

## REVIEW

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

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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.

NSTEMI guidelines published by the British Cardiac Society (BCS),<sup>6</sup> the ACC/AHA,<sup>7,8</sup> and the recommendations of the ESC<sup>9</sup> (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.<sup>10-12</sup> 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

## 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 either by fibrinolytic therapy or primary angioplasty. Both the European Society of Cardiology (ESC)<sup>1</sup> and the American College of Cardiology/American Heart Association (ACC/AHA)<sup>2,3</sup> have issued guidelines for the management of this distinct group.

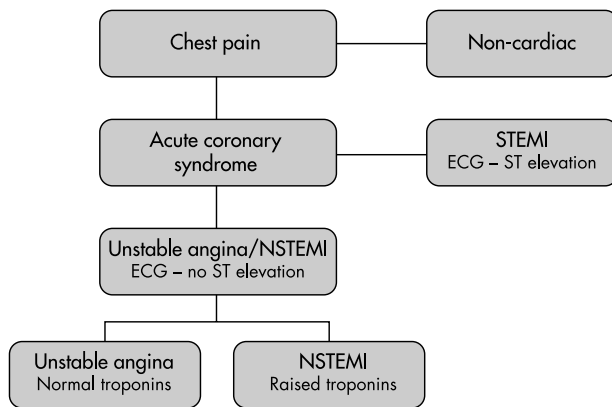
Patients presenting with acute coronary syndrome without ST segment elevation on the electrocardiogram are classified as having unstable angina or NSTEMI depending on the absence or presence of biochemical markers of myocardial necrosis, respectively. Raised creatine kinase and the isoenzyme CK-MB have 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.<sup>4</sup> 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.<sup>5</sup> 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/

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**Abbreviations:** ACC/AHA, American College of Cardiology/American Heart Association; BCS, British Cardiac Society; CK-MB, isoenzyme of creatine kinase; ESC, European Society of Cardiology; LMWH, low molecular weight heparins; MMP, matrix metalloproteinases; NSTEMI, non-ST elevation myocardial infarction; ST elevation myocardial infarction, STEMI; VSMC, vascular smooth muscle cells



**Figure 1** Classification of acute coronary syndrome.

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,<sup>13</sup> 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.<sup>13-15</sup> 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 collateralised 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.<sup>16</sup> Interestingly, it was observed that unstable lesions demonstrated less stenosis despite greater atheromatous 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 literally measure the temperature of the plaque.<sup>17</sup> However, longitudinal data indicate that plaques are biologically complex and have a variable relationship to presentation. In one study, 13% of patients with stable angina had a coronary event during a follow up period of up to 12 months compared with 31% of patients with previous unstable angina, controlled with medical therapy.<sup>18</sup> Interestingly, progression of the previous culprit lesion was the cause for only 54% of these recurrent events. Other investigators have also concluded that patients with one unstable plaque are more likely to develop other unstable plaques,<sup>19</sup> suggesting plaque rupture may be a manifestation of a more systemic process. This is supported by the presence of unsuspected angiographically evident active lesions in the non-culprit vessels of patients undergoing primary percutaneous coronary interventions. Up to 30% of cases in a primary percutaneous coronary intervention trial

had such evidence in the contralateral vessel.<sup>20</sup> Furthermore, postmortem examinations of patients who have died with acute coronary syndrome have shown plaque fissuring in non-culprit vessels.<sup>19</sup> Conversely plaque disruption and microhaemorrhage has been found in clinically silent atheromatous lesions and it appears that plaques may undergo episodes of disruption and repair, largely silent, resulting in growth and progression.<sup>21</sup> So it would seem that acute coronary syndrome may arise in the setting of widespread coronary activation where plaque disruption is necessary but not sufficient for the presentation. In support of this, patients presenting with a transmural myocardial infarction, two fifths have been shown to have angiographic evidence of multiple complex coronary plaques.<sup>20</sup> Evidence of destabilised atherosclerotic plaques throughout the vascular tree was associated with a higher rate of acute coronary syndrome recurrence at one year (19.0% v 2.6%). In patients presenting with unstable angina, it has recently been shown that neutrophils are activated throughout the coronary bed irrespective of whether they traverse the culprit lesion or not.<sup>22</sup> 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<sup>23</sup> 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.<sup>24, 25</sup> 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.<sup>26, 27</sup> Additionally, C-reactive protein elevations that often are low but outside the normal range (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.<sup>28, 29</sup> Proteolytic enzymes called matrix metalloproteinases (MMP) are produced by macrophages which degrade the fibrous cap and their expression is increased in the atheromatous plaques.<sup>30</sup> 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).<sup>31</sup> 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.<sup>32</sup> Platelet adhesion, aggregation, and activation result in local release of vasoconstrictors like serotonin and thromboxane, coupled with mild endothelial dysfunction inducing coronary vasospasm,<sup>33, 34</sup> increasing

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

Vascular smooth muscle cells	Endothelial cells	Tissue monocyte/macrophage	T lymphocytes	Platelets
↑ Apoptosis ↑ Senescence ↓ Proliferation ↑ MMP synthesis ↑ TF expression ↓ Collagen synthesis	↑ Adhesion molecule expression	↑ MMP synthesis ↑ TF expression	Stimulate macrophage MMP synthesis	Vasoconstrictor release

MMP, matrix metalloproteinases; TF, tissue factor.

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 leucocytes. 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.<sup>35-37</sup> These mechanisms seem to be 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 anaemic 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%.<sup>38</sup> 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 subpopulation. 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

**Table 2** Aetiology of myocardial ischaemia

Coronary	Non-coronary
Intravascular Unstable atherosclerotic plaque (plaque erosion or rupture causing thrombosis) Coronary embolus Vascular Epicardial vasoconstriction (Prinzmetal's angina) Microcirculation vasoconstriction Spontaneous coronary dissection Coronary vasculitis Coronary anomaly	↑ Oxygen demand Increased heart rate Thyrotoxicosis Pyrexia Tachyarrhythmia Increased inotropy Sympathomimetic drugs Cocaine intoxication Increased afterload Aortic stenosis Systemic hypertension ↓ Oxygen supply Anaemia Hypoxaemia Hypotension Hyperviscosity states

**Table 3** Clinical markers and biological determinants of risk

Adverse prognostic markers	Biological substrate
History	
Rest pain	Continued plaque instability
Pain in previous 48 hours	
Comorbidity	
Diabetes mellitus	Advanced atherosclerotic disease and high risk of multivessel disease
Systemic hypertension	
Dyslipidaemia	
Renal failure	
Examination	
Signs of LV failure	Culprit lesion subtends large myocardial area or background of previous LV impairment
Electrocardiography	
ST depression	Greater volume of ischaemic myocardium
T wave inversion	
Biomarkers	
Raised cardiac troponins	Myocardial necrosis
Raised C-reactive protein	High pancoronary inflammation
Angiography	
Intracoronary thrombus	Disruption of thrombotic/fibrinolytic cascades
Left main stem disease	Advanced atherosclerotic disease
Multivessel disease	

LV, left ventricular.

where resources are limited. An adverse prognostic marker should be a surrogate for relevant pathophysiological process, which in itself may be linked to several other clinical markers (see table 3). Risk assessment is based on clinical assessment and specific tests.

#### 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.<sup>39</sup> These factors are likely to be linked to advanced atherosclerosis and multivessel disease.

Examination may reveal evidence of left ventricular failure<sup>39</sup> 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.<sup>39</sup> 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.<sup>40</sup> 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 creatine 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 T<sup>41–46</sup> or troponin I<sup>43 45 46</sup> 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).<sup>47</sup>

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.<sup>38</sup>

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.

### 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/NSTEMI 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.<sup>44-48</sup> 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,<sup>49-50</sup> 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.<sup>44</sup> A group with low risk troponin T levels and a low risk predischARGE exercise test had a 1% 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.

### 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.<sup>51-53</sup> In the TIMI IIA substudy patients with both an early positive rapid troponin T and C-reactive protein  $\geq 1.55$  mg/dl had the highest mortality (9.10%), followed by those with either C-reactive protein  $\geq 1.55$  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%).<sup>51</sup> 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.<sup>54</sup> 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.<sup>55</sup> 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.  $\beta$ -Blockers and nitrates improve myocardial oxygenation by reducing myocardial oxygen consumption, though nitrates may additionally relieve epicardial coronary spasm and both improve symptoms. Although  $\beta$ -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 dihydropyridines 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.<sup>56</sup> These observations confirmed the importance of platelets and thrombosis as key pathogenic mechanisms. Pharmaceutical companies realising the deficiencies and relative lack of potency of these agents have invested greatly in the development of new and improved antithrombotic therapies for use in unstable angina/NSTEMI. These efforts have had variable beneficial effects.

### ADP receptor antagonists

Clopidogrel (Plavix) is a thienopyridine derivative, related to ticlopidine, which irreversibly blocks ADP-dependent platelet activation (via inhibition of the P2Y<sub>12</sub> 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.<sup>57</sup> The CURE study examined whether the addition of clopidogrel to aspirin, thereby inhibiting two pathways of platelet activation, would be synergistic.<sup>58</sup> 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 heterogenous 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  $\sim 5000$  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 anticoagulant 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.<sup>59</sup> Shorter polysaccharide 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 anticoagulant 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 plaque rupture.<sup>60</sup> 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.<sup>61</sup> 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.<sup>62-63</sup> 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.<sup>64</sup>

In contrast, two important large randomised control trials, ESSENCE<sup>65</sup> and TIMI IIb,<sup>66</sup> 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 of 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 intravenous or oral agents and the intravenous agents divided into those that are monoclonal antibodies to the  $\beta_3$  integrin of the IIb/IIIa receptor (abciximab) or synthetic molecules mimicking the fibrinogen RGD binding sequence either as peptidomimetics (eptifibatide) or as small inhibitory molecules (tirofiban 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 antiplatelet activity, at least 24–48 hours after termination of an infusion. The affinity of abciximab for  $\beta_3$  integrin in glycoprotein IIb/IIIa has also been shown to mediate binding to other heterodimeric receptors, containing the  $\beta_3$  integrin, notably the  $\alpha v\beta_3$  receptor found on endothelial and smooth muscle cells and the  $\alpha m\beta_2$  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 controlled trials comparing IIb/IIIa inhibitors, in combination with conventional antiplatelet therapy and unfractionated heparin, to placebo. Abciximab in CAPTURE, tirofiban in PRISM<sup>67</sup> and PRISM-PLUS,<sup>68</sup> eptifibatide in PURSUIT<sup>69</sup> and lamifiban in PARAGON A<sup>70</sup> and PARAGON B.<sup>71</sup> Although these trials have shown statistically significant reductions in composite endpoints 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.<sup>72</sup> Meta-analysis of all of these trials shows a small and just statistically significant advantage of IIb/IIIa inhibition,<sup>73</sup> 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 sibrifiban, xemilofiban, and orbofiban showed a 31% increase in mortality in treated patients compared with placebo.<sup>74</sup> 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 apoptosis<sup>75</sup> 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 instability 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.<sup>76</sup> 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.<sup>77</sup> In the MIRACL study, 3086 patients with recent acute coronary syndrome 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 cardiovascular disease were randomised to ramipril or placebo.<sup>78</sup> 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% reduction in worsening angina. These impressive results have encouraged the use of angiotensin converting enzyme inhibitors in acute coronary syndromes. One caveat to this enthusiasm 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 in to the pathobiology and natural history of acute coronary syndromes has highlighted the coronary vasculature as a legitimate target for disease modification. Rapid development 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 stratification 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 determinants including non-invasive stress testing to identify at risk patients. These selected patients are then referred for

angiography and revascularisation as appropriate. The advantages of the latter approach are that low risk patients are not subject to an invasive, potentially hazardous procedure.

Two early large trials, TIMI IIIB<sup>79</sup> and VANQWISH<sup>80</sup> failed to show superiority of the invasive approach over a conservative strategy. Indeed, VANQWISH showed a significant increase in death and non-fatal 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.<sup>81</sup> 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 significant 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 to two treatment arms and, secondly, improved procedural experience. Interestingly, even in FRISC II cardiac events occurred more frequently in the percutaneous coronary intervention 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 revascularisation. 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.<sup>82</sup> Once again there was a statistically significant reduction 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 IIIB showed a benefit from the invasive approach in two subgroups stratified according to risk.<sup>83</sup> While the latter studies 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.<sup>84</sup> 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.<sup>85 86</sup> 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. Ultimately, 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 stratification over the next decade combining cardiac troponins possibly 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 expediently 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 pathobiological 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)  $\beta$ -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
- (D) Intravenous glycoprotein IIb/IIIa inhibitors benefit all patients
- (E) Prolonged treatment with oral glycoprotein IIb/IIIa inhibitors reduces the high rate of recurrent events

### 5. Cardiac catheterisation for unstable angina/NSTEMI:

- (A) Is recommended for patients presenting after a recent STEMI
- (B) Is recommended for patients with refractory ischaemia despite medical treatment
- (C) Is recommended for patients at high risk of recurrent events
- (D) Is recommended for patients with signs of haemodynamic instability

(E) Should be performed with intravenous glycoprotein IIb/IIIa inhibitor therapy

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## ANSWERS (T, TRUE/F FALSE)

### 1. FTTFF

Acute coronary syndrome is term used to encompass unstable angina, NSTEMI, and STEMI. Although these diagnoses share the common pathoetiology 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.

### 2. FTTTT

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-T 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.

### 3. TTTFT

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

### 4. TTTFF

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.

### 5. TTTTT

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.