Management of acute coronary syndrome

This is a review of acute coronary syndrome as a clinical entity. An appreciation of acute coronary syndrome as a disease spectrum is presented along with contemporary evidence for its diagnosis and approach to medical and surgical management.

According to the Department of Health (National Service Framework for Coronary Heart Disease, 2000), coronary heart disease is a preventable disease that kills more than 110 000 people in England every year. More than 1.4 million people suffer from angina and 275 000 people have a myocardial infarction annually, mostly presenting as typical 'cardiac' chest pain.

The management of cardiac chest pain has evolved significantly over recent years but remains varied between hospitals. This is largely the result of previous inconsistencies in the terminology and the thresholds for diagnosis (Fox et al, 2004). In an effort to develop therapeutic strategies the term acute coronary syndrome was proposed as a useful framework. Acute coronary syndrome refers to a spectrum of clinical presentations compatible with acute chest pain caused by myocardial ischaemia.

Significance of acute coronary syndrome

Although the exact incidence of acute coronary syndrome is difficult to ascertain, NHS Hospital Episode Statistics (Department of Health, 1998) suggest that the incidence of unstable angina is around 1000 cases per million of total population per year. Based on these estimates, this implies an annual incidence within the UK of around 60 000 cases, although anecdotally this appears to be an underestimate. This has huge implications for the NHS budget.

Pathophysiology

Work by Davies (Davies et al, 1979; Davies and Thomas, 1984, 1985) has suggested that acute coronary syndrome mainly results from the disruption or erosion of an atherosclerotic plaque. The resultant intra-luminal thrombosis obstructs vascular flow through the coronary artery, which is already narrowed by the encroachment of the disrupted atheroma into the vessel lumen. Coronary flow is further compromised by embolization of thrombus fragments into the distal circulation and changes in vascular tone. The clinical manifestations depend on the severity of myocardial necrosis, which is in turn determined by the degree of vessel occlusion, volume of myocardium supplied by this vessel and the duration of the flow limitation. Because of this considerable variance, acute coronary syndrome ranges from unstable angina and non-ST elevation myocardial infarction to the more severe transmural ST elevation myocardial infarction, which may result in sudden cardiac death.

According to GRACE (Global Registry of Acute Coronary Events) (Fox et al, 2002), a diagnosis of ST elevation myocardial infarction is made when there is new ST segment elevation of ≥1 mm seen in any location or left bundle–branch block and consistent elevation of serial cardiac markers. ST elevation myocardial infarction represents ischaemic damage of sufficient severity and duration to result in permanent myocardial damage (infarction). The diagnosis is typically based on a characteristic rise and fall in serial biomarkers indicative of necrosis alongside characteristic electrocardiogram changes. This may or may not include the development of Q-waves (representing areas of necrotic myocardial tissue that can no longer achieve resting potential) on electrocardiograms. The development of infarction depends on several pathophysiological features such as the extent and locus of the plaque rupture, the nature of thrombotic consequences, the presence of collateral vessels, and the effectiveness and timing of reperfusion.

Non-ST elevation myocardial infarction and unstable angina have lower immediate morbidity and mortality but are a major cause of emergency medical care and hospitalization. Moreover, they are associated with an increased risk of further myocardial infarction and/or death. Work from GRACE (Fox et al, 2002) and PRAIS-UK (Prospective Registry of Acute Ischaemic Syndromes in the UK) (Collinson et al, 2000) has shown that 6-month mortality is 12–13%, which is similar to patients with ST elevation myocardial infarction who reach hospital alive. However, the time course and nature of the cardiac consequences differ significantly.

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The mortality following unstable angina and non-ST elevation myocardial infarction relates to the development of a subsequent, larger infarction complicated by mechanical or arrhythmogenic complications. Ischaemic tissue has impaired contractility, resulting in hypokinetic or akinetic segments, which paradoxically expand or bulge during systole. The size of the affected area or the abnormal rhythm created determines the effect, which ranges from mild heart failure to cardiogenic shock. Consequently, short-term management of non-ST elevation myocardial infarction and unstable angina is directed at prevention of this progression to ST elevation myocardial infarction.

Biochemical markers for acute coronary syndrome

Biochemical cardiac markers are useful for diagnosis of myocardial necrosis and of prognostic value in patients without definitive ST segment elevation and an unclear history. There is a quantitative relationship between the magnitude of elevation of marker levels and the risk of an adverse outcome (Roberts and Fromm, 1998). These markers are released as necrotic myocytes lose membrane integrity allowing intracellular macromolecules to diffuse into the circulation. Troponins have rapidly gained acceptance as the biochemical markers of choice in the evaluation of patients with acute coronary syndrome because of their sensitivity and cardiac specificity. Measurement of troponin levels has largely superseded routine use of creatine kinase, creatine kinase-MB and lactate dehydrogenase.

Troponin is a contractile protein normally not found in serum. It is released only when myocardial necrosis occurs. If levels are not elevated >6 hours after onset of pain, and the electrocardiogram is normal, the risk of missing an myocardial infarction is small at around 0.3%. For early detection of myocardial necrosis, the sensitivity of troponin I is superior to that of creatine kinase-MB or troponin T. It is detectable in serum 3–6 hours after an myocardial infarction, and its level remains elevated for 14 days. Troponin T has similar release kinetics to troponin I, but it has a lower cardiac sensitivity (false positive results may occur in patients with renal failure) and a lower early sensitivity (Panteghini et al, 1999).

According to the British Cardiac Society working group (Fox et al, 2004), if cardiac troponin levels are elevated accompanied by a clinical picture of acute coronary syndrome it is diagnostic of clinical myocardial infarction. If not, the diagnosis of unstable angina is made. Although sensitive at identifying myocardial necrosis, a troponin rise may not be secondary to atherosclerotic coronary artery disease because conditions such as acute pericarditis and pulmonary embolus can also give positive values (Lum et al, 2006). It is therefore important that when making a diagnosis, troponin levels are used in conjunction with appropriate clinical signs and electrocardiogram changes.

It is possible to reliably predict mortality following acute coronary syndrome using models such as the TIMI risk score (see below) (Antman et al, 2000) and the GRACE risk score (Christopher et al, 2003) with certain key indicators.

Components of the TIMI risk score

In patients with unstable angina/non-ST elevation myocardial infarction, the TIMI risk score is a simple prognostication scheme that categorizes a patient's risk of death and ischaemic events and provides a basis for therapeutic decision making. The components are:

- Age >65 years
- History of diabetes, hypertension or angina
- Documented coronary stenosis>50%
- ST deviation
- More than two anginal events in the preceding 24 hours
- Aspirin treatment in previous 7 days
- Increased cardiac markers
- Prior myocardial infarction, congestive cardiac failure, coronary artery bypass grafting or percutaneous coronary intervention.

The formulated additive score relates to 2-week all-cause mortality, new or recurrent myocardial infarction or severe recurrent ischaemia (requiring urgent revascularization). It equates to 5%, 8%, 13%, 20%, 26% or 41% respectively for 1, 2, 3, 4, 5, 6+ points.

Management of acute coronary syndrome

The most urgent priority is to identify patients with an evolving ST elevation myocardial infarction who should be considered for immediate medical or surgical reperfusion therapy (thrombolysis, 'primary' percutaneous coronary intervention or coronary bypass surgery). Unstable angina and non-ST elevation myocardial infarction are considered to be closely related conditions of differing severity. If the ischaemia is severe and persistent enough to release detectable quantities of biochemical markers of myocardial injury in the absence of electrocardiographic changes, it is classified as non-ST elevation myocardial infarction. However, at the time of presentation, since marker release may take hours, patients with unstable angina and non-ST elevation myocardial infarction may be indistinguishable and are therefore considered together in their immediate management.

Guidelines for the management of acute coronary syndrome were set out by the American College of Cardiology and the American Heart Association in 2000 with subsequent updates since (American College of Cardiology/American Heart Association, 2007). The guidelines are based on a comprehensive meta-analysis of clinical trial data. It was not until 2004 that a consensus was finally reached in the UK when the National Institute for Clinical Excellence (NICE) published its guidelines. *Figure 1* gives a management algorithm for acute coronary syndrome.

Historically, the treatment of acute cardiac pain has developed from bed rest to aspirin and analgesics, through the addition of β-blockers and heparin to more recent interventions such as thrombolysis, percutaneous coronary intervention and surgery. More recently the introduction of antiplatelet agents such as clopidogrel and glycoprotein IIb/IIIa antagonists has added to management strategy.

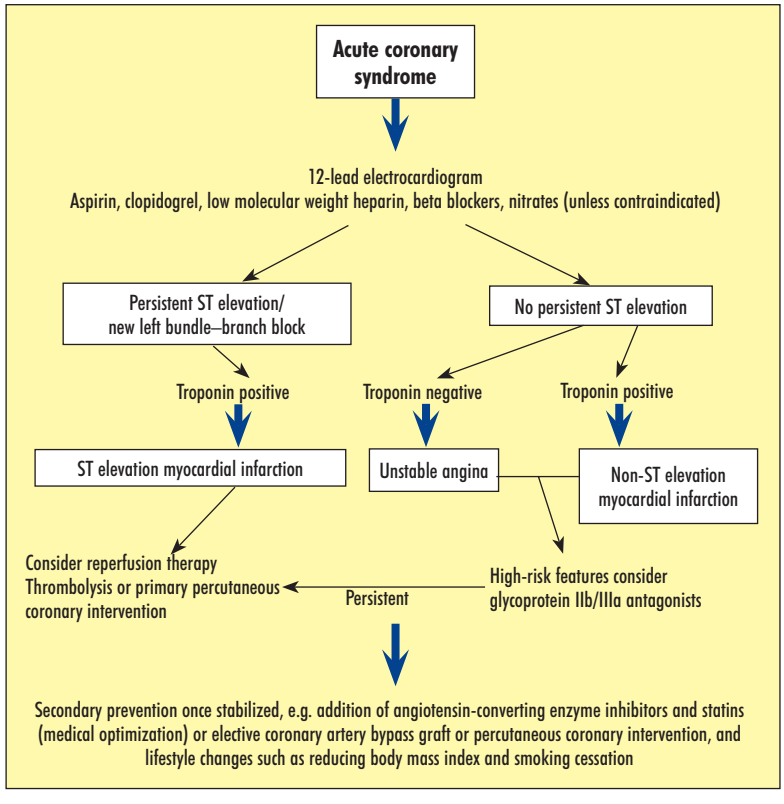
Non-interventional management

Aspirin

Some of the strongest evidence available about the long-term prognostic effects of therapy in patients with coronary disease relates to acetylsalicylic acid (aspirin) (Antiplatelet Trialists' Collaboration, 1994). Aspirin irreversibly inhibits cyclooxygenase-1 within platelets preventing the formation of thromboxane-A2 – a powerful platelet aggregation agent. Platelet aggregation is thereby inhibited.

Two major trials comparing aspirin with placebo in acute coronary syndrome showed an absolute risk reduction of death or myocardial infarction of 8.4% and 5.1% respectively (Lewis et al, 1983; Cairns et al, 1985). This significant risk reduction, drug tolerability and its proven ability to reduce mortality in patients with suspected ST elevation myocardial infarction has led to recommendations that aspirin should be initiated immediately in emergency departments if acute coronary syndrome is suspected. It plays a central role in all management of acute coronary syndrome, unless contraindicated. Major contraindications include intolerance and allergy (primarily manifested as asthma), an active source of bleeding or bleeding disorders.

Figure 1. Management algorithm for acute coronary syndromes.



Clopidogrel

Clopidogrel is also an antiplatelet agent which, after activation in the liver, inhibits platelet aggregation by irreversibly modifying the platelet adenosine diphosphate (ADP) receptor. Because the mechanisms of the antiplatelet effects of aspirin and ADP antagonists differ, a synergistic relationship exists between the drugs. Although clopidogrel takes several days to reach adequate serum levels, significant activity is achieved with a stat dose of 300 mg within hours of administration.

The CAPRIE trial (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events) (CAPRIE Steering Committee, 1996) has shown that clopidogrel has an efficacy at least similar to that of aspirin. The CURE Trial Investigators (2001) randomized trial showed that across a wide variety of subgroups, clopidogrel was associated with significant reductions in severe ischaemia and revascularization rate and the need for thrombolytic therapy or intravenous glycoprotein IIb/IIIa receptor antagonists. However, the study concluded that treatment with clopidogrel was cost effective for only 9–12 months, after which time therapy should revert to the less expensive use of aspirin.

Beta-adrenergic blockers

Beta-blockers competitively block the effects of catecholamines on cell membrane beta-receptors. Beta1-adrenergic receptors are located primarily in the myocardium. Inhibition of catecholamine action at these sites reduces myocardial contractility, sinus node rate and atrioventricular node conduction velocity. Beta-blockers therefore blunt the heart rate and contractility responses to chest pain, exertion and other stimuli. They also decrease systolic blood pressure. All of these effects reduce myocardial oxygen demand. The First International Study of Infarct Survival (ISIS-1, 1986) demonstrated a significant reduction in early mortality when patients were beta blocked immediately post-myocardial infarction. Although evidence for the beneficial effects of the use of beta-blockers in patients with unstable angina or non-ST elevation myocardial infarction is based on limited randomized trial data, along with pathophysiological considerations, certain studies have shown early beta-blocker treatment to be associated with lower mortality and fewer complications (Levy, 1990).

Heparin

Heparin exerts its antithrombotic effect by accelerating the action of circulating antithrombin, a proteolytic enzyme that inactivates factor IIa (thrombin), factor IXa and factor Xa. It prevents thrombus propagation but does not directly lyse existing thrombus. Low molecular

weight heparin behaves more predictably than the unfractionated form and does not usually require laboratory monitoring of activity (activated partial thromboplastin time ratio). The combination of aspirin and low molecular weight heparin significantly reduces the total ischaemic event rate, the rate of recurrent angina and the number of patients requiring interventional procedures (Gurfinkel et al, 1995).

Direct thrombin inhibitors

Direct thrombin inhibitors, e.g. hirudin or bivalirudin, are a new class of anticoagulants that bind directly to thrombin and block its interaction with its substrates (Di Nisio et al, 2005). The role of direct thrombin inhibitors in the management of acute coronary syndromes was reviewed in a meta-analysis of data on individual patients by the Direct Thrombin Inhibitor Trialists' Collaborative Group (2002). As compared with unfractioned heparin, direct thrombin inhibitors reduced the incidence of the composite outcome of death and myocardial infarction both at the end of treatment and at 30 days. However, the role of direct thrombin inhibitors has not yet been established in the setting of the combined use of aspirin and clopidogrel, as well as glycoprotein IIb/IIIa receptor inhibitors.

Selective factor Xa inhibitors:

Fondaparinux is the first in a new class of antithrombotic agents that selectively inhibit coagulation factor Xa. The Fifth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-5, 2006) trial compared the efficacy and safety of fondaparinux and enoxaparin in high-risk patients with unstable angina or non-ST elevation myocardial infarction and found similar efficacy, significant reduction in major bleeding and improvement in long term mortality and morbidity.

Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme (ACE) inhibitors inhibit conversion of angiotensin I to angiotensin II which normally indirectly increases fluid re-absorption in the kidneys and has a direct vasoconstrictive action. They are, therefore, effective antihypertensive agents and help reduce afterload and thus the demand on the myocardium. They are particularly useful in ventricular dysfunction and reduce mortality rates in patients following acute myocardial infarction and a broad spectrum of patients with high-risk chronic coronary artery disease (ACE Inhibitor Myocardial Infarction Collaborative Group, 1998; Flather et al, 2000).

Glycoprotein IIb/IIIa antagonists

The glycoprotein IIb/IIIa receptor is abundant on the platelet surface. When platelets are activated, this receptor undergoes a conformational change that increases its affinity for fibrinogen binding. The binding of fibrinogen molecules to receptors on different platelets results in platelet aggregation. This mechanism is independent of the platelet aggregation stimulus and represents the final and obligatory pathway for platelet aggregation (Lefkovits et al, 1995). Glycoprotein IIb/IIIa receptor antagonists act by occupying these receptors preventing fibrinogen binding and thereby platelet aggregation.

Patients who present without ST segment elevation and who have elevated cardiac-specific troponin levels may receive benefit from platelet glycoprotein IIb/IIIa receptor inhibitors and low molecular weight heparin as suggested by the CAPTURE (c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina) Study Investigators (1999). Similar results have been reported with use of the glycoprotein IIb/IIIa receptor antagonist tirofiban (Heeschen et al, 1999). The efficacy of glycoprotein IIb/IIIa receptor antagonists in prevention of the complications associated with percutaneous interventions has been documented in numerous trials (EPIC Investigation, 1994; EPILOG Investigators, 1997; EPISTENT Investigators, 1998).

Statins

Statins inhibit the enzyme HMG-CoA (3-hydroxy-3-methyl-glutaryl-CoA) reductase, which is involved in cholesterol synthesis. These drugs lower the concentration of low-density lipoprotein cholesterol and raise high-density lipoprotein cholesterol. This reduces the progression of coronary atherosclerosis and may in fact induce regression. Statins have a well-established role in the primary and secondary prevention of coronary and cardiovascular events, especially in high-risk groups.

Thrombolysis

The failure of intravenous thrombolytic therapy to improve outcomes in the absence of ST elevation myocardial infarction was clearly demonstrated in the TIMI IIIB (TIMI IIIB Trial, 1994) and ISIS-2 (ISIS-2 Collaborative Group, 1988) trials. These trials showed no benefit of thrombolysis *vs* standard therapy for the reduction of re-infarction risk. Thrombolytic agents had no significant beneficial effect and actually may increase the risk of myocardial infarction. Consequently, such therapy is not recommended for the management of acute coronary syndrome patients without ST segment elevation. In patients with ST elevation myocardial infarction, the evidence from large randomized trials has demonstrated that fibrinolytic therapy can reduce mortality. The fibrinolytic therapy trialists' (FTT) collaborative group (1994) showed that the benefit from thrombolysis is greatest when given promptly after symptom onset. This indicated a highly significant absolute mortality reduction of about 30 per 1000 for those presenting within 0–6 hours, about 20 per 1000 for those presenting 7–12 hours from onset, and a statistically uncertain benefit of about 10 per 1000 for those presenting at 13–18 hours.

Interventional management

Primary percutaneous coronary intervention

Percutaneous coronary intervention aims to re-establish coronary perfusion to the myocardium. This is achieved either with angioplasty or stenting. Angioplasty is the mechanical widening of these obstructions by inflation of a balloon within the vessel. Following deflation it alleviates the diminished blood flow beyond the obstruction by crushing any atheromatous plaque into the arterial wall and thereby increasing the vessel's internal diameter. Stents are a mechanical framework often used to maintain this adequate blood flow and prevent or reduce restenosis.

A meta-analysis of randomized controlled trials evaluating the optimal management strategy (interventional *vs* non-interventional) in patients with unstable angina or non-ST elevation myocardial infarction has suggested that the invasive approach should be considered for this subset. In the analysis that covered seven randomized controlled trials with over 9200 patients, Choudhry et al (2005) demonstrated a reduction in the occurrence of fatal and non-fatal re-infarction and hospital re-admission.

Primary percutaneous coronary intervention consists of urgent balloon angioplasty (with or without stenting), without the previous administration of fibrinolytic therapy or platelet glycoprotein IIb/IIIa receptor inhibitors, to open the infarct-related artery during an acute myocardial infarction with ST segment elevation. Primary percutaneous coronary intervention is preferred if a skilled interventional cardiologist and catheterization laboratory with surgical backup are available and if the procedure can be performed within 90 minutes after initial medical contact with the patient, provided the duration of the ST elevation myocardial infarction is 12 hours or less. (Antman et al, 2004). The evidence for primary percutaneous coronary intervention is robust in ST elevation myocardial infarctions with a lower mortality and stroke rate favouring an interventional approach (Weaver et al, 1997).

Coronary bypass surgery

Urgent coronary artery bypass grafting is recommended in the face of an acute myocardial infarction only in specific circumstances, usually presenting as ongoing ischaemia unresponsive to maximal medical therapy or as significant haemodynamic compromise. It is primarily for left main-stem disease, severe triple vessel disease or mechanical complications of infarction (ventricular septal defect, free wall or papillary muscle rupture). The operative mortality is thought to be excessive in the first 48 hours after infarction, but even beyond this, it represents a significantly raised mortality rate because of the risk of developing cardiogenic shock. The SHOCK trial (Hochman et al, 1999) suggests this may develop following up to 10% of infarctions and carries mortality as high as 70–80%.

Device therapy

Following ST elevation myocardial infarction patients can develop left ventricular dysfunction leading to heart failure. Cardiac resynchronization therapy can be of long-term benefit, by restoring the mechanical sequence of ventricular activation and contraction. In patients who are at risk of developing arrhythmogenic sudden cardiac death implantable cardioverter defibrillators can also be used following formal risk stratification.

Lifestyle modification

Clinicians must view hospital discharge as an excellent opportunity to re-evaluate long-term care and management of the now 'stabilized' atheromatous plaque. This is primarily achieved through aggressive lifestyle and risk factor modification. This includes addressing smoking cessation, obesity and exercise tolerance as well as treatment of hypertension and hyperlipidaemia. Awareness of the risk of further thrombo-embolic events is a crucial part of rehabilitation. All patients must be referred to cardiac rehabilitation programmes overseen by the British Association of Cardiac Rehabilitation.

KEY POINTS

- Acute coronary syndrome is a spectrum of disease which poses a significant burden to our health-care system because of its common occurrence and potentially serious implications.
- Prompt and appropriate acute management followed by effective secondary prevention can significantly reduced morbidity and mortality.
- Historically, because of a challenging clinical diagnosis, treatment has been inconsistent, but now owing to collaboration of extensive clinical trials we have clearer guidelines based on best available evidence. This should help standardize diagnosis and treatment, and improve patient outcomes.

Conclusions

Historically, because of a challenging clinical diagnosis, treatment of acute coronary syndrome has been inconsistent. Owing to the collaboration of extensive clinical trials we now have clearer guidelines based on the best available evidence. This should help standardize diagnosis and treatment, and improve patient outcomes. **BJHM**

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