MANAGEMENT OF ANGINA PECTORIS: CURRENT AREAS OF INTEREST

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INTRODUCTION

Cardiology is arguably the most exciting branch of medicine, with a proliferation of new ideas and technical innovations which attract eager, bright researchers and practitioners. I hope to show in this article that the problem of ischaemic heart disease is benefitting from this vibrant outlook and I will emphasise newer aspects which are altering our approach and helping patients. Among the key areas in the management of angina pectoris which will be addressed are risk factors and prevention, investigations, new drug treatment, the roles of percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass grafting (CABG) and newer techniques and, where possible, a look into the future.

The size of the problem is awesome; estimates of the prevalence of angina in middle-aged men vary from 3.6% to 7.9%[1] and the most reliable estimate of the incidence of new cases suggests 22,000 each year in the United Kingdom.

RISK FACTORS AND PREVENTION

The reduction in mortality from coronary heart disease in many countries has led to the acceptance that risk factor reduction is responsible for the improved mortality figures, but scientific evidence is lacking where primary prevention is concerned. Attempts to promote a healthy lifestyle by reducing cigarettes or encouraging a healthy diet to reduce cholesterol and blood pressure and to lower weight (in studies such as Oxcheck and the British Heart Family Study[2]) are disappointing. In the latter, for example, there is no reduction in smoking and total cholesterol is lowered by 0.2mmol/L although there is a small reduction in weight (down by lkg) and systolic blood pressure (down by 3mmHg). No benefit on morbidity or mortality is shown. These results suggest that the firm advice on risk reduction laid out in the Health of the Nation is not warranted. There is no justification for widespread systematic screening on this evidence but, nevertheless, a general move towards a more healthy lifestyle on the lines of the Health of the Nation seems to be sensible, despite deficiencies in the scientific background.

Risk factor reduction is much more clearly related to improved outlook in patients with established vascular disease. Three recently debated topics deserve special attention, namely the management of hyperlipidaemia in the light of the 4S Study, the best ways to stop smoking and the possible value of antioxidants.

Hyperlipidaemia

By far the most important and exciting trial report in the past year is the 4S Study[3] (Scandinavian Simvastatin Survival Study). It was presented first at the American Heart Association meeting in Dallas in November 1994 and an impressively large audience greeted the results with enthusiasm. This trial shows conclusively that reduction of LDL cholesterol with Simvastatin in patients with either angina or previous infarction reduces all cause mortality as well as coronary artery mortality and morbidity. It also destroys the belief that lipid-lowering drugs reduce coronary disease at the cost of an increased rate of violent deaths. Combined with trials such as MAAS,[4] which have confirmed the ability of lipid lowering agents to reduce or reverse atherosclerotic lesions in the coronary arteries, there is now clear evidence that we should aim for normal cholesterol in patients with angina which means that total cholesterol should be 5.2mmol/L or below with the LDL cholesterol below 3.4mmol/L.

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Smoking
Evidence linking smoking with ischaemic heart disease is strong. Survival five years after myocardial infarction is doubled among those who stop smoking. Nicotine replacement clearly helps withdrawal with less than 10% staying off cigarettes at six months using a placebo compared with 22% in those using nicotine patches. The gum seems less good than patches and counselling has no extra benefit. Replacement should be continued for no more than eight weeks.

Antioxidants
There is experimental evidence that antioxidants protect tissues from excess of free radicals which may be related to coronary disease. An excess of free radicals is thought to be involved in atheroma production because oxidised LDL cholesterol is incorporated into plaques. Platelet stickiness is increased when antioxidants are low. Free radicals may damage myocardium and vitamin E may protect arterial endothelium. As yet, there are no controlled trials showing the benefit of antioxidants in coronary heart disease and the recently published Finnish trial using vitamins and the Swedish trial using probucol show no cardiac benefit[5]. In the trial from Finland, there are more deaths in patients taking beta carotene. Observational studies show low vitamin E levels in communities with high levels of coronary heart disease but this is often associated with high cigarette intake. Before firm advice on intake of antioxidants is offered, it seems wise to await the large controlled trials such as the Heart Protection Study and the safest strategy now is to encourage a balanced diet to include sources of antioxidants such as cereal oils, olive oil, nuts, citrus fruits, vegetables, potatoes and red wine.

Two other strategies are potentially useful in reducing the toll from coronary artery disease:

1 Early detection of coronary artery disease may become possible if the promise of magnetic resonance imaging of the coronary arterial tree is fulfilled. A non-invasive method of viewing early lesions leads to the possibility of taking active measures to reduce or prevent progression.

2 Early diagnosis in patients with chest pain by open access pain clinics shows promise. In Southampton 467 patients were referred with a diagnosis of angina made by the general practitioner and 44% were considered to have non-cardiac pain; 24% had definite angina; 13% possible and 6% were unstable. Perhaps the most important finding was that follow-up showed that more than half of the major events and deaths occurred within a month of the onset of pain.

REFERRAL TO SECONDARY AND TERTIARY CENTRES

The report from the Working Party of the British Cardiac Society and the Royal College of Physicians[6] provides clear advice on the management of patients with angina. The primary physician should address three aspects when presented with a history of chest pain:

1 A clinical assessment of symptoms and general background.

2 Clinical examination to exclude other causes of chest pain and other conditions causing angina such as aortic stenosis and anaemia.

3 Review possible risk factors including family history, smoking, diabetes, hypertension.

The working party emphasises the value of an ECG to identify high risk patients rather than as a diagnostic tool since many patients with angina have normal resting electrocardiograms.

Most general practitioners will check lipid levels and are aware of the current guidelines for the management of hyperlipidaemia.

Secondary centres
A secondary centre is defined as one where care is provided by a physician with a special interest and training in cardiology and which offers facilities such as treadmill testing, echocardiography, a coronary care unit with dedicated beds and monitoring facilities and possibly a lipid clinic. These services are available in Lancaster and Kendal but there is scope to improve patterns of referral which is being discussed now. Local medical audit is offering guidelines for the management of angina and limited open access to treadmill testing is starting and will be modified in the light of demand and the availability of technical staff and equipment. Referral for exercise testing and/or a clinical assessment should be considered if angina is intruding into a patient's life despite adequate medical therapy. A poor result on the treadmill would usually lead to coronary arteriography in a tertiary referral centre. This may lead to delays in management but the number of angina sufferers could overload the angiography service without the filter of exercise testing which allows objective evidence of disability. Some secondary centres are being encouraged to establish coronary arteriography to speed up anatomical diagnosis and identification of patients requiring CABG or bypass surgery.

Other patients who need referral to the local secondary centre include:

those with valve disorders

patients with deteriorating angina, particularly those with an unstable picture who often require urgent attention and those whose diagnosis is in doubt.

DRUG TREATMENT OF ANGINA

Standard drug treatment is beta blockers, long acting nitrates, calcium channel blockers as appropriate plus aspirin unless contraindicated. All patients should carry short acting nitrates unless they are not tolerated. The failure to prescribe short-acting nitrates and to advise patients how to use them (ie prophylactically) before predictable pain starts are the commonest omissions in patients referred for further testing in a secondary centre.

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For a quarter of a century there have been only the three major classes of drugs. Now a new class is introduced: the potassium channel openers (KCO). Nicorandil is the first KCO drug on the market and has a dual action. The potassium channel opening action causes arterial dilatation reducing afterload and its nitrate component reduces preload by venodilatation. Dilatation of coronary arteries by nicorandil is probably of similar magnitude to nitrates but there is a suggestion from intracoronary injection of the drug that nicorandil is more effective in stenosed segments. An

intriguing further action on myocardial cells raises the possibility of myocardial cell protection by altering ATP controlled potassium channels and reducing cellular activity in vulnerable myocardium.[7] Trials suggest that nicorandil is of equivalent anti anginal activity to the standard drugs but has advantages. It is lipid-neutral, does not affect glucose metabolism and can be used in diabetes, airways disease and heart failure. Headache is its main side effect and appears to be similar in frequency and severity to nitrate-induced headaches. Unlike nitrates, however, it seems to have no problems with tolerance. There is a clear role for nicorandil in patients who cannot tolerate other agents but the real test is whether it has anything to offer as an additional drug in patients who are not satisfactorily controlled on standard drugs.

PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY (PTCA) AND CORONARY ARTERY BYPASS GRAFTING (CABG)

There are considerable differences in the rates of PTCA and CABG between countries and between regions within the UK. The current aim Is to perform 500 by-pass operations and 3-400 angioplasties per million of the population, which compares with approximately 1000 per million for each procedure in the USA per annum. The outstanding problems which are discussed in cardiological circles now include:

the establishment of guidelines for who should perform the angioplasties

where and how to reduce the restenosis rate in PTCA

the appropriateness of PTCA versus CABG

the introduction of newer procedures.

Angioplasty: by whom and where?
It is still widely accepted that angioplasty should be restricted to centres with immediate access to surgery because of a 2-10% risk of dissection of the coronary arterial wall, though a minority believes that it is acceptable to perform the procedure without on-site cardiac surgery and further information on safety is keenly awaited. The placement of a stent in dissected vessels reduces the need for emergency by-pass surgery and may encourage the extension of angioplasty procedures to non-surgical centres if problems with stents are overcome. The question of the standards for technical expertise in doctors performing angioplasty is now under debate by a sub-committee of the British Cardiac Society which has tentatively suggested that an individual operator should perform at least 100 angioplasties per year to retain skills.

Training centres need higher throughput but precise data of the current position is proving difficult to acquire and is hampering progress. Few of the 38 centres providing information are performing over 400 angioplasties per year which is being suggested as necessary for teaching purposes. We await production of the final guidelines.

Restenosis
Restenosis rates after PTCA are still quoted as up to 30% within six months but the introduction of stenting promises to lower this figure[8]. Two trials using the Palmaz-Schatz stent have produced encouraging preliminary results. Elective repeat revascularisation is reduced from 22.1% of control patients to 13.5% with stents in the BENESTENT (Belgium and Netherlands stent) study (520 patients) and from 16% to 9.7% in the STRESS (stent restenosis) trial (410 patients). Major anticoagulation with warfarin and heparin is needed to prevent thrombosis (3.5% in both these studies) and a prolonged hospital stay is usually required for stable anticoagulation and the management of bleeding and vascular complications.

The first drug which reduces restenosis has been evaluated in the EPIC (evaluation of 7E3 for the prevention of ischaemic complications) study. It is a monoclonal antibody fragment known as 7E3 which blocks a platelet receptor glycoprotein and acts as an anti-platelet agent. In the study there was a significant reduction in abrupt closure after angioplasty but bleeding complications need to be overcome before 7E3 is recommended.

Gene therapy is the buzz word in cardiology and it is likely that attempts to reduce neointimal proliferation and restenosis after PTCA will be one of the earliest clinical uses. Two techniques are under investigation. In one of these, adenovirus is used to introduce DNA encoding into cells which produce proteins to inhibit growth factors for intimal hyperplasia. The other technique involves oligonucleotides which are synthetic agents which block RNA sequences and are used to inhibit smooth muscle proliferation.

Even more recently the potential for antiviral therapy with gancyclovir to destroy actively growing cells has been considered but, like gene therapy, it will be some time before the value of this technique is sorted out.

PTCA versus CABG
Hampton in 1992 stated that the use of medical treatment, PTCA or CABG depended on the skills of the operator, availability and resources, the preference of the individual doctor and, not least, the wishes of the patient. Results of major trials have improved our information and hopefully our judgement, but his comments are still relevant today. Three randomised trials comparing angioplasty and bypass surgery are published[9]. The RITA (randomised intervention treatment of angina) trial, a large multi-centre study in the United Kingdom, involves patients with one, two or three vessel disease. After two and a halfyears death, infarction and revascularisation are less common in the bypass groups and at two years angina is 22% in the CABG patients and 31% in those having PTCA with a reduction in the need for antianginal drugs (39% and (66%). The LAUSANNE study restricts patients to those with proximal left anterior descending artery stenosis with good left ventricular function and uses the left internal mammary artery for bypassing the vessel. Both the LAUSANNE study and the ERACI study, (Argentine randomised trial of PTCA versus coronary artery bypass surgery in multivessel disease) which is like RITA, came to similar conclusions and suggest that over a short period CABG is more successful than PTCA. Surgery is, however, more expensive, more inconvenient for the patient, has a higher initial mortality and a longer recovery time. There is the problem with early recurrence of restenosis after angioplasty but there is also a steady recurrence of symptoms over the years after CABG and whether this is less than in those patients who avoid early problems after PTCA is not known yet and awaits longer-term studies. The other suggestion is that PTCA should be considered as a stage along the way to eventual bypass surgery. BARI (bypass angioplasty revascularisation investigation) is an ongoing trial which is designed to show if initial percutaneous transluminal angioplasty rather than coronary bypass grafting

affects survival. In a progressive disorder such as coronary artery disease it makes sense to consider PTCA particularly in the younger patients who may require bypass grafting on more than one occasion in the future. Hopefully during this period the possibility of regression of the atheromatous process will become a reality.

Newer methods of unblocking coronary arteries

Directional atherectomy using a catheter with a groove containing a cylindrical cutter rotating at 2000 rpm is used to shave off the surface of a plaque of atheroma. Two randomised trials have compared this technique with balloon angioplasty showing higher closure rate (7% compared with 3% for balloon angioplasty in CAVEAT) and higher incidence of infarction and similar rates of restenosis. Other methods using the rotablator, a high speed burr rotating at 200,000 rpm and excimer laser with or without balloon angioplasty have their proponents but no randomised trials are available and they are not recommended in place of the established coronary balloon angioplasty.

SUMMARY

I hope that this brief review provides sufficient information to show the treatments available now and the exciting prospects for the future of the management of patients with stable angina pectoris. The ABC rule should be emphasised, ie all patients with angina should receive secondary prevention treatment with aspirin, beta blockers and cholesterol lowering agents (statins) unless contraindicated. Prevention methods should involve discussion of fast track pain clinics, open access treadmill testing and 24 ECG monitoring, health screening of high risk patients and, now that the role of lipid lowering has been clarified, attention may be targeted to antioxidants. The possibilitv of stabilising atheromatous plaques with statins and reversal of coronary arterial disease with gene and antiviral therapy raise tantalising prospects of "clearing" atheromatous disease. In the meantime, improvement in organising appropriate bypass surgery and PTCA for more patients is a top priority and methods to improve the results of angioplasty, particularly stenting in the immediate future, hold out hope of a better, active life for sufferers with angina.

"all patients with angina should receive secondary prevention treatment with aspirin, beta blockers and cholesterol lowering agents"

In Lancaster and Kendal we provide a first-class non-invasive investigation service and aim to remain in the forefront of developments as a secondary centre which is one of the best of its kind. Sometime in the new millennium coronary artery disease should become a historically interesting relic; when this will happen is impossible to predict but the road is being constructed and the ride will be fascinating.

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