Critical review of unstable angina and non-ST elevation myocardial infarction

P J Sheridan, D C Crossman

Within the coronary vasculature the progression of a stable atherosclerotic plaque into a vulnerable and ultimately unstable lesion leads to a cascade of events culminating in the clinical presentation of unstable angina or acute myocardial infarction. In recent years studies have provided new insights in to the pathology and natural history, stimulating advances in diagnosis, treatment, and management. The review discusses the progress made including the role of inflammation, cardiac biomarkers, antiplatelet therapy, and percutaneous intervention. Current issues of debate and future directions are also addressed.

NOMENCLATURE

The term acute coronary syndrome encompasses the complete spectrum of clinical syndromes characterised by acute coronary ischaemia and includes unstable angina, non-ST elevation myocardial infarction (NSTEMI), and ST elevation myocardial infarction (STEMI). Patients presenting with ST segment elevation or new left bundle branch block on an electrocardiogram are diagnosed with STEMI, indicative pathologically as a transmural myocardial infarction usually arising from complete occlusion of an epicardial coronary artery. These patients require urgent reperfusion therapy. Both the European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association (ACC/AHA) have issued guidelines for the management of this distinct group. Patients presenting with acute coronary syndrome without ST segment elevation on the electrocardiogram are classified as having unstable angina or NSTEMI depending on the absence or presence of biochemical markers of myocardial necrosis, respectively. Raised creatine kinase and the isoenzyme CK-MB have been the conventional indices of myocardial injury; however, the elevation of the more sensitive and myocardial specific cardiac troponins is now classified as NSTEMI by the ESC and ACC. It is estimated 30% of patients previously labelled with unstable angina with normal creatine kinase/CK-MB have raised troponins and it is clear that these creatine kinase negative troponin positive patients are at increased risk. The distinction between unstable angina and NSTEMI is therefore retrospective, although valuable in terms of prognosis has less significance on initial management. This is reflected in the combined unstable angina/NSTEMI guidelines published by the British Cardiovascular Society (BCS), the ACC/AHA, and the recommendations of the ESC (see fig 1).

PATHOPHYSIOLOGY

Acute coronary syndrome develops because of an imbalance between myocardial oxygen demand and supply and most usually this is a reduction in supply. Unstable angina and NSTEMI are usually caused by the common pathophysiological mechanism of the unstable atherosclerotic plaque, resulting in the formation of either a non-occlusive thrombus or complete thrombosis of a vessel supplying a well collateralised area. Coronary vasoconstriction of the epicardial coronary segment that is unstable or of the distal microvasculature as well as distal embolisation to the microcirculation undoubtedly contribute to the overall process and have become important targets for therapy. Plaque based mechanisms Pathological studies arising from autopsy specimens have clearly shown that thrombus formation in acute coronary syndrome is associated with plaque disruption. The culprit plaque in two thirds of these cases is characterised by rupture of the plaque cap into the highly thrombogenic tissue factor rich lipid core. In the remaining one third the culprit lesion is characterised by superficial plaque erosion, where there is loss of endothelium with exposure to the thrombogenic subendothelial matrix. In both cases there is platelet activation arising from the exposure of an abnormal surface in the presence of disturbed flow and exposure of tissue factor, the essential cofactor for the activation of the external pathway of the coagulation cascade. Before the development of features that indicate instability atherosclerotic plaques are a relatively benign process enlarging at least initially in an outward direction (compensatory enlargement). Even when the mechanisms of compensatory enlargement are overwhelmed plaques with thick vascular smooth muscle cell and collagen rich caps are remarkably stable and are the substrate for chronic stable angina. For this
reason the hunt for the vulnerable plaque has become a hot topic.

The natural history of atheromatous coronary artery disease is neither simple nor a linear process. The Coronary Artery Surgery Study has shown that the degree of stenosis is significantly correlated with lesion progression and subsequent occlusion, but this does not necessarily bring about presentation with an acute coronary syndrome, presumably because of the development of collaterals. In order to characterise vulnerable lesions, several studies have compared the coronary angiograms of patients who have had angiography before and after presentation with an acute coronary syndrome. Although one third of occlusions occur at the site previously exhibiting the greatest stenosis, the majority (66%–78%) arise from lesions with <50% stenosis and less than 5% arise from lesions exhibiting >70% stenosis. Importantly, lesion stenosis is not correlated with time to presentation with an acute coronary syndrome and is a poor predictor of future events. It is plausible that the well collaterised supply to myocardium subtended by a vessel with a severe stenosis conveys some degree of protection. Luminal encroachment determined by angiography is not necessarily a surrogate for plaque size and qualitative assessment of the plaque and vessel may provide more valuable insights. A recent study using intravascular ultrasound to compare patients with stable and unstable angina, revealed complex plaque morphology and unstable presentation to be associated with lesion progression. Interestingly, it was observed that unstable lesions demonstrated less stenosis despite greater atherosclerotic burden compared with stable lesions. This apparent paradox is explained by the unstable lesions demonstrating an increased capacity for compensatory enlargement (positive remodelling).

Detection of vulnerable plaques may not, however, be easy or even possible. There are currently considerable efforts to detect isolated “hot lesions” and one strategy has been to light the vessel irrespective of whether they traverse the culprit lesion or not. In summary, the evidence indicates biological processes beyond the single vulnerable lesion exert a powerful influence over the natural history of an atherosclerotic plaque.

Factors that precipitate or “trigger” disruption of a vulnerable plaque are relatively poorly understood. Undoubtedly physical stresses such as circumferential wall stress, plaque composition, the quality of the fibrinous cap, and haemodynamic forces are critical and explain the excess of presentations of acute coronary syndrome after severe physical activity and probably explain the rare cases of acute coronary syndrome after dobutamine stress echocardiography.

The role of inflammation in atherosclerosis has become established, and over the last decade we have started to recognise the role of inflammation in plaque instability and disease presentation.

Plasma markers of inflammation such as C-reactive protein and serum amyloid have been shown to relate to outcome in coronary disease. Small “elevations” within the normal range (the upper quartile and quintile of the normal distributions) are indicative of future coronary events in a wide variety of patient groups including those without any history of coronary disease. Additionally, C-reactive protein elevations that are low are more strongly associated with the higher risk (in contrast to the “elevations” mentioned above) for the laboratory and are independent of myocardial necrosis, have been found to be indicative of future coronary events. Indeed, C-reactive protein elevation in patients with unstable angina/NSTEMI is more frequent than in those presenting with unheralded STEMI.

Vulnerable plaques typically contain a large lipid core protected by a thin, collagen poor fibrous cap. Plaque rupture usually occurs at the weakest and thinnest part of the cap, often at the shoulder region. Ruptured plaques contain very large numbers of inflammatory cells specifically of the monocyte/macrophages lineage and T lymphocytes that are concentrated at these sites. Proteolytic enzymes called matrix metalloproteinases (MMP) are produced by macrophages which degrade the fibrous cap and their expression is increased in the atheromatous plaques. Activated T lymphocytes stimulate MMP production by macrophages further weakening the cap. Activated T lymphocytes may also stimulate MMP production by vascular smooth muscle cells (VSMC). The integrity of the fibrous cap is dependent on collagen synthesis, principally the role of VSMC. In unstable plaques there are reduced numbers of VSMC, greater rates of apoptosis and reduced proliferation with VSMC senescence. Stimulated macrophages and VSMC in unstable plaques exhibit increased expression of tissue factor, triggering an enhanced thrombogenic response. Platelet adhesion, aggregation, and activation result in local release of vasoconstrictors like serotonin and thromboxane, coupled with mild endothelial dysfunction inducing coronary vasospasm, increasing

Figure 1 Classification of acute coronary syndrome.
local shear stress, and encouraging further intimal injury. Monocyte/macrophages can induce VSMC apoptosis further weakening the fibrous cap.

Monocytes and T lymphocytes are attracted to the lesion by chemokines and the interaction of adhesion molecules on the surface of endothelial cells with their counter ligands on leukocytes. These endothelial cell adhesion molecules include vascular cell adhesion molecule-1, intercellular adhesion molecule-1, E-selectin, and P-selectin. Increased expression of adhesion molecules has been observed on endothelial cells overlying atherosclerotic plaques.\(^{15-17}\) These mechanisms seem to present at most stages of atherosclerosis and it is unclear whether there is an additional burst of recruitment before instability or merely activation of the cells that are already resident. Results measuring serum levels of adhesion molecules have had inconclusive predictive value in coronary patients and this may indicate that additional bursts of recruitment are not required for the induction of plaque instability (see table 1).

**Non-plaque based mechanisms**

As outlined above plaque disruption is the commonest cause of all forms of acute coronary syndrome. However, there are clearly situations where plaque instability has not preceded presentation with acute coronary syndrome. In a large study of over 5000 patients recruited with unstable angina/NSTEMI who had angiography, 12% had no identifiable angiographic lesion. Any process that creates a mismatch of myocardial oxygen supply and demand may precipitate these clinical syndromes (see table 2). In these angiographic studies it is presumed that there has been transient constriction of microvascular vessels such that the coronary flow reserve becomes negative (that is, insufficient for normal activity). Equally most clinicians are aware of patients who have become anemic presenting with acute coronary syndrome usually as unstable angina, but on occasions NSTEMI may occur. There are no implications of plaque instability in these patients and indeed they settle usually by discontinuation of antiplatelet therapy and blood transfusions.

It should be acknowledged therefore that any number of these processes may be relevant in any single individual and clinical assessment of patients presenting with acute coronary syndrome should be aimed at identifying any of these contributory factors.

**PROGNOSIS AND RISK STRATIFICATION**

The common pathobiology of plaque disruption should be contrasted to the diverse clinical outcome of unstable angina, NSTEMI, and STEMI. The in-hospital mortality of unstable angina is low and the one year mortality approaches that found in chronic stable angina 1.6%.\(^{14}\) The in-hospital mortality of STEMI is high with real world figures from UK coronary care units at 15%–20%. The in-hospital mortality of NSTEMI is lower than STEMI (7%) but between one month and one year the mortality of NSTEMI patients equals or even exceeds STEMI patients. Some of this late increase in NSTEMI mortality arises from the increased age of these patients but even after correction for this NSTEMI has a high long term mortality rate. Certainly there is no room for complacency and reassurance to the patient that they are fortunate to have only had a small heart attack is only justified if aggressive action immediately follows presentation (see below).

None the less these patients represent a large group of medical emergencies. Risk stratification is critical to evaluate treatment options and guide the management of the individual patient. A clinical benefit observed in a clinical trial, recruiting a heterogenous cohort of patients with unstable angina/STEMI may represent a modest benefit throughout the group or a large effect in a high risk subgroup. Similarly, a substantial benefit gained by a small, high risk subgroup may be masked by absence of effect in the larger population. These issues are important for the interpretation of clinical trials and in order to direct treatment with maximal effect

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**Table 1** Cellular changes contributing to plaque instability

<table>
<thead>
<tr>
<th>Vascular smooth muscle cells</th>
<th>Endothelial cells</th>
<th>Tissue macrophage/microphage</th>
<th>T lymphocytes</th>
<th>Platelets</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ Apoptosis</td>
<td>↑ Adhesion molecule expression</td>
<td>↑ MMP synthesis</td>
<td>Stimulate macrophage</td>
<td>Vasconstrictor release</td>
</tr>
<tr>
<td>↑ Senescence</td>
<td>↓ Proliferation</td>
<td>↑ TF expression</td>
<td>MMP synthesis</td>
<td>Release</td>
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<tr>
<td>↑ MMP synthesis</td>
<td>↑ TF expression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓ TF expression</td>
<td>↓ Collagen synthesis</td>
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MMP, matrix metalloproteinases; TF, tissue factor.

**Table 2** Aetiology of myocardial ischaemia

<table>
<thead>
<tr>
<th>Coronary</th>
<th>Non-coronary</th>
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<tbody>
<tr>
<td>Intravascular</td>
<td>↑ Oxygen demand</td>
</tr>
<tr>
<td>Unstable atherosclerotic plaque</td>
<td>Increased heart rate</td>
</tr>
<tr>
<td>(plaque erosion or rupture causing thrombosis)</td>
<td>Thyrotoxicosis</td>
</tr>
<tr>
<td>Coronary embolus</td>
<td>Pyrexia</td>
</tr>
<tr>
<td>Vascular</td>
<td>Tachyarrhythmia</td>
</tr>
<tr>
<td>Epicardial vasoconstriction (Prinzmetal’s angina)</td>
<td>Increased inotropy</td>
</tr>
<tr>
<td>Microcirculation vasoconstriction</td>
<td>Sympathomimetic drugs</td>
</tr>
<tr>
<td>Spontaneous coronary dissection</td>
<td>Cocaine intoxication</td>
</tr>
<tr>
<td>Coronary vasculitis</td>
<td>Increased afterload</td>
</tr>
<tr>
<td>Coronary anomaly</td>
<td>Aortic stenosis</td>
</tr>
<tr>
<td></td>
<td>Systemic hypertension</td>
</tr>
<tr>
<td></td>
<td>↑ Oxygen supply</td>
</tr>
<tr>
<td></td>
<td>Anoxia</td>
</tr>
<tr>
<td></td>
<td>Hypoxaemia</td>
</tr>
<tr>
<td></td>
<td>Hypotension</td>
</tr>
<tr>
<td></td>
<td>Hyperviscosity states</td>
</tr>
</tbody>
</table>
Clinical assessment

Clinical assessment of the patient is imperative to substantiate or refute the diagnosis and to identify causes extrinsic to the coronary vasculature that may be exacerbating myocardial ischaemia and that will require specific and quite separate management. History and examination will provide the most valuable indicators of risk and long term prognosis in the patient presenting with unstable angina/NSTEMI.

The Braunwald classification emphasises the importance of rest pain, particularly within the previous 48 hours, and post-infarction angina, both reflecting continued plaque instability. Multivariate analysis in unstable angina/NSTEMI has consistently shown advanced age, male sex, prior history of coronary artery disease and comorbidity, including diabetes, hypertension, dyslipidaemia and renal failure, to be associated with the poorest outcome.17 These factors are likely to be linked to advanced atherosclerosis and multivessel disease.

Examination may reveal evidence of left ventricular failure18 manifest as pulmonary oedema, hypotension, a third heart sound, or mitral incompetence that suggest the area of myocardium subtended by the threatened artery is large or that myocardial function has been embarrassed by a prior ischaemic insult. These all translate into increased mortality.

Electrocardiogram

In addition to excluding STEMI the electrocardiogram may risk stratify patients at the point of presentation. In one study of nearly 10 000 patients admitted with unstable angina/NSTEMI, ST segment depression and T wave inversion were significant clinical predictors of death or myocardial infarction.18 ST segment depression appears to be consistently important, and a smaller study with a >2 year follow up period calculated hazard ratios for a normal electrocardiogram, T wave inversion, and ST depression as 0.47, 1.38 and 1.91, respectively.19 A normal electrocardiogram therefore is associated with a favourable long term outcome.

Cardiac specific troponins

Troponins are complexed to actin filaments in striated muscle and consist of troponin T, troponin I, and troponin C and less than 6% is cytoplasmic. Specific isoforms are expressed in the cardiac myofibril that are released after an ischaemic insult, resulting in raised serum levels within 4–8 hours and because release comes mainly from a non-cytoplasmic compartment of the cell raised levels may persist for many days (making the diagnosis of reinfarction difficult with this marker). Cardiac troponins are both more specific and sensitive than conventional indices of myocardial injury. Cardiac troponins have clearly increased the number of patients diagnosed with NSTEMI and have allowed the true distinction between unstable angina and NSTEMI to emerge. It is now clear that patients with a positive troponin and a negative creatinine kinase or equivalent are still at increased risk compared with those with neither biomarker detectable at raised levels. The specificity and sensitivity has allowed troponin measurement to become one of the most important methods of risk stratification in this condition. Randomised controlled studies have demonstrated the elevation of troponin T18 or troponin I53 to be an independent and proportionate marker of adverse outcome. The GUSTO IIA investigators found that, of 801 patients with unstable angina/NSTEMI on admission, 289 patients with baseline serum samples had raised troponin T levels (> 0.1 µg/l). Mortality within 30 days was significantly higher in these patients than in patients with lower levels of troponin T (11.8% v 3.9%, p < 0.001).57

The biological substrate for troponin elevation is likely to be multifactorial; however, a recent angiographic substudy of the FRISC II study has correlated it with coronary stenosis, intracoronary thrombus, left main stem disease, and multivessel disease.58

A number of uncertainties remain however regarding troponin levels. While absolutely negative levels appear to be associated with a good outcome the role of only small elevations remains unclear.

The BCS appropriates risk to troponin T level of <0.01 µg/l, 0.01–0.1 µg/l, and >0.1 µg/l as low, intermediate or high, respectively. The data, however, from the trials are limited for this as the risk may vary at these low levels between death, future myocardial infarction, or a combined endpoint in some of the trials. In the context of an acute coronary syndrome it may be best to separate negative and positive results and discriminate thereafter using additional tests such as the exercise test as well as the clinical markers.

The significance of low troponin elevations without apparent clinical events after percutaneous coronary interventions is far from certain and beyond the scope of this article.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Clinical markers and biological determinants of risk</th>
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<tbody>
<tr>
<td><strong>History</strong></td>
<td><strong>Biomarkers</strong></td>
</tr>
<tr>
<td>Rest pain</td>
<td>Continued plaque instability</td>
</tr>
<tr>
<td>Pain in previous 48 hours</td>
<td></td>
</tr>
<tr>
<td>Comorbidity</td>
<td>Advanced atherosclerotic disease and high risk of multivessel disease</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
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<tr>
<td>Systemic hypertension</td>
<td></td>
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<tr>
<td>Dyslipidaemia</td>
<td></td>
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<tr>
<td>Renal failure</td>
<td></td>
</tr>
<tr>
<td>Examination</td>
<td></td>
</tr>
<tr>
<td>Signs of LV failure</td>
<td>Culprit lesion subtends large myocardial area or background of previous LV impairment</td>
</tr>
<tr>
<td>Electrocardiography</td>
<td></td>
</tr>
<tr>
<td>ST depression</td>
<td>Greater volume of ischaemic myocardium</td>
</tr>
<tr>
<td>T wave inversion</td>
<td></td>
</tr>
<tr>
<td>Biomarkers</td>
<td></td>
</tr>
<tr>
<td>Raised cardiac troponins</td>
<td>Myocardial necrosis</td>
</tr>
<tr>
<td>Raised C-reactive protein</td>
<td>High panceoronary inflammation</td>
</tr>
<tr>
<td>Angiography</td>
<td></td>
</tr>
<tr>
<td>Intra coronary thrombus</td>
<td>Disruption of thrombotic/fibrinolytic cascades</td>
</tr>
<tr>
<td>Left main stem disease</td>
<td>Advanced atherosclerotic disease</td>
</tr>
<tr>
<td>Multivessel disease</td>
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</table>

LV, left ventricular.
Exercise testing
For patients with few cardiac risk factors, presenting with atypical chest pain, normal electrocardiography, and cardiac biomarkers a predischARGE exercise test remains a useful diagnostic test. Though much used the amount of data supporting the use of exercise testing for risk stratification in unstable angina is not large. Studies have shown ST segment depression >0.1 mV with or without symptomatic ischaemia at a low workload, irrespective of prescribed antianginal therapy, is associated with an adverse outcome.\textsuperscript{44 45} The number of leads exhibiting electrocardiographic changes, exercise induced arrhythmias, and haemodynamic instability are also considered adverse markers. The lower incidence of coronary artery disease in women and consequent higher false positive rate observed lead to the belief that exercise testing was less reliable in women than men. Recent evidence suggests exercise testing alone,\textsuperscript{46 50} and to a greater extent in combination with other markers, has a high negative and positive predictive value in both sexes. In the FRISC study group, patients were followed up for five months and stratified by troponin and exercise test result performed on a bicycle ergometer.\textsuperscript{51} A group with low risk troponin T levels and a low risk exercise test had 1-year event rate of 2.6%, whereas patients with high risk troponin T levels and a high risk exercise test had a 1-year event rate of 10.1%.\textsuperscript{52} Though many patients presenting with unstable angina/NSTEMI were at high risk for both indices. Whether exercise testing contributes to the management of patients at intermediate risk remains unclear.

C-reactive protein
As previously described raised markers of inflammation, specifically C-reactive protein, in the healthy population have been related to increased future cardiovascular risk and a compelling body of evidence implicates inflammation as causative process behind the presentation of acute coronary syndrome. Several studies have found raised levels of C-reactive protein, independently and in combination with cardiac troponins, at presentation in unstable angina/NSTEMI to be correlated with an adverse outcome.\textsuperscript{55 56} In the TIMI IIA substudy patients with both an early positive rapid troponin T and C-reactive protein >1.55 mg/dl had the highest mortality (9.10%), followed by those with either C-reactive protein >1.55 mg/dl or positive troponin T (4.65%), whereas patients with both a negative troponin T and C-reactive protein <1.55 mg/dl were at very low risk (0.36%).\textsuperscript{57} Although many patients with unstable angina have C-reactive protein levels above the normal range, these small differences in concentration of C-reactive protein within the normal “not overtly inflammatory disease” range require the use of a highly sensitive assay not necessarily available in the clinical arena. Additionally, a recent paper suggested that the predictive value of C-reactive protein may be attenuated or lost by previous treatment with aspirin, limiting the application of this potentially useful tool in the clinical field.\textsuperscript{58} It is clear, however, that C-reactive protein measurements have the potential to identify those individuals who are at high risk of developing an acute coronary syndrome, or those who have sustained an acute coronary syndrome and a high risk of ongoing problems directly attributable to the unstable vessel. What remains unclear is first, the cause of the elevation in the C-reactive protein in these two patient groups, and second, the practical utility of this measurement in day to day clinical practice. The former remains totally unclear. Undoubtedly, genetic factors are going to be important determinants of C-reactive protein level, which has been shown to have high levels of heritability.\textsuperscript{59} On the latter point, despite considerable enthusiasm among physicians who have access to ultrasensitive C-reactive protein measurements in their patients, it has to be recognised that all the studies to date, with the exception of one small study by Liuzzo, have all been retrospective studies. What is urgently needed in this area are prospective studies of “real world” patients.

MEDICAL MANAGEMENT
Established therapy for unstable angina/NSTEMI has two purposes: firstly, to readdress positively the imbalance between myocardial oxygen supply and demand, and secondly, to inhibit thrombus propagation and avoid complete coronary occlusion. β-Blockers and nitrates improve myocardial oxygenation by reducing myocardial oxygen consumption, though nitrates may additionally relieve epicardial coronary spasm and both improve symptoms. Although β-blockers are superior, their efficacy in clinical trials is little studied and in the presence of contraindications, a calcium antagonist such as diltiazem or verapamil is a reasonable alternative. The use of short acting dihydropropyridines alone may best be avoided.

Antithrombotic therapy
Early studies achieved substantial reductions in rates of death and myocardial infarction with antithrombotic therapy. The administration of aspirin lead to a 30%–51% reduction, and in combination with unfractionated heparin, a further 33% in these major endpoints.\textsuperscript{60} These observations confirmed the importance of platelets and thrombosis as key pathogenic mechanisms. Risk of myocardial infarction or cardiac death, compared with 27% in the group expressing high risk for both indices. Whether exercise testing contributes to the management of patients at intermediate risk remains unclear.

ADP receptor antagonists
Clopidogrel (Plavix) is a thienopyridine derivative, related to ticlopidine, which irreversibly blocks ADP-dependent platelet activation (via inhibition of the P2Y12 receptor) of the glycoprotein IIb/IIIa receptor complex, pivotal to fibrinogen binding and platelet aggregation. The CAPRIE study confirmed that in patients with vascular disease, clopidogrel was at least as effective and possibly superior to aspirin at preventing vascular events.\textsuperscript{61} The CURE study examined whether the addition of clopidogrel to aspirin, thereby inhibiting two pathways of platelet activation, would be synergistic.\textsuperscript{62} A total of 12 562 patients presenting with unstable angina/NSTEMI were randomised to aspirin plus placebo or aspirin plus clopidogrel, the latter continued for one year. Combined treatment resulted in a 32% reduction in refractory ischaemia in hospital and a 23% reduction in myocardial infarction. Importantly, there was a 20% reduction in the composite primary endpoint including cardiovascular death. There was a small but significant increase in bleeding, and especially in those undergoing a coronary artery bypass graft as the revascularisation strategy. Therefore, evidence supports the combined use of both antiplatelet agents in acute coronary syndrome, though there must be caution on the timing of its use in those undergoing a coronary artery bypass graft.

Low molecular weight heparin (LMWH)
Unfractionated heparin is a heterogeneous mixture of polysaccharide chains with a molecular weight of 3000 to 30 000 kDa. Various LMWHs can be produced by either chemical or enzymatic cleavage of unfractionated heparin to yield polysaccharides of ∼5000 kDa. Unfractionated heparin has been the standard antithrombotic agent for a range of thromboembolic diseases, including unstable angina/NSTEMI. However, unfractionated heparin has several disadvantages: (1) variable bioavailability usually necessitating intravenous administration, (2) variable anticoagulant effect requiring frequent blood sampling, (3) neutralisation by platelet factor 4 which is released from activated platelets, and (4) potential to induce an immune mediated thrombocytopenia. LMWHs have greater bioavailability than unfractionated heparin, resulting in a more predictable anticoagulant effect. They can be administered by the subcutaneous route and laboratory...
monitoring is rarely necessary. In the context of acute coronary syndrome, LMWHs exhibit comparatively less binding to plasma proteins and inhibition by platelet factor 4 that is likely to favour their pharmacokinetic profile in the acute phase response.

The antiagulant activity of all heparins is dependent on a specific pentasaccharide sequence which binds to anti-thrombin, resulting in a conformational change that accelerates the interaction with thrombin (factor IIa) and activated factor X (factor Xa) by about 1000-fold.36 Second, poly saccharide chains mean the antithrombin activity has a greater affinity to inhibit factor Xa, which is upstream of factor IIa in the coagulation cascade, exerting a greater anti- coagulant effect. There are a number of LMWH preparations available and one can not assume the results from clinical trials of a LMWH can be attributed to a class effect for at least two reasons. First, the anti-Xa:IIa ratio of each LMWH varies from 1.9 for tinzaparin, 2.7 for dalteparin, and to 3.8 for enoxaparin. Secondly, each LMWH stimulates a distinct release profile of tissue factor pathway inhibitor, which opposes activation via the extrinsic pathway during platelet rupture. This point is highlighted by examination of trials with dalteparin and enoxaparin.

The FRISC study showed that in combination with aspirin, dalteparin was superior to placebo in patients with unstable angina/NSTEMI.21 In the FRISC study dalteparin was compared to unfractionated heparin and showed no difference in outcome of ischaemic events at six days, although it was not powered to show equivalence. It has been shown that patients recovering from unstable angina/NSTEMI have continued disruption of their coagulation and fibrinolytic pathways, possibly accounting for their increased risk of recurrent events.22 Both of these trials included a prolonged treatment arm with a lower dose of dalteparin after discharge but failed to show a sustained benefit. One possible explanation for this negative result is that the lower dose of dalteparin was subtherapeutic; hence in the FRISC II study a higher dose of dalteparin administered for three months after discharge achieved a 20% reduction in death and myocardial infarction at 30 days compared to placebo. Although this benefit was lost by three months, the investigators concluded dalteparin could be used to reduce risk while patients await coronary angiography.23

In contrast, two important large randomised control trials, ESSENCE24 and TIMI IIb,25 have shown enoxaparin results in a 20% reduction in death and serious cardiac ischaemic events compared with unfractionated heparin. The benefit is sustained beyond 30 days, even when treatment is confined to the acute phase and is not associated with increased major haemorrhagic complications.

One possible explanation for the apparent superiority of LMWH over unfractionated heparin is the ease of achieving therapeutic anticoagulant levels. For example, in the ESSENCE study between 15% and 20% patients failed to reach a therapeutic activated partial thromboplastin time within 48 hours of starting treatment with unfractionated heparin. Whether the beneficial effects seen are due to the greater attainment of therapeutic range or an improved antithrombotic property of enoxaparin over unfractionated heparin is unclear. However, continued benefit beyond the initial period may favour the latter.

Glycoprotein IIb/IIIa inhibitors

The glycoprotein IIb/IIIa receptor on the surface of an activated platelet has a high affinity for fibrinogen. Binding of fibrinogen to this receptor is the final stage before platelet aggregation and the formation a platelet rich thrombus. From the evidence provided for the beneficial role of antiplatelet therapy in acute coronary syndrome one may anticipate these agents to deliver a profound additional benefit either alone or in combination with other antiplatelet drugs. The glycoprotein IIb/IIIa receptor inhibitors can be broadly divided into two intravenous or oral agents and the intravenous agents divided into those that are monoclonal antibodies to the β3 integrin of the IIb/IIIa receptor (abciximab) or synthetic molecules mimicking the fibrinogen RGD binding sequence either as peptidomimetics (epitibodies) or as small inhibitory molecules (tirofibran and lamifiban). All these molecules have a high affinity for the glycoprotein IIb/IIIa receptor and a short plasma half life (2–6 hours), although the pharmacokinetic profile of abciximab results in significantly prolonged antplatelet activity, at least 24–48 hours after termination of an infusion. The affinity of abciximab for β3 integrin in glycoprotein IIb/IIIa has also been shown to mediate binding to other heterodimeric receptors, notably the αvβ3 receptor found on endothelial and smooth muscle cells and the αmβ2 receptor on leucocytes. These additional properties of abciximab may plausibly relate biological effects distinct from the other glycoprotein IIb/IIIa inhibitors.

Clinical trials have investigated all of the intravenous agents in the context of both acute coronary syndrome and percutaneous coronary interventions. In acute coronary syndrome there have been six large randomised trials comparing IIb/IIIa inhibitors, in combination with conventional antithromplatelet therapy and unfractionated heparin, to placebo. Abciximab in CAPTURE, tirofibran in PRISM and PRISM-PLUS,37 epitibide in PURSUIT,38 and lamifiban in PARAGON A and PARAGON B.39 Although these trials have shown statistically significant reductions in composite endpoint including death, myocardial infarction and refractory ischaemia, the degree of benefit has been inconsistent. The magnitude of benefit was greatest in patients receiving early percutaneous revascularisation. Raised troponin levels, male sex, and diabetes have all been correlated with greater benefit from glycoprotein IIb/IIIa receptor inhibition and it seemed that the recommendations from these trials would be to use these agents in patients with raised troponins as a marker of risk. However, the more recent GUSTO IV acute coronary syndrome trial, where patients in whom there was no specific plan to proceed to percutaneous coronary interventions were randomised to abciximab, showed no benefit from this agent even in diabetics and those with positive troponins.40 Meta-analysis of all of these trials shows a small and just statistically significant advantage of IIb/IIIa inhibition, but this may be too small for its universal recommendation in routine acute coronary syndrome. However, there is little doubt regarding the efficacy of these agents when given at the time of percutaneous coronary interventions either electively or in the context of acute coronary syndrome. As a result it may be that the place of these agents may for those who are scheduled for percutaneous coronary interventions as a result of their presenting with acute coronary syndrome.

There has been some concern over the combining of IIb/IIIa inhibitors with LMWH but the recently presented INTERACT trial (ACC 2002) the combination of LMWH and glycoprotein IIb/IIIa inhibitor appears safe.

The qualified success of the intravenous IIb/IIIa inhibitors suggested that the introduction of oral agents prescribed for a prolonged period after disruption of a vulnerable plaque may reduce the high rates of recurrence. A meta-analysis of four trials examining three different oral agents sibrafiban, xemilofiban, and orfebiban showed a 31% increase in mortality in treated patients compared with placebo.41 The mechanism of this adverse effect is unclear but is unlikely to be due to inadequate inhibition as the treated groups were characterised by increased bleeding complications also. These agents have comparatively poor bioavailability and the effects may be in part explained by the periodicity of under and over treatment. It has also been suggested that partial agonism by these synthetic ligands during phases of under treatment may precipitate an acute thrombotic event. While the development
of oral agents with improved bioavailability may address these
problems other concerns exist. Molecules containing an RGD
binding sequence have been shown to induce apoptosis79 and
one may hypothesise these agents have a direct toxic effect on
vascular cells, promoting plaque instability.

In summary intravenous glycoprotein IIb/IIIa inhibitors
should be used in high risk patients and in particular those
undergoing percutaneous coronary interventions. The oral
agents may be detrimental and improved bioavailability in
newer preparations may still result in poor outcomes due to a
plausible intrinsic harmful property.

Plaque stabilisation
An appreciation of the mechanisms involved in plaque insta-
bility and the continued risk that these patients carry
highlights the limitations of antithrombotic therapy alone in
an acute coronary syndrome. The ideal pharmacological agent
would both inhibit local thrombus formation and produce a
wider effect of plaque stabilisation or “passivation”. From
clinical trial data it has been shown that lipid lowering with
statins reduces cardiovascular events. A possible mechanism
for this effect is stabilisation of the atherosclerotic plaque.
Statins may lead to improvements in endothelial function,
decreased propensity for platelet thrombus formation, and
reduced inflammation.80 In a substudy of the CARE trial, mean
C-reactive protein levels increased over a time period of five
years in patients treated with placebo, compared with a
decrease observed in patients prescribed pravastatin.81 In the
MIRAACL study, 3086 patients with recent acute coronary syn-
drome were randomised to atorvastatin 80 mg/day or placebo
for 16 weeks. Although there was no significant difference in
rates of death or myocardial infarction, perhaps due to the
short period of follow up, there was a significant reduction in
symptomatic ischaemia and hospitalisation. Therefore, there
is good reason to believe that statins convey a beneficial effect
in unstable angina/NSTEMI.

Angiotensin converting enzyme inhibitors are a second
class of drugs that may improve endothelial function and
mediate a beneficial effect. Compelling evidence comes from
the HOPE trial in which nearly 10 000 patients at risk of
cardiocvascular disease were randomised to ramipril or
placebo.82 Over a five year follow up period the ramipril treated
group had a significant 26% reduction in cardiovascular death,
a 20% reduction in myocardial infarction, and an 11% reduc-
tion in worsening angina. These impressive results have
couraged the use of angiotensin converting enzyme inhibi-
tors in acute coronary syndromes. One caveat to this enthusi-
amism is that the rate of unstable angina presentation was not
significantly reduced in the ramipril treated group, although
this was not a primary outcome measurement.

CARDIAC CATHETERISATION
Insight into the pathobiology and natural history of acute coro-
nary syndromes has highlighted the coronary vasculature as a
legitimate target for disease modification. Rapid develop-
ment of catheter based procedures has resulted in improved
outcomes and prompted wider application of percutaneous
coronary interventions. Over the last decade, two strategies
have evolved concerning the role of percutaneous coronary
interventions in unstable angina/NSTEMI. The early invasive
strategy presupposes that non-invasive methods of risk stratifi-
cation are inherently imperfect and that early delineation of
the coronary anatomy efficiently guides future management,
limiting subsequent hospital readmissions. Proponents of this
approach would anticipate catheterisation of >90% of patients
admitted with acute coronary syndrome within 48 hours. The
conservative strategy incorporates a range of clinical determi-
nants including non-invasive stress testing to identify at risk
patients. These selected patients are then referred for
angiography and revascularisation as appropriate. The advan-
tages of the latter approach are that low risk patients are not
subject to an invasive, potentially hazardous procedure.

Two early large trials, TIMI IIB83 and VANQWISH84 failed to
show superiority of the invasive approach over a conservative
strategy. Indeed, VANQWISH showed a significant increase
in death and non-myocardial infarction in the invasive
group however much of this arose from the surprisingly high
mortality in the patients referred for coronary artery bypass
graft (11%). Both of these trials recruited in the early 1990s
before LMWH, glycoprotein IIb/IIIa inhibitors, or coronary
stenting were the clinical standard and had very high rates of
crossovers between the groups. Two more recent trials may
relate more readily to current practice. In the FRISC II study,
2457 patients admitted with acute coronary syndrome were
treated with standard medical therapy including LMWH and
randomised to an early invasive or conservative strategy.85 The
primary endpoint of death or non-fatal myocardial infarction
was reached by 9.4% of patients in the invasive group
compared with 12.1% in the conservative group, representing
a 22% relative risk reduction. The FRISC II results contrast
with those of earlier trials and this may be due to firstly, a
greater difference in the catheterisation rates between
two treatment arms and, secondly, improved procedural
experience. Interestingly, even in FRISC II cardiac events
occurred more frequently in the percutaneous coronary inter-
vention group in the first two weeks, possibly suggesting
intervention encourages plaque instability in the short term
before later benefit accrues. Notably only 10% of patients were
administered abciximab during percutaneous revascularisa-
tion. In the TACTICS-TIMI-18 study, 2220 patients presenting
with acute coronary syndrome were given unfractionated
heparin and the glycoprotein IIb/IIIa inhibitor, tirofiban, for 48
hours.86 Once again there was a statistically significant reduc-
tion in death and myocardial infarction with the invasive
compared to the conservative strategy. It would be simplistic
to conclude that these trials display contradictory results.

Subgroup analysis of both FRISC II and TACTICS-TIMI-18
demonstrate statistically significant benefit only in high risk
groups with raised troponin levels and ST depression on the
electrocardiogram. Similarly a post hoc analysis of the earlier
TIMI IIB showed a benefit from the invasive approach in two
subgroups stratified according to risk.87 The latter stud-
ies support a more aggressive approach than previously
deployed in the UK, cost analysis continues to suggest that the
high initial cost of the invasive approach is only partly offset
by increased hospital readmissions in the conservative
strategy.88 Even if the cost effectiveness of the interventional
strategy is accepted it will be a challenge to implement in the
UK which already has one of the lowest angiography rates in
Europe.89 Over 80% of patients with acute coronary
syndrome present to hospitals which do not have facilities for
cardiac catheterisation, necessitating efficient transfer to
and/or an appreciable expansion of interventional units. Ulti-
mately, provision of a therapeutic intervention depends on
the resource limitations within a particular health care system.

FUTURE
It is likely that there will be further progress in risk stratifica-
tion over the next decade combining cardiac troponins possi-
bly with biomarkers of systemic inflammation, notably C-
reactive protein. Ultimately it may be possible to quantify risk
on a genetic level. Other antithrombotic agents such as direct
thrombin inhibitors and new antiplatelet agents may emerge.
Plaque passivation is likely to be subject to even greater focus
with attention turning to plausible disease modifiers that
inhibit inflammatory cells and MMP. One can anticipate a
more interventional approach in a well defined high risk
group and the possibility of catheter based local drug delivery
to promote plaque stabilisation.
Equally, the future poses problems for health care workers, challenging them to deliver known beneficial therapies to the appropriate group of patients as expeditiously as possible. Full implementation of the best preventative (primary or secondary) treatments will be a huge challenge logistically and economically. Additionally, the facilitation of prompt revascularisation poses considerable practical problems that must require the current working practices of cardiologists to change.

QUESTIONS (ANSWERS AT END OF PAPER)
1. Regarding acute coronary syndromes, which of the following statements are correct?
(A) Acute coronary syndrome is an umbrella term used for unstable angina and non-ST elevation myocardial infarction
(B) Acute coronary syndrome encompasses a range of clinical diagnoses with common pathological aetiologies and similar prognoses
(C) The presentation of acute coronary syndrome with a normal electrocardiogram and plasma CK-MB refutes the diagnosis of NSTEMI
(D) Cardiac troponin measurement is important for immediate management
(E) Anaemia leading to decreased myocardial perfusion never causes myocardial necrosis

2. The following would suggest a favourable prognosis in the context of acute coronary syndrome:
(A) NSTEMI as opposed to STEMI
(B) Absence of rest pain in clinical history
(C) Diabetes mellitus
(D) Normal electrocardiogram
(E) Normal troponin level

3. A 70 year male with an acute coronary syndrome and ST depression on the electrocardiogram and raised troponin levels should be treated with:
(A) Aspirin
(B) Clopidogrel
(C) β-Adrenoreceptor antagonist
(D) Calcium channel antagonist
(E) Heparin

4. Regarding antithrombotic treatment for unstable angina/NSTEMI:
(A) Clinical trial data has confirmed the superiority of unfractionated heparin and aspirin over placebo
(B) Clinical trial data demonstrates a benefit from the addition of clopidogrel in patients already taking aspirin.
(C) LMWH is superior to unfractionated heparin and aspirin over placebo
(D) Intravenous glycoprotein IIb/IIIa inhibitors benefit all patients
(E) Should be performed with intravenous glycoprotein IIb/IIIa inhibitor therapy

Authors’ affiliations
P J Sheridan, D C Crossman, Northern General Hospital, Sheffield, UK

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Unstable angina and non-ST elevation myocardial infarction


NSTEMI or STEMI.

causes may cause or contribute to reduced perfusion and is characterised by intense coronary spasm and non-coronary causes. Both Prinzmetal’s angina and NSTEMI are usually caused by plaque instability.

Although acute coronary syndrome is rather than CK-MB are used to differentiate between unstable and stable syndromes. The electrocardiogram is critical to immediate management to exclude STEMI and biochemical for Acute Coronary Treatment.


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Acute coronary syndrome is term used to encompass unstable angina, NSTEMI, and STEMI. Although these diagnoses share the common pathophysiology of the unstable atherosclerotic plaque, the prognosis varies greatly and hence the importance of risk stratification. The electrocardiogram is critical to immediate management to exclude STEMI and biochemical markers assist subsequent management. Cardiac troponins rather than CK-MB are used to differentiate between unstable angina and NSTEMI. Although acute coronary syndrome is usually caused by plaque instability, both Prinzmetal’s angina characterised by intense coronary spasm and non-coronary causes may cause or contribute to reduced perfusion and NSTEMI or STEMI.

Although the inhospital mortality of STEMI exceeds that of NSTEMI mortality rates over the subsequent 6–12 months catch up and may even surpass that of STEMI. Risk factors associated with coronary artery disease such as diabetes mellitus, dyslipidaemia, and hypertension have all been correlated with an adverse prognosis. ST wave abnormalities on the electrocardiogram have been correlated with an increased hazard ratio, a normal electrocardiogram has a ratio <1.0. Elevations in troponin levels correlate to increased risk.

Unless contraindicated the patient should receive aspirin, clopidogrel, β-blockers, and LMWH. Calcium channel antagonists may be used if β-blockade is contraindicated. Intravenous nitrates may also alleviate symptoms.

Trial data have confirmed a benefit for aspirin, clopidogrel, and heparins in unstable angina/NSTEMI. The CURE study found a 20% reduction in a composite primary endpoint by the addition of clopidogrel to aspirin. Patients enrolled in this study had either abnormal electrocardiography or raised troponins. Only enoxaparin has been shown to be superior to unfractionated heparins during the acute phase of unstable angina/NSTEMI. Intravenous glycoprotein IIb/IIIa inhibitors have only been shown to convey benefit in patients undergoing percutaneous coronary interventions and oral agents have been associated with increased mortality.

These are the groups of patients recognised by the BSC, ESC, and AHA/ACC that are likely to benefit most from urgent catheterisation and revascularisation. Other criteria to identify are recent percutaneous coronary interventions, previous coronary artery bypass graft and associated ventricular arrhythmia. Analysis of the glycoprotein IIb/IIIa trials indicates that the greatest benefit is observed in patients with acute coronary syndrome undergoing in percutaneous coronary interventions. In the UK, the NICE (National Institute for Clinical Excellence) guidelines recommend the use of intravenous glycoprotein IIb/IIIa inhibitors undergoing acute or elective percutaneous coronary interventions.