Reviews in Medicine

Cardioprotective therapeutics – drugs used in hypertension, hyperlipidaemia, thromboembolism, arrhythmias, the postmenopausal state and as anti-oxidants

M.J. Kendall, I. Rajman and S.R.J. Maxwell

Clinical Pharmacology Section, Department of Medicine, Queen Elizabeth Hospital, Edgbaston, Birmingham B15 2TH, UK

Introduction

Coronary artery disease (CAD) remains one of the major causes of mortality in the developed countries of the world. In the last year or two there have been a series of papers reporting the effects of a number of drugs on various management problems. These have shown, for example, that thrombolytic therapy has a major impact on early mortality and have also investigated the most effective way of producing clot lysis.¹ In addition, the role of angiotension converting enzyme (ACE) inhibitors has been extended to include the management of the post-infarct patients. The Survival and Ventricular Enlargement (SAVE) study² suggested a major role for captopril in the long-term management of patients following myocardial infarction who had impaired myocardial function and the more recent Acute Infarction Remipril Efficacy (AIRE) study³ has shown that ramipril reduces mortality in the first 30 days.

Further progress is more likely to be made if a more co-ordinated approach to the management of the at risk patient is developed. The accepting of certain principles is likely to help. Firstly, the importance of prophylaxis in coronary artery disease has to be more widely recognized. At least one half of all myocardial infarcts are silent.⁴ They are recognized because repeated electrocardiograms (ECGs) demonstrate changes over a period of time. These silent infarcts carry a prognosis as bad as having had a recognized clinical infarct.⁵ Since these episodes are by definition not recognized they cannot be treated and the damage which they cause cannot be reduced. If possible, therefore, they must be prevented. Coronary artery disease may also present as sudden death. It is believed that between 1/6th and 1/3rd of all

myocardial infarcts present with sudden death as the first, last and only manifestation of the disease.⁶ Patients who smoke and who have hypertension and particularly those who have left ventricular hypertrophy are at particular risk. Only if medical help is immediately available in a suitable environment can the patient be helped. Once again, therefore, the only effective option is prevention.

Secondly, although it is accepted that there are many risk factors for coronary artery disease, in clinical practice the doctor tends to concentrate on one risk factor. Thus patients attending the hypertension clinic often do not have their plasma lipids measured, and the doctor treating a woman with hyperlipidaemia tends not to consider hormone replacement therapy. Patients who are developing ischaemic heart disease may be at risk from hypertension, hyperlipidaemia, thromboembolism, arrhythmias and, in women, the postmenopausal state. Simple logic suggests that a five-sided attack requires a five-sided pharmacological response: that is, the doctor has to consider the need to create a 'pentagon of protection'. In addition, non-pharmacological measures may be as important as drug treatment and efforts directed towards

Five major coronary risk factors amenable to pharmacological intervention (the 'Pentagon of Protection') include hypertension, hyperlipidaemia, thromboembolism, arrhythmias and the postmenopausal state.

A cardioprotective drug reduces the risk of suffering or dying from a coronary event. Ideally, this should have been proven in properly performed clinical trials of primary or secondary prevention.

One half of all myocardial infarctions are silent and a significant proportion of the rest may present as sudden death.

encouraging smoking cessation, weight loss, increased exercise and better stress management may all be important.

Thirdly, where possible, doctors treating the five disorders described above should use drugs which have cardioprotective potential wherever possible. This implies that cardioprotection is clearly defined, that doctors recognize that preventing the patient dying from a coronary event is a priority for certain 'at risk groups', that the impact of the drugs on coronary artery disease is known and the prescribing doctor is aware of what has been established in this context. Current prescribing practices suggest that this is not the case and this review is written with the intention of addressing this problem. Thus we shall describe briefly the impact of drugs used to treat hypertension, hyperlipidaemia, thromboembolic disease, arrhythmias and the postmenopausal state on the risk of dying from a coronary event. In addition, other pharmacological measures which may be taken to reduce endothelial damage will be described.

At this point the concept of a cardioprotective drug requires consideration. This term will be downgraded and it is often considered a marketing term. In this review cardioprotective is used to describe drugs which reduce the risk of suffering or dying from a coronary event. In most instances this would imply that the drug can be shown to prevent or delay the development of a coronary occlusion and/or reduce the risk of developing ventricular fibrillation. More importantly, a cardioprotective drug should have been shown in properly performed clinical trials to prevent the first coronary event (primary prevention) or prevent death or a recurrence in those who survive their first heart attack (secondary prevention). Since the pathological processes are the same in primary and secondary prevention, a drug which is effective in one should be effective in the other. However, since most of those who have had an infarct have established and often extensive coronary artery disease, they are at much greater risk and therefore it is much easier to demonstrate the efficacy of a drug in secondary prevention trials. By comparison patients selected for inclusion in primary prevention trials may be at low risk and it is virtually impossible to show an effect by correcting one mildly abnormal risk factor. Thus modest reductions in the blood pressures of mildly hypertensive middle aged females will have little impact.

Hypertension

(1) Thiazide diuretics

Thiazides tend to produce metabolic effects which would increase the coronary risk and they have not

been shown to have cardioprotective actions in animal models. In many primary prevention trials such as the Australian Mild Hypertension Trial,⁷ diuretics did not reduce the coronary mortality and morbidity. In the review of the treatment of hypertension by McMahon and colleagues⁸ in which the impact on coronary artery disease was modest, most of the trials quoted were assessing the effects of thiazides. However, the recent Medical Research Council elderly hypertension study⁹ and the SHEP study¹⁰ did show a reduction in coronary events in those on thiazides. This observation has not been explained. In the Systolic Hypertension in the Elderly Programme (SHEP) study there was no reduction in sudden death and no data on this were provided in the MRC study. It is possible that thiazides have some impact on coronary events in the elderly but overall thiazides could not be considered cardioprotective.

(2) Beta adrenoceptor blocking drugs (beta blockers)

There is an extensive literature on the effects of beta blockers on the processes which led to death from ischaemic heart disease. Thus beta blockers reduce endothelial damage,¹¹ atheroma formation^{12,13} and tend to inhibit clot formation.¹⁴ In addition three studies have demonstrated that in three different animal models, in three different centres, beta blockers have been shown to reduce the risk of developing ventricular fibrillation.¹⁵⁻¹⁷ Of some interest is the fact that in one¹⁵ propranolol was given into the cerebral ventricles and in the third¹⁷ a relationship with vagal tone was demonstrated both suggesting that lipophilic beta blockers which enter the brain more readily might be expected to be more effective.

The biochemical effects of beta blockers, however, are a cause for concern. Though they probably produce adverse effects which are less severe and occur less often than after diuretics, there is no doubt that beta blockers, particularly non-selective beta blockers, tend to reduce high density lipoprotein (HDL) cholesterol, increase triglycerides and they have unwanted effects on glucose handling.

Primary prevention studies with beta blockers have been the cause of disappointment and dispute. However, beta blockers appeared to reduce coronary mortality in two non-randomized studies^{18,19} and in men in the MRC trial²⁰ and IPPPSH trial.²¹ The HAPPHY²² and MAPHY²³ studies have provoked considerable debate. Metoprolol appeared to have a positive effect reducing morbidity²⁴ and sudden death²⁵ whereas atenolol did not. This was demonstrable²⁶ on the data available before the MAPHY arm was extended in a way which many found unacceptable. Further, atenolol's relative

lack of effect on coronary mortality has been confirmed in subsequent studies.^{9,27} In our view there is a difference between the impact of lipophilic metoprolol and hydrophilic atenolol but this is not widely accepted as there are genuine concerns about the trials quoted.^{9,22,23,27}

The cardioprotective role of beta blockers in post-infarct patients, in particular their capacity to reduce the risk of sudden death has been shown for three lipophilic beta blockers, timolol,²⁸ propranolol²⁹ and metoprolol,³⁰ but not for the hydrophilic sotalol.³¹ Thus a post-infarct patient leaving hospital will have about a 10% chance of dying over the next year or so, and of those who die about half die suddenly.³² This can be reduced to a one in three risk of sudden death if a lipophilic beta blocker is given (Table I).

In conclusion, therefore, beta blockers are the drugs which come closest to meeting the criteria for being cardioprotective drugs.

(3) Alpha blockers

Alpha blockers are the anti-hypertensive drugs which have been shown to improve^{33,34} rather than worsen the plasma lipid profile. This may be expected to have a beneficial effect on the patients' risk of developing coronary artery disease. Unfortunately, this remains a hope as there is no clinical evidence that alpha blockers reduce coronary risk.

(4) Calcium channel blocking drugs (calcium antagonists)

Calcium antagonists have a reputation for being metabolically neutral and of having the potential to delay atheroma formation. This latter is only apparent early in the disease. It has been demonstrated in animal models^{35,36} and man.^{37,38}

In clinical studies the different types of calcium antagonists need to be considered separately. Dihydropyridines have not reduced clinical events in primary prevention studies^{37,38} nor in secondary prevention studies,³⁹⁻⁴² though the number of new atherosclerotic lesions per patient was significantly fewer in those on nifedipine.³⁷ Verapamil was studied in two major trials DAVIT I⁴³ and DAVIT II⁴⁴. DAVIT⁴³ did not show a difference between

verapamil and placebo in reinfarction and overall mortality though those on verapamil between day 22 and 180 post-infarction did have a lower mortality and reinfarction rate. A beneficial effect was formally confirmed in DAVIT II⁴⁴ which showed a reduction in first reinfarctions over 18 months (11% versus 13.2%) but, though verapamil appeared to reduce sudden deaths (5.7% versus 7.5%) and all cardiac deaths (9.9% and 12.8%), these differences were not statistically significant. Diltiazem also may have a clinically relevant impact. It did reduce 14-day reinfarction rates in patients with non-Q wave infarction.⁴⁵ However, in the long-term follow-up study⁴⁶ diltiazem did not significantly reduce cardiac events (diltiazem 202, placebo 226) nor total mortality. It was noted, however, that patients after myocardial infarction who did not have pulmonary congestion did better on diltiazem, although those with impaired myocardial function did less well.

In conclusion, calcium antagonists may retard the early development of coronary artery disease. However, clinically the dihydropyridines have not been shown to be effective, and the evidence to suggest that verapamil and diltiazem have a cardioprotective effect is, at best, modest.

(5) Angiotensin converting enzyme inhibitors (ACE inhibitors)

ACE inhibitors have recently been shown to have some potential to reduce coronary events in clinical trials.^{2,3,47} Their cardioprotective actions, therefore, need to be reviewed.

High plasma renin activity is an independent marker for increased risk of myocardial infarction⁴⁸ and ACE inhibitors would be expected to reduce the effects of this. Insulin resistance and hyperinsulinaemia have also, more recently, been associated with susceptibility to develop ischaemic heart disease and ACE inhibitors tend to correct this whilst diuretics tend to make the situation worse.⁴⁹

Clinical trial data are derived from heart failure and secondary prevention studies rather than from primary prevention trials. In VHEFT 2⁴⁷ enalapril and in the HY-C trial⁵⁰ captopril reduced the incidence of sudden death in heart failure patients.

Table I Results of beta blocker secondary prevention trials

	Timolol:p1 ²⁸	Propranolol:p1 ²⁹	Metoprolol:p1 ^{30,32}
Cumulative mortality (%)	10.6:17.5 P = 0.0005	7.2:9.8 P < 0.005	7.2:9.8 P < 0.05
Sudden cardiac death (%)	7.7:13.9 P = 0.00001	3.3:4.6 P = 0.05	2.2:3.8 P = 0.002

Myocardial infarcts were less frequent in the enalapril arm of the SOLVD trial (Studies of Left Ventricular Dysfunction)⁵¹ than in the placebo arm. Many of these patients with heart failure would have had extensive coronary artery disease and the means by which the ACE inhibitors seemed to reduce coronary event risk is not adequately explained.

The two secondary prevention studies also show that ACE inhibitors have a cardioprotective effect but pose further questions. In the SAVE study² captopril had little effect for over a year but thereafter, in a large number of post-infarct patients with left ventricular dysfunction, it markedly influenced outcome in various ways including reducing reinfarction rates. In the more recently published AIRE Study¹³ ramipril given between day 3 and day 10 after an acute infarct reduced overall mortality and was seen to have a beneficial effect after 30 days treatment.

In conclusion, ACE inhibitors have not hitherto been considered to be cardioprotective drugs. However, the results of recent studies indicate that ACE inhibitors do have a cardioprotective role so far demonstrated only in secondary prevention studies.

Hyperlipidaemia

The role of hyperlipidaemia and the problems associated with lipid reduction have been the subject of a number of reviews and publications recently.⁵²⁻⁵⁴ It is not necessary to review this important subject again in great detail, we will briefly summarize the situation as we see it and give a few relevant references.

Since hyperlipidaemia has been a subject of some controversy, it is easy to come to the conclusion that nothing about this subject is certain. It may be helpful to state categorically at this stage that there is little doubt that hyperlipidaemia is an important risk factor for coronary artery disease but that the controversy surrounds the benefits to be derived from lowering plasma lipids and perhaps the ways in which this aim is achieved.

Hyperlipidaemia is an important risk factor. One of the major constituents of the atheromatous plaque is lipid. Countries whose populations have a

high intake of saturated fats have an increased risk of developing coronary artery disease, subpopulations within countries who have high lipid levels are at greater risk of developing coronary artery disease, and families who have particularly high serum cholesterol levels and who suffer from familial hypercholesterolaemia are at particularly high risk of developing premature ischaemic heart disease.^{55,56} Furthermore, in general terms, if the cholesterol is lowered the risk of developing coronary artery disease is reduced.^{57,58} In relation to lipid lowering there have been at least three areas of controversy. Firstly though dietary factors are believed to play a part in causing hyperlipidaemia and dietary modification is the first line treatment for hyperlipidaemia, formal trials of dietary modification may not show a significant improvement in plasma lipids,⁵⁹ although many are convinced about the value of dietary intervention. This overall lack of effect is because some patients respond and some do not. Since some who do respond are spared the need to take lipid-lowering drugs, dietary advice is considered 'worth a try' in the first instance in most hyperlipidaemic patients.

The second problem is that lipid-lowering therapy has reduced coronary events rather than total mortality,^{57,58} although in one prolonged study a nicotinic acid derivative did reduce total mortality.⁶⁰ The third concern is that lipid-lowering therapy has been associated with an increase in non-coronary mortality, although the numbers affected have been small and a logical explanation has not been found. These problems have recently been addressed and the guidelines of the British Hyperlipidaemia Association published in the *Postgraduate Medical Journal*.⁶¹

In conclusion, hyperlipidaemia is a coronary risk factor and lipid-lowering drug therapy has been shown to reduce coronary risk. It is not possible to comment on the cardioprotective potential of individual drugs or drug groups. Attempts have not been made in this review to comment further on indications for starting treatment or the choice of therapy.

Thromboembolism

Thrombus formation and plaque rupture are believed to be the final step in the development of a coronary occlusion. It follows that pharmacological interventions directed towards preventing thrombus formation or increasing the rate of thrombus dissolution should reduce the risk of myocardial infarction. Aspirin to reduce platelet aggregation, anticoagulants to prevent clotting and fibrinolytics to encourage thrombus breakdown have all been evaluated in clinical studies.

Although hyperlipidaemia is strongly associated with coronary risk, trials of lipid-lowering drugs have failed to have an impact on total mortality despite a reduction in coronary deaths.

(1) *Acetylsalicylic acid (aspirin)*

Aspirin therapy is now advised for many patients with vascular disease. The results of ISIS-II⁶² added greatly to the credibility of the database on aspirin and the treatment is simple, cheap and relatively free from side effects. However, since there is some slight risk of damage to the upper gastrointestinal tract and it is not desirable to convert a relatively well population into a drug-taking potential patient population, the prescriber needs to keep in mind what benefits of aspirin therapy have been demonstrated.

There was some controversy over the potential benefits of aspirin therapy in individuals with no evidence of vascular disease. The UK physicians trial⁶³ enrolled 5,139 healthy male doctors, randomized half to once-daily aspirin, and failed to show a significant reduction in coronary events but did find a small increase in strokes. By comparison the US Physicians Health Study⁶⁴ asked a similar question in a study involving 22,000 subjects who were a relative select fit group which had a low mortality. In this investigation aspirin was reported to reduce coronary events since the fatal and non-fatal myocardial infarctions were lower in those on aspirin. However, those on aspirin had a greater risk of sudden death, and when myocardial infarcts and sudden deaths were combined the results on and off aspirin were comparable. Thus there is insufficient evidence to suggest that clinically healthy individuals should take aspirin to reduce the long-term risk of a myocardial infarction.

Patients known to have vascular disease are at significantly increased risk and it is therefore easier to demonstrate a beneficial effect. In relation to aspirin, data are available for some patient groups and, in view of the low-cost low-risk nature of this form of treatment there has been an increasing and not unreasonable tendency to assume that aspirin will help all those known to have atherosclerotic vascular disease. In patients with angina, several studies have shown that aspirin reduces the risk of serious end points, death and myocardial infarction.⁶⁵⁻⁶⁷ A second major group at great risk is those who have had a transient ischaemic attack or stroke, and those are also helped by aspirin therapy.⁶⁸

The role of aspirin given acutely as soon as possible after the onset of a myocardial infarction was clearly demonstrated in ISIS-II⁶² in which patients were given aspirin or thrombolysis, neither

or both. Aspirin alone reduced vascular mortality in the first 4 weeks post-myocardial infarct by 25%, and the combination of aspirin and thrombolysis reduced the vascular mortality by 42%. The impact of aspirin in the longer term is also well documented and the trials suggest that daily aspirin to those who survive a myocardial infarct will reduce mortality by about 10% and reinfarction rates by 21%.⁶⁹⁻⁷¹

In conclusion, therefore, it is suggested that any patient with clinical evidence of vascular disease may benefit from daily aspirin therapy, and aspirin should be prescribed to all acute infarct patients and should be continued post-infarction for life. The optimal dose of aspirin is not known. Several trials employed doses up to 1 g daily, but a dose of 150 mg or even 75 mg daily is probably sufficient.⁷²

(2) *Anticoagulants*

Oral anticoagulants are rarely prescribed to reduce coronary mortality. This is not because they are ineffective but because: (1) early trials, many of which were performed over 20 years ago, were not big enough or rigorous enough, and failed to show a convincing effect; (2) anticoagulant therapy requires careful monitoring, and this may be difficult for the patient and carries a long-term risk of haemorrhage; and (3) new therapies have pushed drugs like warfarin into the background.

Recent studies all tend to suggest that warfarin therapy will reduce coronary mortality in post-infarct patients and that further studies specifically designed to assess the role of warfarin in post-infarct patients are needed. An earlier study in patients over 60 years⁷³ showed that when patients on warfarin were randomized to continue or to stop, those who continued had a 26% lower mortality and 55% lower reinfarction rate. In the AIMS trial⁷⁴ infarct patients treated with thrombolysis followed by warfarin had the greatest reduction of in-hospital mortality seen in any trial of thrombolytic therapy. This observation was confirmed in another retrospective analysis of the effects of thrombolysis and oral anticoagulation.⁷⁵ Finally, in the Warfarin Reinfarction trials,⁷⁶ oral anticoagulants or placebo were given to 1,214 patients about 3-4 weeks post-infarction and, over the period of follow-up, the mortality rate and reinfarction rate were 24% and 34% lower, respectively, in the actively treated group.

By today's standards the clinical trial data on warfarin are not good, but the data available strongly suggest that warfarin effectively reduces mortality and morbidity in post-infarction patients. We do not know whether it is more effective than aspirin, nor do we know whether warfarin plus aspirin would be more effective than either given alone.

Low-dose aspirin is to be recommended for any patient with clinical evidence of atherosclerotic vascular disease.

(3) *Thrombolysis*

The benefits of thrombolytic therapy had been suggested by many small studies and were convincingly confirmed in ISIS-II.⁶² There is now no doubt about the value of thrombolytic therapy given early post-infarction. The problems relate to choice of treatment and cost. Two studies, ISIS-III⁷⁷ and GISSI II⁷⁸ did not show any difference between streptokinase and tissue plasminogen activator (tPA). The recently published GUSTO¹ involved 41,021 patients and showed that tPA given in a more rapid regimen together with intravenous heparin produced the lowest short-term mortality. However, many will be influenced by two facts: (1) the difference in efficacy between tPA and streptokinase is modest; and (2) the difference in cost is great.

Arrhythmias

Sudden death is a common mode of death in patients with coronary artery disease and in most instances is due to ventricular fibrillation. This may occur without any kind of warning but is more common in susceptible individuals, that is, those with known coronary risk factors, and may be preceded by other ventricular arrhythmias. This latter would include some types of ventricular extrasystoles (ventricular premature beats). It would seem logical to suggest, therefore, that anti-arrhythmic drugs should be given to at-risk patients who have 'warning' ventricular arrhythmias.

The early studies in which beta blockers were given to post-infarct patients showed that the risk of sudden death could be reduced by timolol,²⁸ metoprolol³⁰ and propranolol.²⁹ Furthermore it has been demonstrated that the life-saving effect was achieved by reducing the incidence of ventricular fibrillation.^{79,80} Since other drugs are much more effective than beta blockers in the short-term control of ventricular arrhythmias, it seemed very logical to assess the effects of newer agents like flecainide and encainide on the long-term suppression of ventricular arrhythmias. However, the CAST study⁸¹ showed that this anti-arrhythmic drug therapy was associated with an increased incidence of arrhythmias and mortality. A meta-analysis of ten randomized trials of all class I anti-arrhythmic drugs⁸² strengthens the findings of the CAST study. Clearly, further evaluation of this problem is needed but, for the moment, this group of drugs cannot be considered as suitable for long-term preventative therapy in the type of patients included in these trials. Further, efforts directed towards providing optimal anti-arrhythmic therapy based on detailed electrophysio-

logical studies failed to show that individualized drug therapies were better than metoprolol.⁸³ The role of amiodarone requires further consideration. This drug causes potentially serious adverse effects in a large proportion of the patients treated.⁸⁴ However, it does appear effectively to reduce the frequency of serious ventricular arrhythmias.⁸⁵

In conclusion there has been a reasonable expectation that antiarrhythmic drugs would reduce mortality and particularly sudden death in patients at risk which would include all post infarct patients. At the moment beta blockers appear to be the simplest and most effect way of achieving this aim.

The postmenopausal state

Coronary artery disease is often wrongly considered a disease which predominantly effects men. However, although in middle age most patients with clinical evidence of coronary disease are male, the female to male ratio increases rapidly in those over 55 years old.⁸⁶ Eventually the overall impact of ischaemic heart disease on the two sexes is comparable. In spite of this, female patients have not been investigated and treated with the same diligence as men.⁸⁷

Hormone replacement therapy (HRT) helps the postmenopausal woman in many ways, but the potential impact on coronary disease is particularly impressive. Unfortunately the relationship between HRT and CAD is not as clearly defined as it should be. The problems are: (a) the effects of oestrogens and progestogens are different; (b) proper randomized prospective double-blind trials have not been performed; and (c) the clinical effect tends to be a reduction in coronary deaths rather than total mortality.

(1) Mechanisms

HRT has marked effects on lipids⁸⁸ but also beneficially influences blood flow, prostacyclin, other relaxing factors and platelet function.^{89,90} The improvement in plasma lipids produced by oestrogen therapy is well documented; there tends to be a return to premenopausal concentrations brought about by a reduction in LDL-cholesterol and an increase in HDL-cholesterol.^{91,92} Progestogens cannot be considered as a single entity as different

The incidence of coronary disease increases rapidly in women during the postmenopausal years.

Hormone replacement therapy has a major protective role against coronary disease in the postmenopausal female.

compounds have different effects. Some studies have shown a tendency of progestogens to reverse the beneficial effects of oestrogens⁹³ and this may be true of the more androgenic agents.⁹⁴ However, several studies have shown that combinations of oestrogens and progestogens tend to produce a beneficial effect⁹⁵ and this may be particularly true of combinations containing more recently developed progestogens.

(2) Clinical studies

Clinical data are largely derived from studies in which women on HRT are compared with those not on HRT. The assumption is that those who choose to have HRT or are offered HRT do not differ from women who opt not to take HRT or are not offered it. This is not a valid assumption and therefore the results available have to be interpreted with caution. Notwithstanding this reservation, the effects of HRT on coronary events are impressive.

Four prospective cohort studies⁹⁶⁻⁹⁹ do merit serious consideration. Bush and colleagues⁹⁶ taking data from the Lipid Research Clinics Study in two groups of women who appeared to be equally well at enrolment showed that HRT users had a 40% lower cardiovascular disease mortality. In the 10-year follow-up of 48,000 postmenopausal women in the Nurses' Health Study,⁹⁷ the relative risk for major coronary disease was 0.56 for those on oestrogens, that is, those on HRT had roughly half the risk of having a myocardial infarct or coronary death. The Walnut Creek Study⁹⁸ showed that those on HRT had a 20% lower total mortality, and this is believed to be an underestimate of the benefit as those with known coronary disease were not included and this group achieves more benefit. Henderson and colleagues⁹⁹ confirmed the reduction in total mortality and found that after 7 years HRT the reduction was 20% and after 15 years 40%.

These and other studies^{100,101} provide striking evidence based on huge numbers of women followed for long periods. Scientifically it may be desirable to wait for the results of placebo-controlled randomized trials but it is readily apparent that trying to recruit women who are willing to be put on or not put on HRT and to continue for 10 years or so is going to be very difficult. In the meantime, should doctors be encouraging or discouraging a form of treatment for which there is compelling evidence to suggest that it can reduce the coronary event rate by up to 50%? Furthermore HRT has other non-coronary beneficial effects.

The concern about HRT is cancer risk. Breast cancer may be slightly more common with a relative risk of 1.07¹⁰² but, even if this is true (and

there are doubts), the risk of dying from carcinoma of the breast does not seem to be increased.^{99,103,104} Provided progestogens are given with the oestrogens in a cyclical way, endometrial carcinoma is not increased and there is no evidence for an increase in ovarian or cervical cancer.

Conclusion

Though further data based on better trials are needed, HRT may be the most effective form of cardioprotective therapy currently available. Surprisingly it is almost never recommended by cardiologists.

Antioxidant therapy

Antioxidants may prove to be effective cardioprotective drugs with the potential to reduce endothelial damage and atheroma formation. The rationale for their use and the evidence that free radical damage is important and that, therefore, antioxidants may have a useful therapeutic role in relation to coronary artery disease are briefly presented to conclude this review.

Introduction to free radicals and antioxidants

The involvement of free radicals and other oxidants in human disease has become an increasingly popular subject of research, not least in cardiovascular medicine. A free radical is defined as a chemical species with an unpaired electron.¹⁰⁵ By their nature such species are highly reactive tending to abstract electrons from (oxidize) other biological molecules to achieve stability. Such reactions can have serious consequences if the targets of oxidation are important structural or functional molecules. Oxidation of polyunsaturated fatty acids (lipid peroxidation) may disrupt cell and organelle membranes and can damage circulating lipoproteins. Similarly, proteins and DNA may be damaged with serious consequences for cellular activity. Because the threat of free radical production (particularly those derived from oxygen) is ever

Oxidatively modified forms of low-density lipoprotein (LDL) are more rapidly deposited in the vascular wall than native LDL.

Low-density lipoprotein supplemented with either vitamin E or probucol is more resistant to oxidative damage.

Antioxidants retard atherosclerosis in animal models. High dietary intakes or plasma levels of antioxidants are inversely associated with atherosclerosis in epidemiological studies.

present in well-oxygenated aerobic environments, a variety of natural antioxidant mechanisms exist.^{106,107} Intracellular enzymes such as superoxide dismutase and glutathione peroxidase are present to detoxify superoxide and hydrogen peroxide, respectively. In addition, a variety of small molecules with powerful reducing (electron-donating) properties are present in the extracellular fluids to react with (scavenge) free radicals preferentially before they can damage more important molecules. These include vitamin C (ascorbic acid), vitamin E (alpha-tocopherol) and beta-carotene. It is also worth remembering that endothelium-dependent vasomotor regulation is based on nitric oxide,¹⁰⁸ itself a free radical species.

Important diseases where free radical damage is believed to have a role in the pathogenesis include atherosclerosis, ischaemia–reperfusion injury and hypertension. In all cases, the potential for antioxidant therapeutic interventions is currently under investigation as a simple means of limiting free radical damage preventing disease progression.

(1) Atherosclerosis: the oxidative-modification hypothesis

Basic research has now advanced our understanding of some of the biochemical events that lead to the development of the atherosclerotic plaque.¹⁰⁹ Most of the cholesterol in the mature lesion originates from circulating low-density lipoprotein (LDL) particles which have been ingested by subendothelial macrophages. However, macrophages in culture when exposed to high concentrations of *native* LDL do not accumulate cholesterol partly due to downregulation of LDL receptor numbers in the cholesterol-replete state. In contrast, *oxidatively modified* forms of LDL are much more avidly taken up by cultured macrophages which are converted to cholesterol-laden 'foam cells' characteristic of the atherosclerotic lesion. The rapid uptake of the oxidatively modified LDL has been attributed to a new receptor known as the 'scavenger receptor' which is not downregulated by cholesterol accumulation^{109,110} (Figure 1). Although oxidation of LDL is not likely in the circulation, all of the cells of the vessel wall – endothelial cells, smooth muscle cells and macrophages – can modify LDL *in vitro* and the presence of oxidized LDL *in vivo* has been established.^{111,112} Not only is oxidized LDL atherogenic by virtue of its rapid uptake by macrophages but it is also a chemoattractant for macrophages, cytotoxic to endothelial cells, stimulates auto-antibody formation and interferes with endothelium-dependent vasodilatation.¹⁰⁹

With these discoveries, the oxidative-modification hypothesis of atherosclerosis was established and further research directed towards the factors that influence the susceptibility of the human LDL

particle to oxidation. One of the most important appeared to be its content of natural antioxidant vitamins, particularly vitamin E and beta-carotene.¹¹³ These vitamins protect the core polyunsaturated fatty acids whose oxidation provides most of the toxic products that produce the altered biological properties of oxidized LDL. *In vitro* measurements of the appearance of these products in LDL subjected to oxidative stress suggest that not until all of the vitamin E is oxidized can lipid peroxidation begin. Accordingly, LDL supplemented with vitamin E is much harder to oxidize *in vitro*. The function of vitamin E in protecting LDL from oxidation may also depend on its close biochemical relationship with the water-soluble antioxidant vitamin C. The latter can regenerate oxidized vitamin E back to its antioxidant form thus maintaining the antioxidant pool within each particle.¹¹⁴ The exact antioxidant function of beta-carotene is unclear but it seems to act synergistically with vitamin E being particularly active at low partial pressures of oxygen.

Initial trials of antioxidant vitamins and drugs such as probucol and beta-hydroxytoluene in animal models of atherosclerosis yielded promising results suggesting that the atherogenic process could indeed be retarded.¹¹⁵ This information suggested that antioxidant therapy might yield positive benefits in the human disease. Evidence for the potential influence of antioxidants on atherosclerosis in man has already accumulated from epidemiological surveys linking low levels of antioxidant vitamins with ischaemic heart disease. The WHO/MONICA project compared the risk of ischaemic heart disease mortality with mean plasma antioxidant levels in 12 European populations with normal cholesterol levels (5.7–6.2 mmol/l).¹¹⁶ Both absolute and lipid-standardized vitamin E concentrations showed a strong inverse correlation with mortality ($r^2 = 0.63$, $P = 0.002$ and $r^2 = 0.73$, $P = 0.0004$, respectively). A similar inverse correlation was found for vitamin C ($r^2 = 0.41$, $P = 0.03$) but not for beta-carotene ($r^2 = 0.21$, $P = 0.14$). In a case control study of 6,000 men aged 35–54 years in Edinburgh, antioxidant vitamin levels were measured in 110 angina patients identified by the WHO Chest Pain questionnaire and compared with 394 controls randomly selected from the sample.¹¹⁷ The unadjusted risk of angina was significantly higher in the lowest quintile compared with the highest for vitamin E (odds ratio 2.51, 95% CI 1.24–5.10), vitamin C (odds ratio 2.35, 95% CI 1.16–4.78) and beta-carotene (odds ratio 2.64, CI 1.32–5.29). The relationship with vitamin E remained significant after controlling for smoking, cholesterol, blood pressure, weight and age. Studies of dietary habits have also associated a high calculated dietary intake of vitamin E, vitamin C and beta-carotene with

Figure 1 The oxidative-modification theory of atherosclerosis.

reduced mortality from ischaemic heart disease.^{118,119} Particularly compelling evidence for the protective effects of vitamin E comes from two large surveys recently published in the *New England Journal of Medicine*.^{120,121} These examined the risk of ischaemic heart disease in cohorts of 39,910 male health care workers and 87,245 female nurses and found the relative risk of major disease to be 0.64 (95% CI 0.49–0.83) and 0.59 (95% CI 0.38–0.91), respectively, in those taking vitamin E supplement. The further complexity of possible dietary antioxidants has been illustrated in two recent papers examining the influence of polyphenolic compounds known as flavanoids. Frankel *et al.* demonstrated the potential for polyphenolic compounds in red wine to increase the resistance of LDL to oxidation and suggest that this might explain the

surprisingly low incidence of ischaemic heart disease in France (the 'French paradox').¹²² The total dietary intake of flavanoids in vegetables, fruits, beverages and wine showed a significant inverse relationship to ischaemic heart disease mortality in 805 men followed up for 5 years in the Zutphen Elderly Study.¹²³

The foregoing discussion provides powerful (but not conclusive) evidence that antioxidants may have some beneficial effects in preventing atherosclerosis. This hypothesis needs to be tested rigorously in prospective studies. Preliminary data are available from the Physicians' Health Study, a randomized, placebo-controlled, double-blind, 2 × 2 factorial design trial of aspirin and beta-carotene in the prevention of cardiovascular disease and cancer in 22,071 male US physicians

originally recruited in 1982.¹²⁴ A history of angina pectoris or revascularization prior to randomization was reported in 333 cases. Of these 160 were assigned to beta-carotene and 173 to placebo. After a mean follow-up of 60.2 months, a significant reduction in cardiovascular events was seen in the actively treated group (relative risk = 0.46, 95% CI = 0.24–0.85). The trial is continuing and further information about the primary prevention of cardiovascular events should be available in the mid-1990s. In Britain the combined Medical Research Council and British Heart Foundation Heart Protection Study is about to begin and will test the effects of a combined antioxidant preparation as well as an HMG CoA reductase inhibitor in a 2 × 2 factorial design in preventing coronary disease in high-risk groups. The effects of a mixture of antioxidants will also be tested in 15,000 men and women in the SU.VI.MAX trial in France. These trials will not only help to define the role of antioxidants in preventing atherosclerosis but will also offer information about the safety of long-term vitamin supplementation, so far assumed to be free of risk.

(2) *Ischaemic–reperfusion injury*

Reperfusion of ischaemic myocardium is a common phenomenon in cardiological practice. For patients with established ischaemic heart disease episodes of angina that terminate spontaneously or in response to pharmacological intervention are regular events. Many episodes may even occur unnoticed (silent myocardial ischaemia). Reperfusion is an increasingly available therapeutic option with the advent of post-infarction thrombolysis, surgical revascularization, coronary angioplasty and cardiac transplantation. The readmission of blood and oxygen to previously ischaemic tissues often results in the release of large amounts of oxygen-derived free radicals.¹²⁵ This probably occurs because during the ischaemic period the handling of oxygen by the mitochondrial electron transport system and enzymes such as xanthine oxidase is disrupted yielding incomplete reduction products, most notably the superoxide radical. While the reactivity of superoxide alone is not high it has the potential to interact with transition metal ions (also made available in ischaemic damaged tissues) to produce the highly damaging hydroxyl radical. The harmful effects of free radical activity may be exerted on the sarcoplasmic reticulum and other membranes where loss of the ability to handle calcium and other ions is a hallmark of reperfusion.¹²⁶ When the myocardium is reperfused potentially harmful sequelae include post-ischaemic contractile dysfunction ('stunning'), reperfusion-induced arrhythmias and endothelial damage.^{127–129} These pathophysiological changes are paralleled by

biochemical evidence of free radical activity and consequent oxidative damage. Increased levels of lipid peroxides have been detected after successful thrombolysis following acute myocardial infarction¹³⁰ and following percutaneous coronary angioplasty.¹³¹ Coronary angioplasty has also been associated with increases in the markers of endothelial damage.¹²⁹

A number of therapeutic options exist for reducing the impact of reperfusion on the myocardium with almost all of the evidence deriving from animal studies. Agents such as superoxide dismutase, catalase, vitamin E, allopurinol and its metabolite oxypurinol (inhibitors of xanthine oxidase), sulphhydryl compounds such as glutathione and captopril, and iron-chelating agents such as desferrioxamine have been used to improve outcome in various animal models.^{132,133} However, the design and end-points of the studies have been variable and it is not clear if the results can be easily extrapolated to the clinical setting. The human myocardium differs in some respects in possessing little xanthine oxidase and having a collateral circulating unlike some other species. Defects in calcium homeostasis are also a feature of reperfusion injury, possibly as a direct result of free radical activity,¹²⁶ and calcium-channel blocking drugs such as verapamil and diltiazem have been shown to reduce stunning, infarct size and endothelial disruption in animal models.^{133,134}

(3) *Hypertension*

The possible role of oxidative mechanisms in the pathophysiology of hypertension is less clear. Hypertension has been associated with low levels of antioxidant vitamins, particularly ascorbic acid,¹³⁵ and infusions of antioxidants into hypertensive subjects can reduce blood pressure.¹³⁶ This approach is supported by studies that have linked hypertension to antagonism of nitric oxide vasodilatation by the superoxide radical.¹³⁷ Some commonly prescribed anti-hypertensive agents including the angiotensin-converting enzyme inhibitor captopril are acknowledged as free radical scavenging agents *in vitro*. However, the low circulating concentrations (nanomolar) found *in vivo* are strongly against a bulk scavenging role for these agents when compared with the natural scavenging antioxidants (micromolar). Since the goal of anti-hypertensive therapy is to avoid the major complications of which atherosclerosis is the most common, we might still be persuaded to adopt antioxidants for their preventative role even in the absence of benefits in blood pressure reduction.

Conclusion

The possibility that antioxidant therapy may have an impact on human disease looks particularly

Table II The potential use of antioxidant therapy in cardiovascular medicine

<i>Antioxidant agent</i>	<i>Comment</i>
<i>Natural antioxidants</i>	
Ascorbic acid (vitamin C)	Water-soluble. Regenerates alpha-tocopherol in lipoproteins and membranes. Powerful inhibitor of lipid peroxidation. Low plasma concentrations associated with angina, hypertension and diabetes. Regenerated intracellularly
Alpha-tocopherol (vitamin E)	Major lipid-soluble antioxidant found in lipoproteins and membranes. Low plasma concentrations associated with angina. Dietary intake inversely related to coronary mortality. Regenerated by ascorbate
Beta-carotene	Lipid-soluble. Antioxidant function not clear. Inhibits lipid peroxidation weakly. Quenches singlet oxygen
Superoxide dismutase	Intracellular enzyme facilitating the removal of superoxide radical. Some benefits seen in animal models of reperfusion injury. Circulation half-life can be prolonged by conjugation with albumin or polyethyleneglycol
Glutathione	Involved in reduction and detoxification of xenobiotics. Contains thiol group. Linked with antioxidant enzyme glutathione peroxidase
<i>Synthetic antioxidants</i>	
Probucol	Lipid-soluble. Circulates in lipoproteins. Reduces susceptibility of LDL to oxidation. Mild hypocholesterolaemic effect. Retards atherosclerosis in animal models. Causes regression of some lipid deposits (xanthelasmata) in man
Captopril	ACE inhibitor with efficacy in hypertension and left ventricular failure. Has antioxidant properties by virtue of its thiol group. Unlikely to be an efficient free radical scavenger <i>in vivo</i>
Desferrioxamine	Chelates iron and prevents it acting as a template for formation of the highly damaging hydroxyl radical
Allopurinol	Inhibits production of the superoxide radical by the enzyme xanthine oxidase. Used with some success in some animal models of reperfusion injury

promising in atherosclerosis. In this preventative role, treatment will necessarily last for many years and for this reason supplementation of the diet with natural antioxidants seems to be the safest approach. The results of prospective studies are keenly awaited. Many episodes of myocardial reperfusion following ischaemia are predictable (thrombolysis, coronary angioplasty, cardiac surgery) and therefore potentially amenable to intervention with antioxidant therapies. As yet convincing evidence for any benefit of antioxidant intervention is not available. The finding that streptokinase thrombolysis is associated with *excess* mortality in the first 24 hours compared to placebo⁷⁷ will continue to stimulate interest in the biochemical events associated with reperfusion and in adjunctive therapy that might make this period safer.

Although several drugs used in cardiovascular

therapeutics are claimed to have antioxidant properties, it is unlikely that any play an important role in scavenging free radicals *in vivo* because of their low concentrations. This does not rule out the possibility that they reduce free radical activity secondary to modification of the underlying disease process. Work is continuing to discover agents that can supplement the natural antioxidant systems (Table II). However, synthetic compounds are unlikely to possess the versatility of their natural counterparts. For instance, vitamin C is not only a scavenging antioxidant in its own right but can regenerate other antioxidants such as vitamin E, and can itself be regenerated by intracellular reduction.¹⁰⁶ At present, the most attractive approach to antioxidant therapy appears to be manipulation of endogenous antioxidant systems and natural vitamins.

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