Acute coronary syndromes

Akhil Kapur

Akhil Kapur MRCP, Consultant Interventional Cardiologist, London Chest Hospital, Barts and the London NHS Trust

This conference was held at the Royal College of Physicians on 2 February 2005

Clin Med 2005;**5**:406–8

Pathophysiology

The pathological basis of the vast majority of acute coronary syndromes (ACS) is the coronary atherosclerotic plaque. The process probably begins with fissuring or erosion of the plaque, resulting in plaque instability. Other patient specific factors that combine with the unstable plaque include abnormalities in coagulation and platelet factors, as well as the amount of myocardium at risk. This gives rise to the notion of the 'vulnerable plaque' and the 'vulnerable patient'.

There are two types of ACS: STEMI and NSTEMI. STEMI (ST elevation myocardial infarction) is complete epicardial occlusion following plaque disruption, and leads to propagation of thrombus and concomitant epicardial vasoconstriction. NSTEMI (non-ST elevation myocardial infarction) is incomplete and transient epicardial occlusion with platelet-rich thrombus and phasic distal embolisation. It can occur in the context of complete epicardial occlusion if there is partial collateralisation or in circumflex occlusions, which probably explains why fibrinolytic therapy does not work in NSTEMI ACS.

The pathogenesis of the atherosclerotic plaque is based on a classical model of inflammatory cell recruitment. Which inflammatory mechanisms result in plaque instability, rather than expansion, are uncertain, but specific changes in T-cell signals to the macrophage and smooth muscle cell are probably involved.

TRIAL ACRONYMS

GRACE	Global Registry of Acute Coronary Events
PRAIS UK	Prospective Registry of Acute Ischaemic Syndromes in the UK
ISIS II	Second International Study of Infarct Survival
REACT	Rescue Angioplasty versus Conservative treatment or repeat Thrombolysis
FRISC 2	Fragmin and fast Revascularisation during InStability in Coronary artery disease 2
TACTICS TIMI 18	Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy Thrombolysis In Myocardial Infarction 18
MIRACL	Myocardial Ischema Reduction with Aggressive Cholesterol Lowering
DIGAMI 1 and 2	Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction 1 and 2

Inflammatory patient-specific factors are suggested by the observation that patients with higher than average C-reactive protein (CRP), whether they have evidence of vascular disease or not, are all at increased risk of myocardial infarction. In fact, aspirin is more protective in the context of raised CRP. The cause of the elevation of inflammatory markers is likely to be infectious triggers that either acutely trigger plaque instability or chronically activate the inflammatory system. It has been found that multiple active plaques exist beyond the culprit lesion, and that at the time of the event there exists a state of pan-coronary tree inflammation.

Modern treatments of ACS recognise the basis of the disease in terms of the relative importance of coagulation and platelet activation, but specific anti-inflammatory therapies have yet to be developed.

Epidemiology

As a nation we are benefiting from an increasing life expectancy of a year each decade. However, our risk of coronary events is also increasing. This vascular risk is not just confined to the coronary tree but also includes the brain, peripheral vascular disease and the aorta. In developed countries the absolute number of deaths is stabilising and the age-adjusted risk of vascular death is declining, but the death rate in emerging economies is increasing rapidly.

The reasons for the increase in cardiovascular disease in the world as a whole include increasing longevity; increasing use of tobacco; increasing urbanisation, which results in decreasing physical activity; increasing calorie intake; increasing fat intake; and increasing psychosocial stress. This results in increasing weight and increasing levels of obesity, leading to dyslipidaemia, dysglycaemia and hypertension. By 2020, ischaemic heart disease will be the leading cause of death in the world, overtaking respiratory infection.

The relative contributions of risk factors in different countries is broadly similar with, for example, similar protective effects in all countries from fruit and vegetables, exercise and alcohol in moderation.

The UK still has the highest rates of death and disability from heart disease relative to its economic status. Of the half a million deaths per year in the UK, 60% are due to diseases of the heart and circulation. Rates of death from ACS vary widely in the UK,

with much higher rates in the north west compared to the south east, and considerable intra-regional variation also.

The proportions of patients with STEMI, NSTEMI and unstable angina are roughly equal. According to the Global Registry of Acute Coronary Events (GRACE), the risk of death from STEMI and NSTEMI is greater than with unstable angina, although patients with unstable angina themselves have an increased risk even without an enzyme rise. The in-hospital risk of death from STEMI is 8%, from NSTEMI is 5% and from unstable angina is 3%. PRAIS UK showed that the overall risk of death from an NSTEMI was 25% over four years. This is a similar result to that demonstrated in ISIS II, which showed that STEMI has a mortality risk at four years of 25%.

Classification

The World Health Organization (WHO) has defined a myocardial infarction as requiring two of the following three features:

- characteristic chest pain for 20 min
- typical ECG changes
- elevation of serial cardiac enzymes.

The European Society of Cardiology (ESC) consensus redefined myocardial infarction to take into account any associated damage, as manifested by an elevated troponin, as this is associated with a poor prognosis. The ESC prefers the term ACS, subdivided into STEMI and NSTEMI, which itself has been redefined to take into account the typical rise and gradual fall of troponin.

Troponin can help risk stratify patients with an ACS. It is specific for myonecrosis and not infarction, but a negative troponin does *not* mean low risk.

Acute treatment

STEMI

Early general treatment measures include the use of aspirin and pain relief. The timing of reperfusion is all important, whether undertaken with thrombolysis or primary angioplasty. Several standards exist and these should be strictly adhered to, including, for thrombolysis, the call to needle time, which should be within 30 min; the door to needle time, which should be within 60 min; and, for primary angioplasty, the door to balloon time, which should be within 90 min.

All trials comparing thrombolysis to primary angioplasty, even those involving the transfer of patients from a district general hospital to a tertiary centre, have shown superior results with primary angioplasty. However, there are obstacles to setting up a 24/7 primary angioplasty service throughout the country. Also, the benefits of primary angioplasty may not be so great when compared to prehospital thrombolysis. Rather than competing with a primary angioplasty service, prehospital thrombolysis may in fact be a complementary therapy in remote areas. Legislation now allows paramedic teams to administer thrombolysis on arrival at the patient's home or in the community.

Conference programme

Pathophysiology: biological aspects of ACS
Professor David Crossman, University of Sheffield

Epidemiology of ACS
Dr Marcus Flather, Royal Brompton Hospital, London

Diagnosis, classification and prognosis of ACS
Dr Peter Stubbs, Mayday University Hospital NHS Trust, Croydon

The current standard
Dr Stephen Campbell, Northern General Hospital, Sheffield Teaching Hospitals NHS Foundation Trust

Primary PCI and thrombolysis: horses for courses
Dr Iqbal Malik, St Mary's Hospital, London

Pre-hospital thrombolysis
Dr Howard Swanton, The Heart Hospital, London

Failed reperfusion: what next?
Dr Anthony Gershlick, Glenfield General Hospital, Leicester

The current standard and the future
Professor Keith Fox, University of Edinburgh

The role of PCI
Dr Nick Curzen, Wessex Cardiothoracic Centre, Southampton

The diabetic patient
Dr Simon Heller, Northern General Hospital, Sheffield

Post-discharge issues
Dr Jamil Mayet (Conference Organiser), International Centre for Circulatory Health, St Mary's Hospital and Imperial College London

Therefore, in future, geography will probably influence treatment. Groups of cardiologists in large urban areas are likely to offer primary angioplasty on a 24/7 basis, but in more remote regions, prehospital thrombolysis may be the initial treatment of choice. Further trials on upfront antithrombotic therapy prior to immediate angioplasty are required.

The recent REACT trial has demonstrated that patients who have had a myocardial infarction and who have received thrombolysis once do worse with re-thrombolysis compared to transferring them for rescue angioplasty. This emphasises the need to monitor patients given thrombolysis for evidence of reperfusion and to transfer those who clinically have not reperfused to an angioplasty centre. Of course, this issue is largely negated if angioplasty rather than giving thrombolysis is the primary treatment.

NSTEMI

The GRACE registry demonstrated that death, stroke and readmission rates for NSTEMI at six months were similar to those for STEMI. The one-year death rate for those who survived to reach hospital from STEMI was 21% and from NSTEMI was 31%. To identify those patients at highest risk from ACS, the GRACE risk score has been developed; this identified the highest tertile of at-risk patients who had an in-hospital death rate of

6.7% and a six-month death rate of 13.7%. However, the GRACE registry also demonstrated that the frequency of revascularisation in each of these tertiles does not correlate to their relative risks, suggesting that more needs to be done to risk stratify these patients appropriately so that those at highest risk receive commensurate levels of intervention.

In both the FRISC 2 and TACTICS TIMI 18 studies, an improvement in outcomes was seen in those patients treated with an invasive (angioplasty) compared a conservative strategy, although this benefit appears to be confined to patients who are troponin positive and in the highest risk groups generally. The highest risk group should include not only patients who have a positive troponin but also those who have ST segment depression on ECG, an abnormal exercise test and ongoing ischaemia or pain. While it is accepted that the advent of troponin had improved our ability to identify high-risk patients, there is still room for the refinement of markers. For example, the pan-vascular inflammation that occurs at the time of an ACS must not be ignored. Also, the CD40 ligand is a marker of future events in ACS. In the MIRACL study, patients who had a high CD40 ligand level had an event rate similar to those with a low CD40 ligand level if they received treatment with atorvastatin at high doses.

The diabetic patient

Diabetic patients with an ACS are a special case with specific problems. This patient group is increasing in number and has not benefited from the age-adjusted risk reduction seen in non-diabetic patients with an ACS. Patients with diabetes have significantly more ACS, whether this is STEMI, NSTEMI or unstable angina. They have a higher risk in the first year post STEMI and their total mortality after an ACS is significantly higher. This is emphasised by the observation that a diabetic patient with no history of cardiovascular disease has a comparable risk of mortality after an ACS to a non-diabetic with a previous history of cardiovascular disease.

Several risk factors exist in patients with diabetes which accelerate progression of coronary disease and worsen prognosis. Patients with diabetes have an increased prothrombotic state mediated by increased levels of plasminogen activator inhibitor 1 and increased numbers of glycoprotein IIb/IIIa (GPIIb/IIIa) receptors, and they have increased levels of endothelial dysfunction mediated by hyperglycaemia, free fatty acids and lipid abnormalities. The burden of atherosclerotic disease is worse in these patients on presentation with more multivessel disease and diffuse disease, as well as increased levels of associated conditions, including renal disease, left ventricular dysfunction and peripheral vascular disease.

Despite their worse prognosis, patients with diabetes who have known coronary disease receive several treatments less often than non-diabetic patients, even though they may benefit from these treatments disproportionately. For example, heparins, beta-blockers and reperfusion therapies are all underutilised in patients with diabetes, and this contributes to their poorer outcomes.

Patients with diabetes and ACS may require specific treatments. There is evidence that in the first three months after an ACS, diabetic patients benefit from glucose-lowering therapy with insulin sensitising treatments, more than they do from insulin-providing treatments. Conflicting results, however, have come from the DIGAMI 1 and 2 trials in which a glucose/insulin infusion is used post STEMI. While DIGAMI 1 showed the benefits of an intravenous glucose/insulin infusion post STEMI followed by three months of insulin, DIGAMI 2 has not been able to clarify whether this benefit arises from the first or second component, or whether there is a benefit at all from this regimen over standard therapy. Therapies used in percutaneous coronary intervention, such as GPIIb/IIIa inhibitors and drug-eluting stents, are proving valuable in patients with diabetes. It should be noted, however, that it is difficult to draw conclusions from available clinical studies because all the results pertaining to patients with diabetes have been derived from subset analyses involving composite endpoints. The way forward may be to undertake trials specifically in patients with diabetes.

Post-discharge issues

Post-discharge following an ACS the importance of behavioural modification, including smoking cessation and weight reduction, must be stressed to patients. Antihypertensive therapy has direct benefit on reducing deaths from coronary heart disease. ACE inhibitors, independent of hypertensive disease, can result in positive remodelling post STEMI. Also, aggressive lipid lowering is associated with improved prognosis, which is probably independent of the statin agent used.

Conclusion

Tremendous strides that have been made in the treatment of ACS over the past few decades. The profile of the treatment of ACS in the UK has changed dramatically in recent years with a much greater emphasis on invasive management of these patients who are amongst the sickest in our hospitals (despite often looking well from the end of the bed!). This is a reflection of the evidence base which emphasises the benefit of invasive management in many of these patients. This trend is likely to continue with invasive treatments increasingly being delivered immediately the patient presents. While levels of ACS in the UK may be stabilising, the burden of this disease is still enormous, there remain many unanswered questions and, with demographics changing in this country, new challenges will need to be confronted.