Myocardial infarction

A conference on myocardial infarction (MI) was held at the Royal College of Physicians on 6 June 1994, organised by Dr K S Channer. The management of myocardial infarction has changed dramatically in the last few years with the introduction of effective measures to reduce early mortality and improve long-term prognosis. The purpose of this conference was to review these approaches and determine how they may be introduced into practice. The conference was divided into three sections: preventing myocardial infarction, acute intervention at the time of infarction, and preventing reinfarction.

Preventing myocardial infarction

The role of the physician in encouraging patients to stop smoking was reviewed by **Dr C Steele** (general practitioner and director of the Stop Smoking Clinic, University of South Manchester). He began by outlining the pleasures of nicotine addiction and the miseries of withdrawal. Although it kills 300 people per day in the UK, cigarette smoking brings a net gain of £16 million per day to the Treasury. The success rate of strategies such as counselling, drugs, hypnosis, and aversion therapy is less than 10% cessation at one year. Nicotine replacement therapy more than doubles the rate of success. His advice to patients wishing to stop was to set a date on which to stop abruptly and use nicotine replacement patches of decreasing strength at monthy intervals for a total of three months. GPs, spouses, friends and colleagues should be encouraged to provide regular support. The best success rate was 25% cessation at one year, but doctors should encourage patients to keep trying since most successful ex-smokers have failed many times before.

Professor L E Ramsay (Royal Hallamshire Hospital, Sheffield) reviewed the relationship between hypertension and myocardial infarction. Hypertension has long been known to increase the risk of a first MI, death at first MI and sudden death; however, most of the patients who die are those with mild hypertension. The early trials of the treatment of hypertension showed little discernible effect on coronary artery disease despite a reduction in stroke, heart failure, malignant hypertension, and renal disease. More recent overviews [1], however, have estimated a 14% reduction in coronary events with the treatment of hypertension. Nonetheless, about 80% of MIs in hypertensive patients are not prevented by treatment. Why? Presumably, multiple other risk factors have a part to play. The SHEP [2], EWPHE [3], and MRC [4] trials showed a reduction in coronary events in elderly patients, and low-dose thiazides have a 'cardioprotective effect'. Professor Ramsay thought that thiazides are the best first-line therapy for hypertension in those over 60 years of age.

Professor H D Tunstall-Pedoe (University of Dundee) discussed the value of lipid screening. He felt it was only worth while as part of a 'total coronary risk' assessment in selected patients. Although the serum cholesterol level is predictive of the development of coronary heart disease, the screening of individuals should be for coronary risk without undue emphasis on the serum cholesterol. Risk factors multiply in their effects: in the absence of other risk factors a serum cholesterol in the highest quintile poses a relatively low coronary risk; and a moderate elevation of three or more risk factors is much worse than the gross elevation of a single factor. The serum cholesterol should be measured last, not first, and interpreted in context. The cut-off point algorithms as used in many cholesterol screening programmes are 'naive, misleading and dangerous'. Also, the algorithms fail to take into account the rise in serum cholesterol with age, especially in post-menopausal women. Serum cholesterol levels are very variable, and three to five readings are required to establish the true level for a given individual. Therefore, much of the current management of hypercholesterolaemia is based upon 'random error'. The public perception of lipid screening is such that many patients feel cheated if their doctor refuses to measure their serum cholesterol, but if no indications for testing exist, or there is no motivation to carry through a change in lifestyle, the serum cholesterol should not be measured.

Professor S E Humphries (University College London Medical School) gave a resumé of the development of gene markers of cardiovascular risk. The role of the genes is to maintain homeostasis, and vascular disease is the result of failure of homeostasis. Specific gene mutations may confer a high degree of risk. More common are the effects of multiple mutations, each having smaller effects individually. At present, molecular genetic techniques are most effective for identifying the rarer single gene defects and work is only beginning on gene-gene and gene-environment interactions. The process of myocardial infarction involves atheroma formation, plaque rupture, and thrombosis. A number of genes have now been identified which may be involved in each of these processes. Mutations of the LDL receptor gene cause familial hypercholesterolaemia, a single gene defect with a large effect. It has an incidence of 1 in 500, and 50% of affected men will die before the age of 55. Over 150 mutations have now been defined on the LDL receptor gene, so it will be difficult to devise a genetic screening test. Different mutations may cause different expressions of the disease and may confer different

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degrees of risk. An insertion/deletion polymorphism on the angiotensin converting enzyme (ACE) gene is strongly linked to the serum ACE level. The deletion allele has been linked to the development of myocardial infarction, and appears to be acting most strongly in young subjects with low serum lipids [5]. Polymorphisms of the fibrinogen gene are linked to serum fibrinogen expression, a well-known risk factor for ischaemic heart disease. As fibrinogen is an acute phase protein, knowledge of the gene status may give a better measure of risk than the serum fibrinogen level. Professor Humphries believed that, ultimately, an individual's gene profile may give a better assessment of coronary risk than studies at the protein level.

These presentations provided a fascinating insight into the 'clinical evolution' of a coronary risk factor. The effects of hypertension are well defined, intervention is of proven benefit but less effective in preventing coronary artery disease than was initially supposed. The risks of a high serum cholesterol are well described, effective therapy exists, but who will benefit from treatment is not fully defined, and the results of intervention are disputed. The molecular markers of coronary disease are still in the early stages of development and effective therapies need to be found. The new risk factors must be rigorously assessed before their measurement is introduced into routine clinical practice. Professor Ramsay thought that enthusiasm for the clinical application of genetic techniques must not be allowed to run too far ahead of detailed epidemiological study.

Acute intervention at the time of myocardial infarction

Professor D P de Bono (University of Leicester) asked for aspirin, analgesia, access to a defibrillator, and thrombolysis if he were to have an acute MI. GPs should have a good reason not to give 150mg or more of aspirin, which should be chewed. Every patient should be considered for thrombolysis and age should not be a contraindication. Streptokinase is effective and cheap but there are problems with allergy. Tissue plasminogen activator (t-PA) may be slightly better (one extra life saved for every 100 patients treated with front-loaded t-PA and heparin rather than streptokinase) but it is costly, more difficult to administer, and causes more cerebral haemorrhage [6]. The major problem with thrombolytics is failure to use them (eg only 25-55% of patients in Trent region receive thrombolysis [7]). More energy should be directed toward facilitating early use rather than further complicating the mode of their use.

Dr K L Woods (University of Leicester) discussed the controversy over the use of magnesium in acute MI. LIMIT-2 studied the use of intravenous magnesium in 2316 patients with MI and showed a 24% reduction in death (95% CI: 1% to 43%) and a 25% reduction in left ventricular failure (95% CI: 7% to 39%) [8]. However, the massive ISIS-4 trial with 60,000 patients failed to detect any reduction in mortality from the use of magnesium [9]. Dr Woods argued that the reason for the discrepancy was that in LIMIT-2 magnesium was given prior to thrombolysis, whereas in ISIS-4 magnesium was generally given after thrombolytics and aspirin. He cited the experimental animal models which showed that myocardial injury also occurs when the myocardium is reperfused from a previously occluded coronary artery but this injury is attenuated by the presence of magnesium at the time of reperfusion. He thought that the trials had been undertaken without a clear understanding of the mechanism of action of magnesium. Professor Sleight disagreed. He felt that 'front loading' the magnesium would have little effect on outcome and noted that there had been no improvement in survival in those patients who received magnesium but not streptokinase in ISIS-4.

Professor P Sleight (John Radcliffe Hospital, Oxford) discussed the use of ACE inhibitors and nitrates at the time of infarction. While showing no benefit, CONSENSUS II had shown no evidence of harm from intravenous enalapril given early after infarction [10]. In ISIS-4 [9], captopril was given orally approximately one hour after thrombolysis to an unselected population with acute MI, and the dose was carefully titrated upwards over a 24-hour period to 50mg bd for 28 days. Captopril reduced overall mortality by 0.5% at 35 days ($2p = 0.04$). Professor Sleight agreed that the reduction in mortality was likely to be greater in higher risk groups, such as those with left ventricular dysfunction. Likewise GISSI-3 showed a 0.8% reduction in overall mortality at six weeks with oral lisinopril started on the day of infarction ($2p = 0.03$) [11]. On the other hand, nitrates did not reduce mortality and he recommended their use only for pain relief.

Preventing reinfarction

Professor S G Ball (University of Leeds) subtitled his talk 'data torture', and warned against the use of redefined end-points or the retrospective elimination of patients from clinical trials. He illustrated this with an example from the recent literature: the reported prevention of reinfarction by ACE inhibitors. In the original SOLVD treatment arm trial [12] there were 53 deaths from reinfarction on placebo and 40 deaths in the enalapril-treated group, whereas in the later *Lancet* paper [13] this had become 91 deaths from infarction on placebo and 69 deaths in the ACE-inhibitor-treated group ($p < 0.02$). Where had the extra deaths come from? This latter paper also reported a reduction in the incidence of hospital admissions for angina (240 placebo *vs* 187 captopril $p < 0.001$) although neither angina nor the number of hospital admissions were defined as primary or secondary end-points in the SOLVD trial. The SAVE trial reported a reduction of 23% in the rate of reinfarction in the captopril-treated

group [14]. However, the Food and Drug Administration criticised this 'post-hoc reanalysis' on the grounds that the diagnostic criteria for reinfarction were changed from those stated when the trial was begun [15]. The AIRE, ISIS-4, and GISSI-3 trials have shown no reduction in the rate of reinfarction by ACE inhibitors to date, and Professor Ball concluded that, at present, there was little evidence that ACE inhibitors prevent reinfarction.

Professor Ball considered that all patients with clinical or radiological evidence of heart failure after MI, even if transient, should be given an ACE inhibitor [16]. Professor Ramsay expressed concern about missing the patients with 'silent' impairment of left ventricular function for whom ACE inhibitors are of proven benefit [17]. Professor Ball agreed this was a considerable problem and recommended that all those at risk should have a MUGA scan or echocardiogram, although the current shortage of resources made this difficult to institute.

Professor J R Hampton (University Hospital, Nottingham) discussed the role of beta blockers and aspirin in preventing reinfarction. Aspirin works and everyone with vascular disease should have it. Intravenous beta blockade at the time of infarction worked in the 'pre-thrombolysis' ISIS-1 trial [18], but does the benefit still exist in the thrombolytic era? It cannot be assumed that the benefits of individual therapies will be additive. Starting beta blockers more than 48 hours after MI appears to reduce mortality but this is not proven since thrombolysis has become available. The question of combination therapies with a beta blocker and ACE inhibitors has arisen and the possible use of beta blockers in milder heart failure is beginning. However, for the time being, Professor Hampton recommends ACE inhibitors for patients fulfilling the AIRE criteria, and beta blockade for those who do not.

Dr D P Lipkin (Royal Free Hospital, London) reviewed the 'Cinderella' of cardiology, cardiac rehabilitation. Does exercise prevent reinfarction? The answer remains unknown. It is clear that fit people have fewer MIs than those who are unfit. However, the safety of early ambulation after MI was only established in the 1960s. Meta-analyses of the numerous small trials suggest some benefit from exercise-based rehabilitation, with a reduction of up to 25% in post-infarction mortality [19]. Exercise tolerance improves with rehabilitation and, as expected, there is a proportionately greater improvement in those with the poorest initial capacity. Exercise training after MI favourably affects many of the coronary risk factors, raising the ischaemic threshold, ejection fraction and serum HDL cholesterol, while reducing blood pressure, weight, and platelet stickiness. Rehabilitation does not appear to affect the incidence of depression after MI, which is known to be an independent risk factor for poorer outcome. Rehabilitation is relatively cheap (£4-£15 per patient). Dr Lipkin concluded that cardiac rehabilitation is cost-effective and should be made available to all who would benefit, especially those with poorer cardiac function and reduced exercise tolerance. In the subsequent discussion, Professor Sleight said that he thought lifestyle changes, including regular exercise, were at least as important as all pharmacological measures in reducing cardiac morbidity after MI.

Mr T Treasure (St George's Hospital, London) gave a surgeon's view of when to intervene operatively in myocardial infarction. The place of surgery, he believed, was to prevent reinfarction rather than to intervene during the acute phase of an MI. Immediate coronary artery bypass surgery is compatible with good survival but is logistically impossible in the UK. Similar logistic difficulties exist for acute percutaneous coronary angioplasty. He disagreed that later intervention should only be considered for symptomatic patients, but felt that patients with a poorer prognosis should be considered for surgery as well. This included patients with proximal coronary lesions and those with impaired left ventricular function and extensive coronary artery disease. Previous trials of surgical and medical therapy took place in the pre-thrombolytic era, and a different patient population may exist now. For example, thrombolysis may result in patients with smaller infarcts but more residual ischaemia.

Conclusion

The conference was well attended and provided 'state of the art' views on current prevention and management of MI by some of the world's leading investigators. Much controversy still exists in the application of the findings of the mega-trials, and this was reflected in the diversity of opinions expressed. However, several messages came through clearly. Coronary risk should be seen in the light of multiplying interactive risk factors. Thrombolysis and aspirin should be given more often and more quickly. ACE inhibitors are indicated for all patients with left ventricular dysfunction and, probably, beta blockers for those without. Lifestyle modification after MI remains important and worthwhile. Several topics were not addressed, particularly the use of coronary angioplasty early in the history of MI; perhaps an American or European perspective would have been valuable, although a declared aim of the conference was to see how current knowledge may be introduced into UK practice.

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College Tutors' Seminar

The College Tutors' Seminar was held at the Royal College of Physicians on 3 March 1994

Current affairs

Professor Sir Leslie Turnberg (President, RCP) reminded College Tutors that the far reaching changes imposed on the Health Service will have an impact not only on medical education but also on the workload and necessary commitment of the tutors at grassroots level.

Although the Calman report *Hospital doctors: training for the future* has been accepted by government, no new resources will be allocated to implement its proposed changes. It is envisaged that these changes will take place slowly enough to allow them to be funded by a shift of resources from within the Health Service itself; yet the timetable set out in the report is relatively short.

The planned demise of the regional health authorities and the relocation of postgraduate deans also creates as yet unresolved problems. It is unclear whether the deans will become responsible to the regional offices of the Medical Executive (ROME), to the head office of the Medical Executive (HOME), or to the universities. The College itself sees a need to strengthen its own involvement at regional level and a proposal has been made to the NHSME at regional level that there should be 'regional chapters' comprising several Colleges.

The President also touched on the plight of SHOs, their need for a core curriculum and the benefits of protected formal education time. This last issue stimulated a lively discussion during question time.

Implications of the Calman report

Professor Brian Pentecost (Linacre Fellow of the RCP) described the effects of the Calman report on shortening the period of higher specialist training and reducing the number of doctors in training. To achieve these aims, the new combined registrar/senior registrar grade trainees would require more structured training programmes supported by specific curricula

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