Acute coronary syndromes

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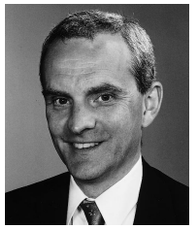

This article is based on the regional lecture given at Whipps Cross Hospital on 29 June 2000 by **Professor David Crossman** FRCP FACC FESC, Professor of Clinical Cardiology, University of Sheffield

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ABSTRACT – Acute coronary syndromes have been subject to revisions of both definition and treatment in recent years. As a result, more patients with these conditions are seen by physicians and more are considered for varied forms of treatment. Much of the clinical decision making is based upon trials that have identified reductions in relative risk for the treated patients. This review discusses the pathophysiology of the condition as well as the therapeutic options (without issuing guidelines). There are considerable challenges for physicians managing patients with these conditions. These challenges are in the conventional areas of risk stratification and cost, but are also in the logistics of investigating and revascularising these patients as quickly as possible.

Patients with acute coronary syndromes (ACS) occupy a great deal of time for those involved in acute medical admissions, cardiologists and more recently those who write and publish in medical journals. This preoccupation arises from a number of sources: an apparent increase in the number of admissions with unstable angina, a recent spate of publications in the area and recent pronouncements from NICE. The bulk of this article will concern unstable angina/non-ST elevation myocardial infarction.

Taxonomy

A number of new terms has arisen within the group ACS (see Table 1). The new names are an attempt to classify on the basis of therapeutic action rather than on pathological exactness. As a result the 12-lead ECG in large part determines the diagnostic group. ACS includes acute myocardial infarction (AMI), which pathologically and practically is acute full-thickness or transmural myocardial infarction and was recently renamed ST elevation myocardial infarction (STEMI). This group needs urgent revascularisation, and includes proven new bundle branch block and probably also definite true posterior infarction, though there is debate over the latter. The other large group within ACS contains the unstable coronary syndromes that lump together unstable angina (clear evidence of ischaemia at very low levels of myocardial oxygen consumption but with no elevation of biochemical markers of MI) or non-Q wave myocardial infarction where there are biochemical markers of MI. Non-Q wave MI is also known as subendocardial MI, as this is the region of the left ventricle that undergoes infarction because of the watershed nature of the blood supply to the subendocardium. Both of these terms are unhelpful at the time of presentation, as the former diagnosis requires the passage of time to substantiate and the latter is, strictly speaking, a pathological diagnosis. As a result, the term non-ST elevation MI (non-STEMI) is encouraged[1] because at the time of clinical presentation, the key distinction for therapeutic and prognostic purposes is between STEMI and everything else. These two groups have, however, remarkably similar pathogenesis (see below).

Within the unstable angina/non-STEMI (USA/non-STEMI) group there is a further stratification and some movement of the goal posts. In MI of any type there has to be elevation of biochemical markers. High creatine kinase levels, however measured, signify MI. Troponin measurement, using the available antibody-based techniques, is highly specific for myocardium and any elevation above the limit of sensitivity of the assay indicates myocardial damage. The current debate/reclassification concerns the group of USA patients that are CK negative but troponin positive; this may be as much as 30% of the USA population. These patients either have poor prognosis unstable angina or small myocardial infarcts (minimal myocardial infarction, minor myocardial damage, micro-infarction). The European Society of Cardiology is encouraging the classification of these as MI[2] and this seems appropriate because they have a worse prognosis than those with ischaemia but without troponin elevation. The appellation 'MI' based on troponin measurements may therefore be viewed as shorthand for this prognostic distinction.

Pathogenesis

Plaque based mechanisms

The pathogenetic paradigm for ACS is the unstable atherosclerotic coronary plaque. The hallmark lesion of atherosclerosis is the fibro-fatty plaque, which in its stable state is collagen rich with a smooth luminal surface. It only produces symptoms in the heart

when there is encroachment upon the lumen to such an extent that coronary flow is reduced below metabolic demands. This is a flow-limiting stenosis, by common agreement >50% of cross-sectional area, and results in stable angina. An unstable plaque is the site where disruption of the plaque has occurred, producing an intravascular thrombus. The plaque disruption in patients that come to autopsy is either plaque fissuring (~2/3 cases), where the internal thrombogenic components of the plaque are exposed to blood, or superficial erosion of the plaque (~1/3 cases), where there is loss of endothelium with exposure of a thrombogenic subendothelial matrix[3–5]. In all cases there is platelet adhesion and activation and exposure of tissue factor, the essential co-factor for the activation of the extrinsic pathway of coagulation. The thrombus so formed may be sufficient to be occlusive in its own right, may embolise small platelet-rich particles that occlude the microcirculation[6]; or may produce vasoconstrictor substances (eg 5HT and thromboxane)[7,8] that can constrict the epicardial coronary at the site of the plaque and/or the microcirculation at the level of the resistance vessels. These mechanisms in large part form the basis of all ACS and are the targets for most of the medication used.

A point of current interest is the widespread nature of activation of plaques in patients with ACS. Plaque fissuring (and presumably healing) occurs in patients with atherosclerosis most of the time. Patients coming to autopsy for non-coronary reasons have evidence of fissured plaques that have not presented clinically[9]. In patients who died from AMI plaques in the non-culprit vessel have also fissured[10]. This is supported by clinical studies showing that in patients having angiograms at the time of AMI (for percutaneous revascularisation), up to 1/3 have irregular complex lesions (the angiographic surrogate of plaque instability) in the non-culprit vessel[11].

These data indicate that ACS arise in the setting of widespread coronary activation where plaque disruption is necessary but not sufficient for the presentation of the syndrome. It is tempting to speculate that the other (unknown) factors that ensure presentation with ACS are random stochastic events. The epidemiology of the presentation of AMI does not support this. There is clear evidence of excess of AMI in the early hours of the morning[12], the beginning of the week[13,14] and the winter months[15]. These observations argue that there are specific biological events that determine the presentation of coronary plaque disruption rather than a random interaction of additive events.

A unifying mechanism for ACS is the inflammatory hypothesis of atherosclerotic disease. Within the plaque there is a number of inflammatory cells (macrophages and T cells) that are plausibly linked with plaque instability through their capacity to digest the extracellular matrix of the plaque and induce death (via apoptosis) of vascular smooth muscle cells (the latter being the only source of the collagen that gives the plaque its strength). In patients, elevated serum markers of inflammation indicate a greater likelihood of coronary events in a number of settings. Small elevations in CRP measured by sensitive assays (within the range of normality in the context of overtly inflammatory disease) predict coronary events in a number of patient groups, those without a history of CAD[16–20]; are additive to other risk factors[21] or predict poor outcome in those admitted with unstable angina[22–24]. These data fit well with the observation mentioned above, that presentation is associated with a state of widespread vascular activation.

The implications of this are important. Therapy that is solely based on or directed at the hot culprit plaque will always be a palliative measure. Widespread vascular passivation through anti-inflammatory or other mechanisms is therefore the necessary therapy at the time of presentation, for secondary prevention and probably primary prevention. This aim is currently only achievable with aspirin and statins, drugs that had previously been believed to work in other highly specific ways. For example, aspirin, which was viewed as an antiplatelet drug at the level of platelet accumulation on an activated plaque, has significant preventative activity in patients with mildly elevated CRP, suggesting its action as an anti-inflammatory[19]. Consistent with this is the absence of beneficial effects of oral GpIIbIIIa inhibitors despite more powerful anti-platelet effects than aspirin[25–27]. Statin drugs possibly work in a similar manner. Pravastatin reduces CRP levels in infarct survivors[28]. The unresolved question here is whether this is all secondary to cholesterol lowering or secondary to other biochemical effects of statin such as posttranslational modification of proteins with prenyl groups.

Table 1. Classification of acute cardiac syndromes and definition of terms.

	Acute coronary syndromes		
Clinical entity – defined by history and ECG at presentation ± first biochemical marker	**Acute myocardial infarction**	**Unstable coronary syndromes**	
	STEMI Proven new BBB ? True posterior MI	Non-STEMI	Unstable angina
Pathological or pathophysiological definition	Full thickness MI Transmural MI	Subendocardial MI	Near zero coronary flow reserve
Biochemical markers	CK↑+ troponin ↑	CK↑+ troponin↑ or CK – + troponin↑	CK – + troponin –

ECG = electrocardiogram; STEMI = ST elevation myocardial infarct; BBB = bundle branch block; MI = myocardial infarct; CK = creatine kinase

Non-plaque mechanisms

Both AMI and unstable syndromes can arise for reasons other than plaque instability, though these are unusual (Table 2). In unstable angina where angiography has been performed, there is a small proportion of individuals with either minimal disease or no angiographic disease in the coronary circulation. In a large study of over 5,000 patients, recruited for a study of unstable angina/non-Q wave MI and who had angiography, 12% of patients fell into this category[29] and in the TIMI-IIIa trial of USA this figure was 14%[30]. This

fits well with smaller scale observational studies of people who present with USA/non-QMI who have had angiography prior to the event and then have a second angiogram after the event. In this group of patients between 24%[31] and 31%[32] may have no detectable change in their coronary angiogram. While patients in this group have a good prognosis, this clearly identifies vascular reactivity at the level of the microcirculation as a mechanism that is powerful enough to induce ischaemia in its own right.

Other mechanisms are highlighted in the table. These should always be considered as therapy is often very different where these occur. Some are more likely to present with USA/non-STEMI rather than STEMI but physicians need to be alert to the possibility of these conditions.

Assessment of risk

When patients present either with the potential for a disease or with a condition that has a potentially serious outcome, physicians ideally assess the likelihood, or risk, of an adverse outcome. In conditions such as ACS, where an adverse outcome is by no means inevitable, the measurement of risk and categorisation of the patient by that risk is highly desirable. It allows the rational allocation of different intensities of treatment, which at its best tailors specific therapy for an individual or can influence the allocation of restricted resources. The latter is only really possible when society has defined the boundaries of acceptable or unacceptable risk.

Risk assessment should be viewed and measured as a continuous variable. This requires evaluating many patient characteristics and then applying a sophisticated tool (such as mathematical models or tables). Binary decisions (treat or not treat) are then made. The risk stratification tables for primary cardiovascular disease prevention is a good example[33]. Doctors in day to day practice managing ACS, however, derive their binary categorisation on a number of patient characteristics which are still poorly worked out.

ACS should ideally be stratified by risk, but mega-trials militate against this because of the inclusivity inherent in such trials. Moreover, government organisations such as NICE are obliged to make inclusive recommendations about treatment options. Trials usually apply one therapy to one condition. This is helpful when the condition is a circumscribed, well-defined event with a reasonably high risk of a poor outcome. The early trials of STEMI would be a good example. USA/non-STEMI, however, is not a single condition (pathologically) and these patients have a very wide range of risk. The physicians' problem is that the mechanisms for immediate identification of the risk in this condition are poor. As a result trials have applied treatments that cannot possibly produce a therapeutic benefit in certain subgroups of patients. For example, the 12% of patients in the GpIIbIIIa trials without angiographically identifiable coronary disease were unlikely to benefit from therapy[29].

Risk stratification in USA/non-STEMI is becoming clearer[34], though the definition of the 'acceptable' boundaries is wanting and some of the risk measures identified are unlikely to yield widely acceptable criteria (eg gender) for defining treatment, when taken in isolation. Risk factors for poor outcome which is usually viewed as death or myocardial infarction, are a complex mixture of intuitive pathological factors, and surrogate markers for these. A number of the identified risk categories interact with each other both statistically and at a plausible biological level. For example, the location of the unstable plaque within the coronary artery defines the amount of myocardium subtended and this must be critically linked to patient risk. This is by and large unknown at the time of presentation but a proximal lesion in a large vessel is hinted at by widespread, significant ST changes and elevation in troponins. The coexistence of multivessel disease similarly predicts a poor outcome, though this too cannot be known at the time of presentation but can be anticipated by the greater age of the patient and the presence of co-existing diabetes or hypertension. In both of these situations the extent and severity of the ECG changes are likely to be greater and this is supported by the observation that it is only ST depression (and not T wave inversion) that is a predictor of poor outcome[35]. Clinical factors identify other surrogates such as the failure to settle on medical therapy identified by continuing pain or continuous ST[36,37] segment changes which both indicate continuing plaque instability. Some of the factors and their mechanisms of engendering risk are identified in Table 3.

Table 2. Causes of acute cardiac syndromes.

Vascular
Intravascular obstruction
Atherosclerotic plaque instability (causing luminal obstruction and distal embolisation)
Coronary embolus (enlarged left atrium, mitral valve disease, prosthetic valve, right to left shunt, pulmonary AVM)
Spontaneous coronary dissection.
Coronary vasculitis
Vascular reactivity
Complete constriction (spasm) of epicardial coronary artery – Prinzmetal's variant angina
Microvascular coronary constriction with or without stable coronary disease
Coronary anomaly
Extravascular
Perfusion/oxygen consumption mismatch
Stable or unstable zero coronary flow reserve with forced increase in myocardial oxygen consumption or sudden drop in perfusion pressure beyond autoregulatory range
Anaemia
Thyrotoxicosis

AVM = arterio-venous malformation

Cardiac specific troponin measurements

Cardiac specific troponin (cTn) measurements as an assessment of risk deserve further comment. Elevation of cTn in patients with USA/non-STEMI, whatever the taxonomy, brings with it

risk proportional to the degree of elevation[38] and this has been advocated for triage of patients[39]. In recent trials of low molecular weight heparins (LMWH) and platelet GpIIbIIIa antagonists (see below) it is evident that benefit from these drugs was largely restricted to those with cTn elevations[40]. cTn elevation can arise for a number of reasons, however, and indicates that the true risk is variable even within the group of troponin positive patients. For example, when there is a brief episode of ischaemia cTn release will be a function of the area of myocardium at risk (high risk). Alternatively, a sustained episode of ischaemia to a small area of myocardium will also raise cTn but presumably the patient is at less absolute risk. In addition, cTn elevation may arise from repeated episodes of ischaemia that would also indicate a higher risk. Thus, interpreting the impact of a raised cTn is best viewed in the context of all other available information. Nonetheless, cTn measurements seem to be a step forward. The use of cTn -T or -I is best left to the laboratory where issues of quality control will determine the assay that is used. There needs to be care in the interpretation of cTn levels in renal failure[41].

The mechanisms by which antithrombotics and GpIIbIIIa antagonists are of particular benefit in this group are uncertain. It may be that this arises for statistical reasons alone, ie these are the only patients truly at risk and therefore this is the only group in which a benefit can be recorded. Alternatively, there may be good biological reasons that indicate specific mechanisms in this group of patients that are mutable by these drugs. One of these is that the troponin release arises from small micro-infarcts secondary to distal embolisation of plaque associated thrombus and troponin measurements merely identify the group that has continuously activated plaques. Alternatively the micro-infarcts themselves may carry prognostic implications and this is supported by the observations that small troponin rises during percutaneous coronary interventions are associated with a poorer prognosis. Whatever the mechanism, troponin measurement should now be standard as it helps to decide how to treat patients and to identify those who need further investigation.

New therapies

Most of the trials with large numbers of patients included have been in America or in Continental Europe and their immediate applicability to patients in UK hospitals is questionable. One major problem is that these trials do not address the issue of the type of patient produced by having to wait for transfer to an NHS specialist unit. These are the patients who appear as high risk at presentation but who settle on medical therapy (whilst waiting). In the trials, these patients will not have had to wait and the high rates of revascularisation used suggest that they were not only identified early but were also treated promptly. In the UK we have been tempted to examine a number of these trials in terms of whether the drugs used may help settle the patients either to make waiting for further investigation safer or to discharge them and avoid further investigation. In general these trials have thrown little light on this important issue.

Low molecular weight heparin (LMWH)

The use of intravenous unfractionated heparin has been a standard therapy in USA/non-STEMI on the basis of rather variable evidence. LMWH has a number of advantages over unfractionated heparin; high amongst them is their greater reliability in providing anticoagulation. Two well designed double blind trials (ESSENCE[42] and TIMI 11b[43,44]) have identified the advantage of the LMWH (enoxaparin) over unfractionated heparin. Though there are good biochemical reasons for differences between LMWH and unfractionated heparin[45], one suspects that the benefit arises from the fact that more patients were actually achieving effective anticoagulation. Other advantages are cost, as therapeutic monitoring is not needed and there may be fewer incidences of over (or under) anticoagulation. These may have an impact upon medical litigation. LMWH in USA/non-STEMI is therefore of benefit. These compounds should be prescribed on the recommended weight adjusted dose and great care should be taken in patients with

Table 3. Risk and acute cardiac syndromes. Basic mechanisms and how these can be appreciated using clinical tests.

Substrate for risk	Predictor/surrogate	Measurement of risk
Site of unstable plaque/amount of myocardium at risk	ECG changes	Number of leads with changes ST depression > T wave Inversion > normal ECG
	Troponin elevation	Risk proportional to elevation
Widespread coronary disease	Age	Risk increase with age
	ECG changes	As above
	History of CAD	
	History of diabetes	
	History of hypertension	
Plaque fails to heal	History of continuing pain	
	ECG changes	Continuous changes despite treatment
	Troponin elevation	As above
Development of complications	History of CAD	
	Reduced LV function	
Reduced LV function	Signs of heart failure	Risk increases with increased heart rate
	Heart rate	
	SBP at presentation	Risk increases with lower SBP
	History of CAD	
	History of hypertension	
Uncertain	Gender	Male >female risk

LV = left ventricular; ECG = electrocardiogram; CAD = coronary artery disease; SBP = systolic blood pressure

Key Points

The use of troponin measurements in patients with unstable angina/non-ST elevation myocardial infarction (USA/non-STEMI) identifies patients with an increased relative risk of an adverse outcome

Other clinical features (age, ECG changes, diabetes etc) add to the absolute risk in these patients

Patients identified as higher risk will benefit from intensive therapy including PCI

The logistics of intensive therapy for USA/non-STEMI provides a considerable challenge for admitting physicians, cardiac centres, their physicians and surgeons

renal impairment, where over-anticoagulation is a considerable risk. Information on their use in conjunction with GpIIbIIIa inhibitors is in hand and encouraging[46] but if the latter are also to be used, then unfractionated heparin is still currently recommended.

GpIIbIIIa inhibitors

These compounds, which block the fibrinogen receptor on the surface of activated platelets, have profound effects on platelet function over and above drugs such as aspirin. Their use in cardiovascular disease has been extensively reviewed elsewhere[47,48]. There are three groups of drugs in this class: monoclonal antibodies to the β3 integrin of the GpIIbIIIa complex (which may be viewed more appropriately as the heterodimer of the αIIa and β3 integrins) of which abciximab (Reopro) is the licensed drug; peptidomimetics (which mimic the RGD consensus binding site at the GpIIbIIIa complex) of which eptifibatide (Integrilin) is the licensed compound; non-peptidomimetics that block the RGD site, of which tirofiban (Aggrastat) is the licensed compound in the UK. These compounds have been used in three settings: at the time of either high risk of low risk percutaneous coronary intervention (PCI); intravenously for a short period of time at the presentation of USA/non-STEMI; and orally in patients with significant coronary risk.

Huge amounts of money and patient events have generated a number of points of agreement.

- These compounds have particular benefit at the time of PCI[47,48] especially in the context of PCI to treat USA/non-STEMI[49] and in diabetics. The weight of data favours abciximab which may have advantages over the other agents in this context (TARGET trial presented at AHA 73rd Scientific Sessions, 2000). This drug will bind other integrins, in particular the αvβ3 integrin (or vitronectin receptor). Its biological actions may well be relevant to the response of the vessel wall to injury. Other agents in this group do not appear to bind to the other integrins and this may be the basis of the possible differences in clinical effectiveness of these agents and abciximab.
- Intravenous use of these compounds in patients with USA/non-STEMI, many of whom were to require revascularisation, showed a small benefit from the use of tirofiban and eptifibatide and weakly for lamifiban (PRISM, PRISM-PLUS, PURSUIT, PARAGON)[50–53]. Meta-analysis of all the available ACS trials shows that there is no significant reduction in death rates at any time point[47]. The combined end point of death or MI at early time points and at 30 days were, however, significantly different with treatment. The risk reduction is approximately 10 events per 1,000 patients treated by 48–96 hours and approximately 13 fewer events at 30 days. Subset analysis suggests that the benefit was particularly marked or possibly only seen in those with elevated troponin measurements[40] and that the effect was particularly beneficial in reducing periprocedural MI at the time of PCI[49]. An economic analysis of the eptifibatide trials showed a cost of $16,491 per year of life saved and $19,693 per added quality-adjusted life-year[54]. On the basis of this, widespread use of these agents has been endorsed by a recent document from NICE for use in high-risk patients.
- The use of these agents in their oral form in a variety of settings, including at the time of PCI[25–27], is without benefit and may be harmful. The explanation for this is unclear. It maybe that the pharmacokinetics of these compounds have been under-appreciated. Subtherapeutic levels may not completely block the receptor in its low and high affinity states, allowing a virtual partial agonist type action.
- Use of these drugs at the time of PCI in all comers may be associated with a more favourable outcome in terms of adverse events. This has also prompted NICE to recommend that these drugs are used in all elective PCI, a decision that has surprised some cardiologists.
- Data available only in abstract form (GUSTO IV) suggest that abciximab used in patients with USA/non-STEMI who are unlikely to require PCI will have no benefit from the drug.

A number of unresolved issues remains (Table 4), and the least that the recent NICE guidelines have done is to make this an issue of considerable debate. It seems likely that patients with

Table 4. Some unresolved questions concerning the use of GpIIbIIIa inhibitors in acute cardiac syndromes.

Do these drugs help patients to settle without PCI?
Would there be measurable benefit over aspirin combined with LMWH rather than unfractionated heparin?
Why were the results different between Prism and Prism plus for the same dose of tirofiban?
Why are the lamifiban trials less positive?
Is there a superiority of abciximab over other GpIIb/IIIa inhibitors at the time of PCI?
Why have the oral agents shown no benefit?
Are these compounds safe when used in combination with LMWH?

PCI = percutaneous coronary intervention; LMWH = low molecular weight heparin

USA/non-STEMI who have positive troponin measurements or who are failing to settle will receive these compounds intravenously whilst awaiting PCI (see below). Because the duration of the infusions in the trials is between two and five days the practical implication will be to make sure these patients receive their PCI whilst on the drug. There are no data on what to do if they have had the drug but not the PCI; it would be difficult to justify the use (and expense) of a second infusion for the delayed PCI. Also, the available data suggest that these compounds should only be used in combination with unfractionated heparin. This seems a backward step, especially when there has been no trial to examine the benefit of GpIIbIIIa inhibitors in patients receiving LMWH, but it has to be the current recommendation as stated by NICE. New data are certain to appear which will clarify this issue.

PCI and ACS

Persuasive evidence from clinical practice has established a cadre of enthusiasts for PCI in virtually all patients with USA/non-STEMI. This enthusiasm is based on the clinical evidence that patients who could not get out of hospital because of recurrent angina are symptomatically 'cured', at manifestly low risk, by PCI. Such enthusiasm for PCI in ACS was in the face of two trials (TIMI IIIB and VANQWISH)[55,56] which suggested that PCI in this type of setting was associated with no difference in or worse outcome than medical therapy. The enthusiasts argued that these trials, which had low stent numbers and did not use GpIIbIIIa inhibitors, were not relevant to current practice. A recently published trial (FRISC II) has shown, however, that with modern PCI techniques a favourable outcome can be expected from PCI at the time of USA/non-STEMI[57] with differences in treatment groups preserved at one year of follow-up[58]. At one year an invasive approach saves 1.7 lives for every 100 treated patients. The enthusiasts suggest this is the treatment for everyone, whereas the sceptics point out differences in the definition of MI between the two groups and that there are no data on the cost effectiveness of this blanket approach. From my own perspective I believe PCI at the time of USA/non-STEMI is a very reasonable treatment if this is felt to be necessary on clinical grounds.

The current recommendation is that in the context of USA/non-STEMI, angiography and PCI should be undertaken in centres with extensive PCI experience and with CABG surgery available. There are moves for this to be undertaken in hospitals where surgery is not available. It is perhaps worth noting that in the four GpIIbIIIa trials referred to above[50–53] the angiography rate was between 50.2 and 89.8%, the PCI rate was 13.8–30.5% and the referral rate to CABG was 11–23.3%. These figures suggest that in the centres recruiting for those trials approximately four coronary angiograms in USA/non-STEMI patients generated one CABG. In trials where angiography in the invasive group was aimed at generating PCI cases, the 1,201 coronary angiograms generated 522 PCI cases and 430 CABGs[57]. These figures, coupled with the increased risk of angiography in patients with USA/non-STEMI (over those with stable coronary disease), do suggest that every effort should be directed towards boosting services in centres with surgery to provide for the increasing demand rather than exposing patients with USA/non-STEMI to the risks of coronary angiography in centres without facilities for CABG.

Conclusions

Our management of USA/non-STEMI patients will have to develop and we will have to become more aggressive in treating these patients. Each patient with this condition may be presenting with their particular window of opportunity for therapy that may save their life or avoid considerable morbidity. In addition, modern therapy with PCI will reduce the disruption of recurrent admissions with chest pain. One problem is to identify those who will most benefit from aggressive therapy and early investigation. There are still many unresolved questions but close clinical consideration of the patients and the use of ECG and troponins would be a very considerable help. The logistics of how the drugs are paid for and how tertiary centres will deliver the numbers of investigations and revascularisations promptly, remains a serious challenge to cardiovascular physicians.

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