as well as the reduction in cardiac afterload and myocardial oxygen demand. Reflecting the invasive nature and the associated potential vascular complications of this approach, the insertion of an intra-aortic balloon pump is usually reserved for patients with haemodynamic instability or severe refractory angina, especially as a bridge to coronary angiography and definitive coronary revascularisation. Although there have been no randomised controlled trials in patients with unstable angina, its use is associated with marked clinical improvements in refractory unstable cases.
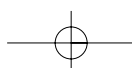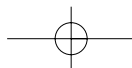
Later in-hospital management

Risk assessment

The identification of patients at risk of future events will help guide the further investigation and management of patients with unstable angina. Those at particular high risk, have most to gain from further intensive and invasive treatment[6,22].

There are several useful clinical markers of risk that have been identified from trial data (Table 2)[48,49]. These factors are associated with failure of medical therapy and can be used to help guide the identification of patients who should be considered for cardiac catheterisation and potential coronary revascularisation.
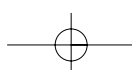
Non-invasive stress testing

Pre-discharge non-invasive stress testing is often employed in low-risk patients who have been free of ischaemia for 12–24 h, or intermediate risk for 2 or more days. This is performed in the absence of direct evidence since the prognostic information it provides is based on patients with stable ischaemic heart disease. It should be appreciated that non-invasive testing may be falsely re-assuring since in many cases unstable angina is precipitated by thrombus formation on a small non-stenotic plaque. Moreover, an initially positive stress test may become negative following a period of convalescence due to plaque remodelling.

There are three main modalities of stress testing: electrocardiography, radionuclide myocardial perfusion scintigraphy and echocardiography. There are significant advantages and disadvantages with each modality, but exercise electrocardiography remains the most widely used non-invasive test since it is easily performed and has been extensively validated. However, the sensitivity and specificity of exercise electrocardiography is

Table 2 Variables associated with an adverse prognosis in patients with unstable angina[48,49]

- Age 65 years or older
- Three or more risk factors for coronary artery disease*, particular family history of coronary disease
- Prior coronary stenosis of more than 50% or previous history of angina
- ST segment deviation on the electrocardiogram at presentation
- ST segment deviation despite medical therapy
- Two or more anginal episodes within previous 24 h
- Aspirin use prior to admission
- Elevated cardiac markers (creatinine kinase and troponin)

•*Family history of coronary artery disease, hypertension, diabetes mellitus, smoking habit, hypercholesterolaemia.
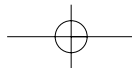
Table 3 Non-invasive stress testing in patients with ischaemic heart disease: features that are particularly associated with a poor prognosis and indicative of severe disease

EXERCISE ELECTROCARDIOGRAM

- Poor maximal exercise capacity (< stage 3 of the Bruce Protocol)
- ≥ 1 mm ST depression during stage 2 or less (Bruce Protocol)
- ≥ 2 mm ST depression at any time
- Limited blood pressure response, *i.e.* fall or no rise from baseline

MYOCARDIAL PERFUSION SCINTIGRAPHY

- Reversible radionuclide perfusion defect in more than one territory
- Reduced radionuclide ejection fraction with exercise
- Increased lung uptake of radionuclide

STRESS ECHOCARDIOGRAPHY

- Wall motion abnormality involving more than two segments developing at low stress
- (dobutamine dose of ≤ 10 mg/mg/min) or heart rate
- Evidence of extensive ischaemia

reduced by intraventricular conduction defects, repolarization abnormalities, poor exercise tolerance and concomitant cardiac medications such as digitalis. Myocardial perfusion scintigraphy, during pharmacological or exertional stress, provides a method of visualizing myocardial perfusion more directly and can circumvent some of the electrocardiographic artefactual problems associated with, for example, digitalis therapy or repolarization abnormalities. The indicators of high risk during non-invasive stress testing are shown in Table 3.

Coronary angiography

The American Heart Association and American College of Cardiology guidelines[50] recommend cardiac catheterisation in patients with unstable angina in the following circumstances:

- recurrent angina/ischaemia at rest or low-level exercise despite therapy
- recurrent angina/ischaemia with symptoms or signs of acute heart failure
- high-risk findings on non-invasive stress testing
- reduced left ventricular function (ejection fraction <40%)
- haemodynamic instability or angina at rest accompanied by hypotension
- sustained ventricular tachycardia
- percutaneous coronary intervention (PCI) within the previous 6 months
- prior CABG

In the light of the evidence from the FRISC II and TACTICS trials[6,22] (see below), patients with raised cardiac troponins or electrocardiographic abnormalities should also be considered for cardiac catheterisation with a view to coronary revascularisation.
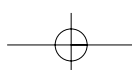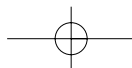
There are a number of patients who continue to have chest pain but either cannot perform an exercise tolerance test or have satisfactory non-invasive investigations. These patients may have frequent admissions to hospital with chest pain and take empirical anti-anginal medication with little objective evidence of its benefit to them. In this context, a normal coronary angiogram can be very helpful in excluding obstructive coronary artery disease, removing uncertainty about the diagnosis, reassuring the patient, and thereby reducing their use of health care resources.

Coronary revascularisation

Initial randomised studies looking at early invasive interventions suggested that there was either a neutral or harmful effect of such approaches in patients with acute coronary syndromes[51,52]. However, these studies have been heavily criticised for the high cross over rates with a half of the patients in the conservative management group undergoing cardiac catheterisation. Moreover, the coronary revascularisation rates were very similar at 44% and 33% for the invasive and non-invasive groups, respectively. It is likely, therefore, that high-risk patients had an intervention irrespective of their randomised treatment and the lower risk patients only received revascularisation if they were in the invasive treatment group. From the ACME and RITA-2 trials, we already know that there is an excess of events in lower risk patients treated with percutaneous coronary intervention[53].

Observational data from the OASIS registry have indicated that an early invasive strategy is likely to be particularly beneficial in patients with refractory symptoms and may reduce the rate of re-admission with unstable angina[54]. Recently, two randomised controlled trials have been reported that demonstrate an early invasive strategy is appropriate, especially in the presence of electrocardiographic changes or elevations in cardiac enzymes[6,22]. From the 1-year follow-up of the FRISC II trial, an early strategy of coronary revascularisation is associated with major reductions in the risk of death (RR 0.57, CI 0.36–0.90; $P < 0.02$), myocardial infarction (RR 0.74, CI 0.59–0.94; $P < 0.02$) or re-hospitalisation (RR 0.67, CI 0.62–0.72; $P < 0.001$)[55]. These findings have been supported by the subsequent TACTICS trial of 2220 patients that demonstrated a 22% risk reduction ($P = 0.03$) in the primary end-point of death, myocardial infarction or re-hospitalisation for an acute coronary syndrome at 6 months' follow-up. Both these trials had significant differences in the rate of early intervention between the invasive and non-invasive strategy groups: for example, 71% *versus* 9%, respectively, in the FRISC II trial[55]. However, the benefits of
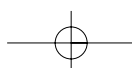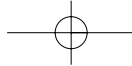
interventional strategies are not yet clear as they may first appear. Both trials employed a more sensitive threshold for the diagnosis of myocardial infarction for non-procedure related myocardial infarction, thereby favouring the diagnosis of myocardial infarction in the conservative group. This is particularly pertinent given that the majority of the absolute clinical benefit was seen in the incidence of myocardial infarction.

**Coronary artery bypass surgery or percutaneous coronary intervention**

Selection of the type of revascularisation procedure will be heavily influenced by technical aspects of the coronary anatomy as well as factors such as co-morbidity and patient preference. For example, in many patients, a policy of initial percutaneous coronary intervention may simply delay the subsequent need for revascularization with coronary artery bypass surgery, especially in younger patients.

Meta-analysis[56] of the three major randomised controlled trials comparing coronary artery bypass surgery with medical therapy in patients with chronic stable angina has suggested that this is the most appropriate in patients with a significant left main stem stenosis of 50% or more, triple vessel disease or two vessel disease including a significant proximal LAD stenosis. These benefits are most marked if the left ventricular function is impaired or the stress test is strongly positive. Patients with single or two-vessel coronary artery disease may be appropriately revascularised by either coronary artery bypass surgery or percutaneous coronary intervention.

Early in-hospital initiation of secondary prevention

Cardiac rehabilitation, risk factor management and the use of secondary prevention therapy in patients recovering from an episode of unstable angina are discussed elsewhere in this volume.

Where appropriate, all patients should be maintained on aspirin, clopidogrel and β-blocker therapy at the time of hospital discharge. However, in the LIPID trial incorporating patients with unstable angina, the initiation of lipid lowering therapy was between 3–24 months from the index event. Recently, the MIRACL trial assessed the effect of early in-hospital initiation (within 24–96 h of admission) of atorvastatin 80 mg daily in 3086 patients with unstable angina and non-Q wave myocardial infarction[57]. Within 16 weeks of therapy, the composite end-point of death, myocardial infarction or re-hospitalisation for myocardial ischaemia was reduced by 16% ($P = 0.048$), predominantly due to a reduction in re-hospitalisation for myocardial ischaemia (26%, $P = 0.02$). These data require confirmation but it would, therefore,
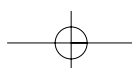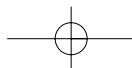
appear that aggressive lipid lowering therapy can be safely initiated in-hospital[57].

Conclusions

There is now a substantial evidence base to guide therapeutic interventions in the treatment of patients presenting with unstable angina (Fig. 2). The combined use of potent anti-platelet and anti-coagulant therapies has markedly reduced the rate of thrombotic coronary artery occlusion. Moreover, targeted invasive intervention and revascularisation in high-risk patients is associated with major clinical benefits with a reduction in the rate of progression to myocardial infarction and associated cardiovascular death. Finally, intensive secondary preventative strategies in the early acute phase appear to be associated with substantial benefits.
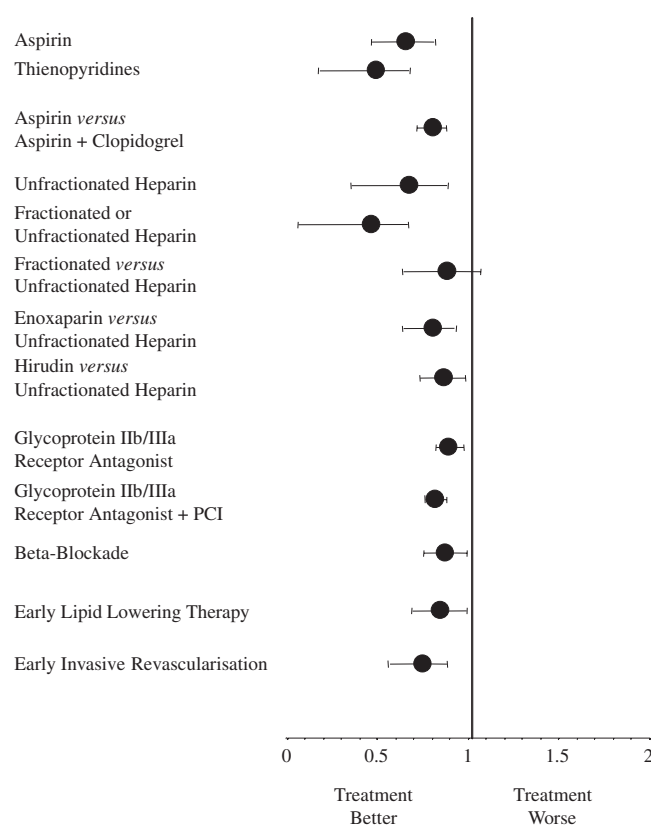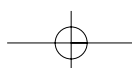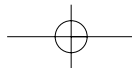
Fig. 2 Evidence base for the in-hospital treatment of patients with unstable angina.

References

1   Fox KAA, Cokkinos DV, Deckers J, Keil U, Maggioni A, Steg G. The ENACT study: a pan-European survey of acute coronary syndromes. European Network for Acute Coronary Treatment. *Eur Heart J* 2000; **21**: 1440–9

2   Collinson J, Flather MD, Fox KA *et al*. Clinical outcomes, risk stratification and practice patterns of unstable angina and myocardial infarction without ST elevation: Prospective Registry of Acute Ischaemic Syndromes in the UK (PRAIS-UK). *Eur Heart J* 2000; **21**: 1450–7

3   Hamm CW, Braunwald E. A classification of unstable angina revisited. *Circulation* 2000; **102**: 118–22

4   Holmvang L, Clemmensen P, Wagner G, Grande P. Admission standard electrocardiogram for early risk stratification in patients with unstable coronary artery disease not eligible for acute revascularization therapy: a TRIM substudy. ThRombin Inhibition in Myocardial Infarction. *Am Heart J* 1999; **137**: 24–33

5   Lindahl B, Toss H, Siegbahn A, Venge P, Wallentin L. Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. FRISC Study Group. Fragmin during instability in coronary artery disease. *N Engl J Med* 2000; **343**: 1139–47

6   The Fragmin and Fast Revascularisation during InStability in Coronary artery disease (FRISC II) investigators. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. *Lancet* 1999; **354**: 708–15

7   Antman EM, Tanasijevic MJ, Thompson B *et al*. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. *N Engl J Med* 1996; **335**: 1342–9

8   Hamm CW, Heeschen C, Goldmann B *et al*. Benefit of abciximab in patients with refractory unstable angina in relation to serum troponin T levels. c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) Study Investigators. *N Engl J Med* 1999; **340**: 1623–9

9   Heeschen C, Hamm CW, Goldmann B, Deu A, Langenbrink L, White HD. Troponin concentrations for stratification of patients with acute coronary syndromes in relation to therapeutic efficacy of tirofiban. PRISM Study Investigators. Platelet Receptor Inhibition in Ischemic Syndrome Management. *Lancet* 1999; **354**: 1757–62

10   Haverkate F, Thompson SG, Pyke SD, Gallimore JR, Pepys MB. Production of C-reactive protein and risk of coronary events in stable and unstable angina. European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group. *Lancet* 1997; **349**: 462–6

11   The Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy – I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994; **308**: 81–106

12   Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997; **336**: 973–9

13   Lewis HD, Davis JW, Archibald DG *et al*. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina. Results of a Veterans Administration Cooperative Study. *N Engl J Med* 1983; **309**: 396–403

14   Balsano F, Rizzon P, Violi F *et al*. Antiplatelet treatment with ticlopidine in unstable angina. A controlled multicenter clinical trial. The Studio della Ticlopidina nell'Angina Instabile Group. *Circulation* 1990; **82**: 17–26

15   The CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events. *Lancet* 1996; **348**: 1329–39

16   The CURE investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001; 345: 494–502

17   The Platelet Receptor inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and symptoms (PRISM-PLUS) study investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q wave myocardial infarction. *N Engl J Med* 1998; **338**: 1488–97

18   The Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial investigators. Inhibition of platelet glycoprotein IIb/IIIa with
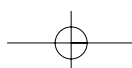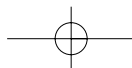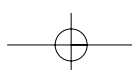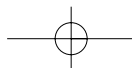
eptifibatide in patients with acute coronary syndromes. *N Engl J Med* 1998; **339**: 436–43

19 The EPIC investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. *N Engl J Med* 1994; **330**: 956–61

20 The CAPTURE study investigators. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE Study. *Lancet* 1997; **349**: 1429–35

21 The TARGET Investigators. *Do Tirofiban and ReoPro give Similar Efficacy Trial*. New Orleans, LA: The American Heart Association, 2000

22 The TACTICS investigators. *Treat angina with Aggrastat and determine the Cost of Therapy with Invasive or Conservative Strategies*. New Orleans, LA: The American Heart Association, 2000

23 The Global Use of Strategies To Open occluded coronary arteries (GUSTO) IV investigators. *GUSTO-IV: Abciximab in Unstable Angina*. Amsterdam: The European Society of Cardiology, 2000

24 Kong DF, Califf RM, Miller DP *et al*. Clinical outcomes of therapeutic agents that block the glycoprotein IIb/IIIa integrin in ischemic heart disease. *Circulation* 1998; **98**: 2829–35

25 Oler A, Whooley MA, Oler J, Grady D. Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina. A meta-analysis. *JAMA* 1996; **276**: 811–5

26 Klein W, BuchWald A, Hillis SE *et al* for the FRagmin In unstable Coronary artery disease (FRIC) study investigators. Comparison of low-molecular-weight heparin with unfractionated heparin acutely and with placebo for 6 weeks in the management of unstable coronary artery disease. *Circulation* 1997; **96**: 61–8

27 Cohen M, Demers C, Gurfinkel EP *et al* for the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events (ESSENCE) study group. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. *N Engl J Med* 1997; **337**: 447–52

28 Antman EM, McCabe CH, Gurfinkel EP *et al*. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction. Results of the thrombolysis in myocardial infarction (TIMI) 11B trial. *Circulation* 1999; **100**: 1593–601

29 The FRAXIS Study Group. Comparison of two treatment durations (6 days and 14 days) of a low molecular weight heparin with a 6-day treatment of unfractionated heparin in the initial management of unstable angina or non-Q-wave myocardial infarction: FRAXIS (FRAXiparine in Ischaemic Syndrome). *Eur Heart J* 1999; **20**: 1553–62

30 Eikelboom JW, Anand SS, Malmberg K, Weitz JI, Ginsberg JS, Yusuf S. Unfractionated heparin and low-molecular-weight heparin in acute coronary syndrome without ST elevation: a meta-analysis. *Lancet* 2000; **355**: 1936–42

31 Goodman SG, Cohen M, Bigonzi F *et al*. Randomized trial of low molecular weight heparin (enoxaparin) versus unfractionated heparin for unstable coronary artery disease: one-year results of the ESSENCE Study. Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q Wave Coronary Events. *J Am Coll Cardiol* 2000; **36**: 693–8

32 The Global Use of Strategies To Open occluded coronary arteries (GUSTO) IIb investigators. A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndromes. *N Engl J Med* 1996; **335**: 775–82

33 The Organisation to Assess Strategies for Ischemic Syndromes (OASIS-1) investigators. Comparison of the effects of two doses of recombinant hirudin compared with heparin in patients with acute myocardial ischemia without ST elevation: a pilot study. *Circulation* 1997; **96**: 769–77

34 The Organisation to Assess Strategies for Ischemic Syndromes (OASIS-2) investigators. Effects of recombinant hirudin (lepirudin) compared with heparin on death, myocardial infarction, refractory angina, and revascularisation procedures in patients with acute myocardial ischaemia without ST elevation: a randomised trial. *Lancet* 1999; **353**: 429–38

35 Greinacher A, Lubenow N. Recombinant hirudin in clinical practice : focus on lepirudin. *Circulation* 2001; **103**: 1479–84

36 Mark DB, Cowper PA, Berkowitz SD *et al*. Economic assessment of low-molecular-weight heparin (enoxaparin) versus unfractionated heparin in acute coronary syndrome patients:
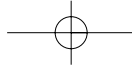
results from the ESSENCE randomized trial. Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q wave Coronary Events. *Circulation* 1998; **97**: 1702–7

37 Stone PH, Gibson RS, Glasser SP *et al*. Comparison of propranolol, diltiazem and nifedipine in the treatment of ambulatory ischemia in patients with stable angina. *Circulation* 1990; **82**: 1962–72

38 Dargie HJ, Ford I, Fox KM. Total Ischaemic Burden European Trial (TIBET). Effects of ischaemia and treatment with atenolol, nifedipine SR and their combination on outcome in patients with chronic stable angina. *Eur Heart J* 1996; **17**: 104–12

39 Freemantle N, Cleland J, Young P, Mason J, Harrison J. β-blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ* 1999; **318**: 1730–7

40 Yusuf S, Wittes J, Friedman L. Overview of results of randomized clinical trials in heart disease. II. Unstable angina, heart failure, primary prevention with aspirin, and risk factor modification. *JAMA* 1988; **260**: 2259–63

41 Cotter G, Metzkor E, Kaluski E *et al*. Randomised trial of high-dose isosorbide dinitrate plus low-dose furosemide versus high-dose furosemide plus low-dose isosorbide dinitrate in severe pulmonary oedema. *Lancet* 1998; **351**: 389–93

42 Friedensohn A, Meshulam R, Schlesinger Z. Randomised double-blind comparison of the effects of isosorbide dinitrate retard, verapamil sustained-release, and their combination on myocardial ischaemic episodes. *Cardiology* 1991; **79 (Suppl 2)**: 31–40

43 Chrysant SG, Glasser SP, Bittar N *et al*. Efficacy and safety of extended release isosorbide mononitrate for stable effort angina pectoris. *Am J Cardiol* 1993; **72**: 1249–56

44 Lubsen J, Tijssen JG. Efficacy of nifedipine and metoprolol in the early treatment of unstable angina in the coronary care unit: findings from the Holland Interuniversity Nifedipine/metoprolol Trial (HINT). *Am J Cardiol* 1987; **60**: 18A–25A

45 The Danish Study Group on Verapamil in Myocardial Infarction. Effect of verapamil on mortality and major events after acute myocardial infarction (The Danish Verapamil Infarction Trial – DAVIT II). *Am J Cardiol* 1990; **66**: 779–85

46 The Multicenter Diltiazem Post Infarction Trial (MDPIT) research group. The effect of diltiazem on mortality and reinfarction after myocardial infarction. *N Engl J Med* 1988; **319**: 385–92

47 Patel DJ, Purcell HJ, Fox KM. Cardioprotection by opening of the K(ATP) channel in unstable angina. Is this a clinical manifestation of myocardial preconditioning? Results of a randomized study with nicorandil. CESAR 2 investigation. Clinical European studies in angina and revascularization. *Eur Heart J* 1999; **20**: 51–7

48 Stone PH, Thompson B, Zaret BL *et al*. Factors associated with failure of medical therapy in patients with unstable angina and non-Q wave myocardial infarction. A TIMI-IIIB database study. *Eur Heart J* 1999; **20**: 1084–93

49 Antman EM, Cohen M, Bernink PJ *et al*. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA* 2000; **284**: 835–42

50 Braunwald E, Antman EM, Beasley JW *et al*. ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). *J Am Coll Cardiol* 2000; **36**: 970–1062

51 Anderson HV, Cannon CP, Stone PH *et al*. One year results of the Thrombolysis In Myocardial Infarction (TIMI) IIIB clinical trial: a randomized comparison of tissue-type plasminogen activator versus placebo and early invasive versus early conservative strategies in unstable angina and non-Q wave myocardial infarction. *J Am Coll Cardiol* 1995; **26**: 1643–50

53 The RITA-2 Trial Participants. Coronary angioplasty versus medical therapy for angina: the second Randomised Intervention Treatment of Angina (RITA-2) trial. *Lancet* 1997; **350**: 461–8

52 Boden WE, O'Rourke RA, Crawford MH *et al*. Outcomes in patients with acute non-Q wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy: Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) trial investigators. *N Engl J Med* 1998; **338**: 1785–92
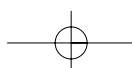
54 Yusuf S, Flather M, Pogue J *et al* for the OASIS registry investigators. Variations between countries in invasive cardiac procedures and outcomes in patients with suspected unstable angina or myocardial infarction without initial ST elevation. *Lancet* 1998; **352**: 507–14

55 Wallentin L, Lagerqvist B, Husted S, Kontny F, Ståhle, Swahn E for the FRISC II investigators. Outcome at 1 year after invasive compared with a non-invasive strategy in unstable coronary-artery disease: the FRISC II invasive randomised trial. *Lancet* 2000; **356**: 9–16

56 Yusuf S, Zucker D, Peduzzi P *et al*. Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. *Lancet* 1994; **344**: 563–70

57 Schwartz GG, Olsson AG, Egekowitz MD *et al*. Effects of atonastatin on early recurrent ischemic events in acute coronary syndromes. JAMA 2001; 285:1711–18