Current treatment and future prospects for the management of acute coronary syndromes

K BHAGAT

Abstract
The impact of ischaemic heart disease on the burden of cardiovascular disease continues to escalate worldwide. Although international statistics suggest a levelling off in Western world, in the less industrialised parts of the world the effects of this disease are only beginning to be documented. Nonetheless, rapid advances have been made in the diagnosis and management of the acute coronary syndromes (the term which encompasses the protean clinical manifestations of the ischaemic process). The therapeutic strategies discussed in this article cover two broad subjects that have been found to be critical in the evolution of the disease: i. interfering with the haemostatic balance by retarding the thrombotic process; ii. modifying local and systemic vasoconstricting stimuli.

Introduction
Acute coronary syndromes (unstable angina, Q-wave and non-Q-wave myocardial infarction) represent one of the fastest growing socio-economic problems facing medicine. Some idea of the prevalence of these clinical manifestations of atherosclerosis in the population can be obtained from consideration of the following international data:

a. Four of every six hospital beds in Western countries equipped with the most sophisticated means are occupied by patients with acute coronary syndromes.\(^1\) Furthermore, from 1995 to 1997, the mean stay in hospital for patients with acute coronary syndromes was 3.5 days in South America, 2.2 in North America and 4.4 in Europe.\(^2\) In addition, these mean durations of stay assumed that there were no complications deriving from the disease itself during the time spent in hospital.

b. In the USA alone, nearly 900,000 citizens were admitted to hospital centres with acute coronary syndromes in 1994.\(^3\) In the UK, the cost of acute coronary syndromes in 1998 is expected to amount to £1 800 million (personal communication).

Figures on the incidence of ischaemic heart disease in Southern Africa are scanty. There are, as yet, no systematic studies addressing this evolving problem.\(^4\) However, it is clear from the increasing number of patients admitted with this disease that the incidence is rising and will inevitably follow the same trends documented in other emerging economies such as South East Asia and South America.

Furthermore, the costs of hospital stay, human resources, professional fees, drug therapy, supplementary investigations and the temporary absence of the patient from the workforce (assuming no complications) of acute coronary syndromes amounted to approximately $US 12 000 million.\(^5\)

Prognosis and Clinical Classification.
Prognosis: It is important to establish the prognosis of all patients admitted with an acute coronary syndrome while these patients are in an acute phase. Approximately 0.5 to 1% of these patients will die in the acute phase, 4 to 6% will develop a Q-wave infarction, and 17 to 20% will develop angina that is refractory to established therapy.\(^6\)

The incidence of non-Q-wave infarction in the acute phase is similar to that of Q-wave infarction. Nevertheless, because of the sub total occlusion of the involved vessel in non-Q-wave infarction that threatens the remaining myocardium,
the incidence of death within a year approximates that of type Q infarction.6

Clinical classification: The most widely used clinical classification of angina is that recommended by the Harvard group directed by Dr Braunwald and published in 1989.7 This classification is based on consideration of the severity of the angina (as assessed by clinical symptoms), the circumstances in which angina occurs, and documentation of prior ischaemic load (as assessed by ECG signs of infarction or prior intake of anti-ischaemic drugs). The model is being analysed for its ability to provide prognostic data and has been a component of most clinical studies on the subject.

Pharmacological Recommendations.

The therapeutic strategy in patients with primary unstable angina has two broad aims:

i. Interfering with the haemostatic balance by retarding the thrombotic process,

ii. Modifying local and systemic vasoconstricting stimuli.

Aspirin: The drug that has been shown to be most effective in reducing the risk of death and acute infarction in patients with primary unstable angina is aspirin,8,9 at dosages ranging from 75 to 1250 mg/day. This drug had a significant absolute benefit (in terms of the number of attacks prevented per 100 patients treated per month) in all studies conducted, although the benefit was lower in studies with long follow up periods.

It is interesting to note that research studies have clearly modified the use of aspirin in clinical practice. Prior to 1984, only 25% of patients with coronary disease took aspirin regularly, whereas in 1995, 84% were using it regularly. Ticlopidine (a new adenosine-antagonist, at doses of 500 mg/day, has also been recognised as an effective drug for reducing major ischaemic events.10

Most centres now recommend that patients with acute coronary syndromes should take aspirin at a starting dose of 300 mg by the oral route, followed by a daily dose of 75 to 325 mg, unless its use is absolutely contra-indicated. In that case, ticlopidine should be taken at dosages of 500 mg/day, remembering that its action begins 72 hours after the onset of therapy. If the use of aspirin is relatively contra-indicated, the doctor in charge should weigh the risk benefit ratio associated with its use in terms of potential to induce bleeding/allergy versus the benefit derived in preventing progression to a myocardial infarction.

Nitrates: Nitroglycerin was first used as an antianginal drug by Brunton in 1867, after which it became the most commonly used drug in these conditions. When given intravenously, nitroglycerin has been shown to decrease the number of ischaemic attacks in coronary patients.11,12

Once again the consensus of opinion is that intravenous nitroglycerin (in titrated dosages) should be used in patients admitted to hospital with pain for at least 24 hours up to a maximum of 48 hours except in cases of recurrent angina, persistence of ECG changes, or heart failure, when more prolonged treatment may be required. In other cases, isosorbide mononitrate (one oral tablet every eight hours) can be used in the acute phase. Application of a transdermal nitroglycerin patch every 24 hours, or sublingual nitrates in sufficient therapeutic doses are alternatives.

Beta-blockers: Beta-blockers have been shown to have significant anti-ischaemic effects when used as antiarrhythmic or antihypertensive agents.13 Beta-blockers should be recommended, except when absolutely contra-indicated or when there is a strong suspicion of vasospasm as a dominant mechanism of angina. Administration by the intravenous route is suggested (e.g. the selective beta blocker atenolol, the nonselective beta blockers propranolol, or esmolol) when there is tachycardia, arterial hypertension or angina. In all other cases, the oral route should be used, titrating the agent chosen according to the heart rate and blood pressure.

Calcium antagonists: Use of nifedipine, indicated with no other pharmacological association, worsened the prognosis in a population of patients with unstable angina, and its use as monotherapy is, therefore, contraindicated.14,15 Verapamil has been shown to reduce anginal attacks in patients admitted with a diagnosis of angina and a clear vasospastic component in the course of their attacks.13 There are no clear data to assess the efficacy and tolerability of diltiazem, which has a less potent vasodilating action than nifedipine and is a less potent depressant of the myocardium and of sinoatrial and atrioventricular conduction than verapamil. Its antianginal effect appears to be based on a decrease in heart rate.

Similarly, as yet insufficient data are available to assess amlodipine (a third generation dihydropyridine), which produced neutral results with regard to mortality due to ischaemic heart disease in the Prospective Randomised Amlodipine Survival Evaluation (PRAISE) study.16 Use of calcium antagonists is therefore not generally advised as first choice therapy, except in those cases where use of beta-blockers is contraindicated or where suspected coronary vasospasm is suspected as a dominant mechanism. However, calcium antagonists can be usefully combined with other drugs, in patients, with arterial hypertension or recurrent angina not controlled with previous therapies. Use of calcium antagonists that decrease heart rate is recommended.

Angiotensin-converting enzyme (ACE) inhibitors: At present there are no conclusive data so far to warrant the routine use of ACE inhibitors in patients with acute coronary syndromes.

Indirect antithrombin drugs: Non-fractionated heparin has been shown to add benefit to the use of aspirin1 for the treatment of unstable angina when a suitable intravenous infusion nomogram can be established. Injection of an intravenous bolus of 5 000 IU followed by continuous administration until an activated partial thromboplastin time (APTT) ranging from 55 to 85 seconds is achieved appears to be appropriate.17 It is interesting to note that APTTs above this range not only expose patients to a greater risk of bleeding but also clearly reduce the efficacy of the drug. Thus, it is important to monitor the use of non-fractionated heparin carefully and serially.18

Low molecular weight heparins (i.e. heparins with molecular weights ranging from 5 000 to 8 000 daltons) have greater bioavailabilities and half-lives than standard heparin. They are extremely well tolerated and easy to use, and their efficacy in acute coronary syndromes is currently
being assessed. Since they have lower anti IIa and greater anti-Xa activity than non-fractionated heparin, together with a reduced tendency to interact with platelets of certain peptides such as platelet factor 4, a significant decrease in bleeding is achieved with these agents.

Several important clinical trials following the Argentine pilot study of nadroparin calcium have overall drawn highly positive results. These are the FRISC (Fragmin during Unstable Coronary Artery Disease) study which compared aspirin with aspirin plus dalteparin, the ESSENCE (Efficacy and Safety of Enoxaparin in Coronary Events) study which compared standard heparin plus aspirin with aspirin plus enoxaparin at doses of 1 mg/kg twice a day by the subcutaneous route, and the FRIC (Low Molecular Weight Heparin in the Treatment of Unstable Coronary Artery Disease) study which compared aspirin plus standard heparin with aspirin plus dalteparin at doses of 120 IU/kg twice a day by the subcutaneous route during the acute phase.

The current opinion remains that use of low molecular weight heparins by the subcutaneous route is associated with similar results to those reported with non-fractionated heparin, administered intravenously. This statement is based on the results of the FRIC and ESSENCE studies, in which dalteparin and enoxaparin were used, respectively. If non-fractionated heparins are used, the APTT should be increased to twice the baseline value (between 55 and 85 seconds). Low molecular weight heparins should be administered subcutaneously in the abdominal wall at the following doses: enoxaparin 1 mg/kg twice a day; dalteparin 120 IU/kg twice a day. The use of these anti-thrombin agents is strongly advised in those patients showing confirmed depression or transient and resolved elevation of the ST segment (assuming that the latter is not considered to be an acute ST segment myocardial infarction in progress). At present the evidence suggests that heparins should be prescribed for a minimum of 72 hours and a maximum of eight days.

**Future Prospects.**

Pharmacological developments: Platelet IIb/IIIa receptor antagonists. Antagonists of platelet receptors IIb/IIIa are currently undergoing clinical testing. Use of these agents with aspirin has provided encouraging results particularly in coronary transluminal angioplasty using abciximab (or ReoPro®). In the EPIC (Evaluation of Platelet IIb/IIIa for the Prevention of Ischaemic Complications) trial, this combination showed greater efficacy than heparin alone in lowering the rate of combined events such as death, infarction or emergency revascularisation within 30 days of the procedure (35% reduction in patients administered bolus plus continuous infusion versus heparin alone; 8.3 versus 12.8%, p = 0.009). Substantial bleeding occurred in 12% of patients in the combined treatment arm, however.

In the EPILOG study patients admitted for unstable angina were randomised, after demonstrating recurrent angina and before being referred for angioplasty, to aspirin plus heparin or to aspirin plus heparin plus ReoPro® administered at a substantially lower dose (0.25 mg/kg in bolus, followed by continuous infusion of 10 ug/kg/min for 18 to 24 hours before angioplasty and up to one hour after). While ReoPro® decreased the incidence of death, infarction or emergency revascularisation within 30 days of the procedure to 10.8%, incidence in the conservative arm reached 16.4%, with a 9.7% rate of overall haemorrhagic complications in the ReoPro® arm.

Other inhibitors such as lamifiban (PARAGON A study) obtained neutral results compared with heparin in a dose-ranging trial, the study accordingly being discontinued in the interim. However, encouraging results were reported with tirofiban.

The first important trial of these drugs by the oral route (Ro 48-3657) passed through its phase II study which is known as TIMI-12.

**Clopidogrel**: Clopidogrel, a recently developed trienopyridine derivative chemically related to ticlopidine and able to inhibit ADP-induced aggregation, was evaluated in the CAPRIE (Clopidogrel vs Aspirin in Patients at Risk of Ischaemic Events) study at a dose of 75 mg/day in atherosclerotic patients. The results of this study can be considered neutral in comparison with aspirin. The drug demonstrated a slight benefit improving strength in patients with intermittent claudication of the lower limbs.

With respect to events of greater clinical significance, however, such as stroke and acute myocardial infarction, the efficacy demonstrated by clopidogrel was no greater than that of aspirin, although it was better tolerated than the latter agent.

**Direct antithrombin drugs**: The thrombin inhibitor hirudin is obtained from Hirudo medicinalis, the leech. It can now be manufactured by recombinant technology, thus facilitating its production and reducing costs. Hirudin is in the investigation stage, and while some data are encouraging other studies (TIMI-9; GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries) III have yielded less favourable results. The haemorrhagic complications of hirudin mean that dosages must be titrated in the meantime, while further consideration of the best use of this agent is undertaken.

**New Drugs**: Antithrombotic drugs currently under development and about to enter research phase include those able to block directly the activity of factor Xa (anti-Xa), and lower molecular weight anti-thrombin peptides, e.g. pentasaccharide. Molecules that can interfere with the activity of tissue factor are also in early development phase. Research is also being conducted on new IIb receptor-blocking compounds, which may have antiplatelet activity.

Drugs that have effects on the vascular endothelium are also under investigation. Phase III studies will soon be conducted on an inhibitor of the Na+/H+ exchange pump active in the cell membrane (HOE 642), the effect of which will be to decrease, during the ischaemic phase, the secondary influx of Ca++ into diseased cells with increased intracellular H+ levels. The aim of such therapy will be to restrict the area of necrosis by controlling cellular acidosis.

Pilot studies are also being conducted with macrolide antibiotics, which can act within macrophages to reduce the infectious burden, thereby decreasing the associated inflammatory process. Preliminary studies to identify a
particular allele in the HLA system have led to the first step in the development of a DR system blocker. Preliminary data are expected to be available towards the end of 1999.

References


