Clinical Review

Acute Coronary Syndromes I:
Non ST-segment elevation myocardial infarction and unstable angina.

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Abstract

The acute coronary syndromes form a clinical spectrum, which ranges from unstable angina without myocardial injury, non-ST segment elevation and ST segment elevation myocardial infarction. All three conditions share a common pathophysiological basis. The management of acute ST segment elevation myocardial infarction however, is distinct from the other syndromes and therefore forms the basis of another article in this series. In this article we concentrate on the recognition and management of unstable angina and Non ST-segment elevation myocardial infarction (NSTEMI).

Keypoints

1. Mortality from acute coronary syndrome without ST elevation may be as high as 12%
2. Initial investigation of suspected acute coronary syndrome should include resting ECG with serial assessment and troponin T or I measurement, repeated 12 hours from onset of symptoms if normal.
3. A variety of medical therapies may reduce symptoms and improve mortality and morbidity from this condition.
4. Risk stratification should enable identification of those patients in need of early revascularisation

Keywords

Acute coronary syndromes (ACS), Unstable angina, Non-ST-elevation myocardial infarction (NSTEMI)

Introduction

The acute coronary syndromes represent a major health burden and are responsible for considerable morbidity and mortality. The EuroHeart Survey conducted across 25 countries in Europe from September 2000 to May 2001 showed that the 6-month mortality from acute coronary syndromes without ST segment elevation was 12%.[1]

Nevertheless a clinical strategy which involves early recognition, appropriate therapeutic intervention, risk stratification and, where appropriate, early revascularisation, can lead to an improved early and long-term outcome.

Pathophysiology

Current management and novel therapies have arisen from an improved understanding of the pathophysiology of acute coronary syndromes.[2] It should be remembered that this is a very dynamic process.

The initiating event is atherosclerotic plaque rupture or erosion. Plaque rupture may occur actively, as a result of proteolytic enzymes secreted by macrophages or passively as a result of physical forces acting at the weakest point of the fibrous cap. Once exposed, the lipid-rich core of an atherosclerotic plaque is highly thrombogenic and results in platelet aggregation, activation and thrombus formation. The development of a platelet rich thrombus at the site of vessel stenosis causes a sudden change in the degree of stenosis and gives rise to the clinical presentation of acute myocardial ischaemia. Release of vasoconstrictors such as serotonin and thromboxane A2 from activated platelets causes local vasospasm. In addition to endoluminal obstruction, this limits myocardial perfusion further. Distal embolization of platelets and clot fragments, as well as the release into the distal circulation of platelet-derived vasoactive substances, further impairs coronary flow.

The role of inflammation has been extensively studied and evidence suggests a significant role in the initiation of plaque rupture and progression of plaque instability. In pathological studies the proportion of macrophages, representing an inflammatory process, is six to nine times greater in ruptured compared to stable plaques.[3] Elevated CRP, reflecting the presence of an underlying inflammatory process, has been suggested as an independent risk marker for the progression of unstable coronary disease

Clinical Presentation

The clinical presentation of unstable angina is usually indistinguishable from that of NSTEMI.

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History

Traditionally, unstable angina has referred to three typical presentations:

I) prolonged (>20mins) anginal pain at rest

II) recent onset of severe angina

III) destabilisation of previously stable angina pectoris.

In one observational study, it was found that the most typical presentation was that of prolonged pain at rest, with only 20% of presentations arising as a result of recent onset of angina.[4] Pain may be atypical in location (epigastric, arm), in nature (burning, stabbing) and may be absent (silent ischaemia). An atypical presentation is more common in the elderly, the young, in diabetics and in women. Clinical suspicion should be heightened in those with significant risk factors for the development of coronary artery disease.

Examination

Physical examination of the patient with an acute coronary syndrome is often normal but is important to rule out non-cardiac causes of chest pain, to search for haemodynamic instability and evidence of left ventricular dysfunction.

The Electrocardiogram

The resting 12 lead ECG plays a central role in the assessment and management of patients with an acute coronary syndrome. A normal 12-lead ECG does not rule out the presence of cardiac ischaemia as a cause of chest pain, but a normal ECG taken during significant pain is helpful in pointing to a non-cardiac cause of chest pain. For those seen at a time when chest pain is absent and with a normal baseline ECG, continuous multi-lead ST segment monitoring can identify transient episodes of ischaemia. The most reliable indicators of unstable coronary artery disease are ST segment depression and T wave inversion[5,6] (See Figure 1). T-wave inversion is less specific than ST depression but both are a significant finding if the change is greater than 1mm in two or more contiguous leads. The ECG at presentation may also give an indication as to other causes of chest pain such as pericarditis and pulmonary embolism. Where possible the ECG should be compared with a previous ECG to note any new changes such as the development of bundle branch block.

Cardiac Markers

Cardiac troponins, T and I, are structural proteins only found in cardiac myocytes and are sensitive and specific markers for myocardial cell damage. Even very small amounts of myocardial cell injury are associated with elevated cardiac troponin compared with a normal population and they have become reliable indicators of myocardial cell necrosis. According to a recent consensus document published by the European Society of Cardiology and The American Heart Association, ischaemic chest pain, associated ECG changes and a rise in cardiac troponin should be labelled myocardial infarction(MI).[7] This means that many patients previously diagnosed as having 'unstable angina' could now be diagnosed as having had a MI. However, this has important epidemiological, psychological and social implications. Argually cardiologists should diagnose MI in the accepted way using total CK or CK-MB subfraction until evidence emerges to justify total acceptance of the new definition.[8]

Levels of troponins are also helpful in risk stratification. Levels start to rise three to four hours after

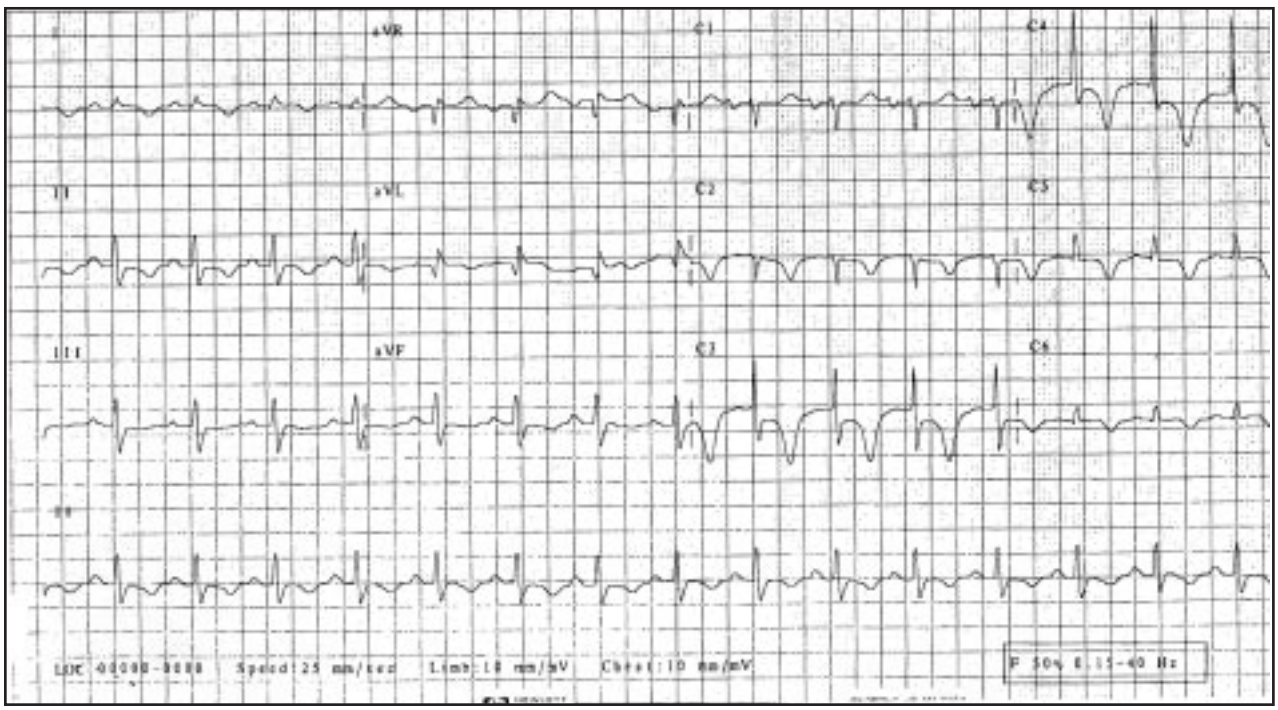

Figure 1. 12 lead ECG showing significant ST segment depression in arterior leads(c2-c4), along with widespread T wave inversion, indicative of acute coronary syndrome

the onset of symptoms but can only be reliably considered as negative if taken 12 hours after the onset of symptoms. Current European guidelines recommend measuring cardiac troponin I or T on admission and, if normal, again 6-12 hours after admission.

Troponins remain elevated for up to two weeks. From a practical point of view this makes re-infarction difficult to assess, and in this scenario measurement of serial creatinine kinase or its MB subfraction may be more helpful.

Other causes of chest pain such as pulmonary embolism and dissecting aortic aneurysm may be associated with raised cardiac troponin. Raised markers in association with arrhythmias, left ventricular failure and myocarditis reflect the sensitivity of the test. True 'false positive' results may occur in patients with chronic renal failure.

Management of patients with ACS

Managing patients with unstable angina and NSTEMI involves two important steps:

1. Medical therapy aimed at relieving symptoms, reducing myocardial ischaemia and modifying the progression to myocardial infarction.
2. Risk stratification so that those patients potentially benefiting from early intervention and revascularisation can be identified (see figure 2).

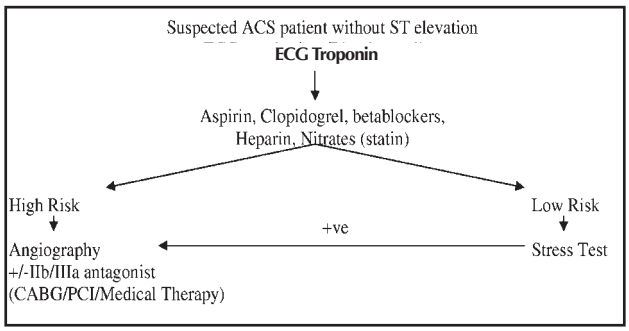

Figure 2. Management of suspected ACS.

1. Medical Therapy

Patients should be treated with oxygen and receive adequate analgesia with opiates. Therapy is then aimed at reducing myocardial ischaemia and preventing the generation of occlusive, platelet-rich thrombus.

a) Antiplatelet Agents

I) **Aspirin** should be given to all patients unless there is a true history of hypersensitvity. Aspirin inhibits the release of thromboxane A2, a powerful vasoconstrictor and mediator of platelet aggregation. Aspirin reduces the incidence of progression to myocardial infarction and mortality.[9] Patients should receive an initial dose of 300mg, followed by a maintenance dose of 75-150mg daily.

II) **Clopidogrel** is a thienopyridine, which acts as an ADP receptor antagonist, inhibiting ADP-mediated platelet aggregation. The CURE study[10] investigated the use of clopidogrel in patients with acute coronary syndromes. In this study patients were treated concomitantly with aspirin and clopidogrel. Over 12,500 patients were enrolled in the study. All patients had ECG changes or raised biochemical markers at the time of presentation. The primary endpoint of death, non-fatal myocardial infarction or stroke occurred in 9.3% of the clopidogrel treated group compared to 11.4% of the aspirin alone group (relative risk: 0.8; 95% CI: 0.72-0.90).

American and European guidelines recommend the use of clopidogrel in all patients presenting with an acute coronary syndrome. 300mg should be given initially followed by a maintenance dose of 75mg daily. The optimal duration of treatment is unknown.

III) **Glycoprotein** IIb/IIIa receptor antagonists have now established a role in the management of acute coronary syndromes. IIb/ IIIa receptors on the surface of activated platelets bind fibrinogen and serve as the final common pathway in the formation of platelet rich thrombus. Parenteral IIb/ IIIa receptor antagonists have been studied in the treatment of acute coronary syndromes and their role has been demonstrated in patients undergoing percutaneous revascularisation.[10] The benefit seems to be most apparent in high-risk patients presenting with elevated troponin I or troponin T.[11,12] The National Institute of Clinical Excellence (NICE) published its second technology appraisal document on the use of GP IIb/IIIa receptor antagonists in September 2002.[13] Specific guidance was given on the use of these agents during percutaneous revascularisation and their role in high risk patients during the initial medical phase of management. Unless there are contraindications IIb/IIIa receptor antagonists should be given to all patients undergoing percutaneous revascularisation (in the setting of ACS) and should be considered as part of the initial medical therapy in high risk patients where there is a delay in referral for revascularisation. There is currently no clear role for the use of these agents in the management of patients for whom revascularisation is not intended. Oral IIb/IIIa antagonists have been developed but results of randomised trials have not supported their use.

b) Antithrombotic therapy

I) **Unfractionated heparin** indirectly inhibits thrombus formation by binding antithrombin III, enhancing its ability to bind and inactivate

thrombin. Heparin also inhibits factor Xa. Thrombus formation plays a critical role in the progression of acute coronary syndromes and heparin has a long established role in the treatment of unstable angina and myocardial infarction. It is surprising that large trials powered to show the benefit of unfractionated heparin have not been carried out. A meta-analysis of six randomised trials does suggest a benefit with a 7.3% death or reinfarction rate in the aspirin + heparin treated group compared to 10.3% with aspirin alone (absolute risk reduction 2.4%, OR:0.74 (95% CI 0.5-1.09), P=0.10).[14]

II) **Low molecular weight heparin (LMWH)** has been shown to be superior to placebo when added to aspirin.[15] LMWH offers significant advantages over unfractionated heparin. They are easier to administer, provide a more reliable antithrombin activity and are less liable to inhibition by platelet factor 4 when compared to unfractionated heparin. Studies also show that these agents are as safe as unfractionated heparin when administered with IIb/IIIa antagonists.[16] Thus LMWH is at least as effective as unfractionated heparin and randomised trials have demonstrated superiority of enoxaparin over unfractionated heparin for combined endpoints of death, MI and recurrent angina[17]

III) **Direct thrombin inhibitors,** such as hirudin, have shown benefit but currently do not have a licence for the treatment of ACS.

c) Anti-ischaemic Agents

I) **Beta-blockers** should be prescribed to all patients without contraindication (asthma, acute heart failure, impaired atrioventricular conduction.). Beta-blockers act by competitively inhibiting circulating catecholamines and reduce myocardial oxygen demand. Randomised trials using beta-blockers in the setting of ACS have been small and have not demonstrated a reduction in mortality but a meta-analysis has demonstrated a 13% reduction in progression to myocardial infarction.[18] There is no evidence to suggest that any particular beta-blocker is better than any other but where there are concerns about tolerance a short acting agent such as metoprolol should be the preferred agent. The dose should be titrated to obtain a resting heart rate of 50-60 beats per minute.

II) **Nitrates** may be administered orally, topically, sublingually or intravenously. Intravenous administration offers the advantage of more consistent control of ischaemic episodes and it is usual to use this route of administration during the first 24 hours. Nitrates act by dilating normal and atherosclerotic coronary arteries, improving global and regional LV function by reducing pre and afterload and have been shown to inhibit platelet aggregation. The dose of intravenous nitrates can be titrated every 10 minutes until there is relief of symptoms or limiting side effects (headache, or hypotension with a systolic BP of less than 90mmHg). It is recommended that patients should be converted to oral nitrates once they have been symptom free for 24 hours.

III) **Calcium channel blockers** can reduce ischaemic symptoms in addition to nitrates and beta-blockers. There are three groups of calcium channel blockers which have varying actions on myocardial contractility, peripheral vasodilatation and atrioventriculer conduction. All three have similar effects in terms of coronary vasodilatation. The dihydropyridines, such as nifedipine, produce predominantly peripheral vasodilatation. Pooled data from observational studies suggest a dose dependent detrimental effect on mortality from short-acting nifedipine in patients with coronary artery disease and it is recommended that these agents are not used without concomitant use of beta-blockers. On the other hand diltiazem, a benzothiapine, has shown some benefit in patients with NSTEMI.[19] Verapamil, a phenylalkylamine, slows conduction at the AV node and has more marked negative inotropic effect. Diltiazem or verapamil are particularly useful in patients with contraindications to beta-blockade but should be avoided in patients with signs of significant LV dysfunction or impaired AV conduction.

IV) **Nicorandil**, a potassium channel activator, is often added to relieve ischaemic symptoms but there are currently no data regarding its use in ACS.

d) HMG CoA Reductase Inhibitors ('Statins')

Statins have been shown to have an important role in the secondary prevention of adverse cardiac events. Observational angiographic studies have also suggested a role in plaque stabilisation or 'passivation' and for this reason statins are often prescribed empirically once a diagnosis of ACS is made. Specific trials are currently underway to determine whether statins do indeed provide immediate benefit in ACS.

e) Intra-aortic Balloon Pump Counterpulsation

In a small number of patients, insertion of an intra-aortic balloon pump is a useful adjunct to medical therapy or a useful bridge to revascularisation. Deflating during systole and inflating during diastole, an intra-aortic balloon pump augments coronary perfusion during diastole and reduces LV afterload during systole. Both of these measures address the imbalance of myocardial oxygen supply and demand. Balloon pumps are typically

inserted in patients with refractory angina and/or haemodynamic compromise as a bridge to surgical revascularisation. Significant aortic regurgitation is a contraindication.

2. Risk stratification

The process of risk stratification is critical in determining the specific nature of early and later treatment for patients with ACS. The process begins immediately with clinical assessment, ECG, biochemical parameters, and non-invasive testing.

A patient may be defined as **high risk** on the basis of:

a) Their clinical course (continued symptoms despite appropriate treatment, evidence of haemodynamic instability or cardiac failure),
b) ECG at presentation (ST segment depression or widespread T wave inversion),
c) Biochemical marker results (positive cardiac troponin, elevated CRP) or
d) Following non-invasive testing (early or widespread evidence of cardiac ischaemia during stress testing).

Under these circumstances early invasive treatment and appropriate revascularization is indicated. In the absence of any of these markers of high risk an initial conservative approach to treatment can reasonably be adopted. It should be emphasized that **low risk** does not mean **no risk** and that this decision may need to be revised over the days, weeks and months after presentation in the face of emerging clinical evidence.

Revascularisation

Patients referred for angiography may undergo revascularisation, comprising either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), in order to relieve symptoms, reduce ischaemia or to prevent progression to MI/death. The mechanism of revascularistion is determined largely by anatomical findings at angiography.

It is beyond the scope of this article to address this in detail, but generally patients with left main stem disease or three vessel disease with LV impairment are referred for surgical revascularisation. Data from the TIMI IIIB and FRISC II studies show that 30-38% of patients with ACS have single vessel disease and 44-59% have multivessel disease. The incidence of left main stem disease is 4-8%.[20,21] Studies in the recent past have also suggested that diabetic patients fare better with a surgical approach. However, this is a changing landscape with the advent of novel therapeutic interventions, in particular, drug eluting coronary stents.

Patients with ACS undergoing PCI will, unless contraindicated, receive abciximab (the only IIb/IIIa receptor antagonist licenced for coronary intervention) and heparin. The recently published PCI-CURE study studied the benefit of pre-treatment with clopidogrel.[22] At 30 days, there was a significant reduction in cardiovascular death and MI (from 4.4% to 2.9%). It has been usual practice to treat patients with clopidogrel for one month following PCI but data from PCI-CURE indicates that long-term administration (average of 8 months in PCI-CURE) is associated with a lower rate of death, MI or need for revascularisation. Coronary stents are now inserted in the majority of patients undergoing PCI. Continuing improvements in technical aspects and operator experience has led to improved procedural success rates. This has occurred despite a broadening of inclusion criteria to include more elderly, sicker patients and more complex anatomical lesions.

Coronary bypass grafting should be considered for those patients not suitable for PCI and those in whom, regardless of symptoms, there is prognostic benefit from surgical revascularisation. Clopidogrel administration within five days of CABG has been associated with excessive major bleeding episodes[23] and aggressive antiplatelet regimens may require specific surgical measures, such as platelet transfusion, to minimise bleeding complications.

Conclusion:
'If I had ACS without ST elevation.....'

I would like to be given aspirin (300mg initially then 75mg daily) in addition to clopidogrel 75mg daily. I should be commenced on LMWH, intravenous nitrates (which should be uptitrated to relieve symptoms), and a regular beta-blocker. My fasting cholesterol will have been measured on admission but I should be commenced empirically on a statin. If I had recurrent angina, dynamic ECG changes or raised cardiac troponin I would wish to be referred for coronary angiography and revascularisation as appropriate. Prior to discharge, I would be encouraged strongly to stop smoking, eat a healthy diet and take up a less sedentary lifestyle.

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