SECONDARY PREVENTION OF HEART DISEASE

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This article discusses specific therapeutic interventions that have a significant impact on cardiovascular risk in coronary heart disease and reviews the evidence behind their use.

Secondary prevention is defined as the prevention of the progression of a disease in symptomatic patients. In terms of coronary heart disease (CHD), this usually applies to people who have survived a myocardial infarction (MI), but it may include those who present with angina, have had a revascularisation by angioplasty and intra-coronary stent insertion or coronary artery bypass graft surgery, or patients with any other manifestation of atherosclerotic disease such as stroke, peripheral vascular disease or diabetes.

Patients with CHD are a high risk group (each year in the United Kingdom more than 135,000 people die from this disease and 50,000 of these are under the age of 75) so secondary prevention is, potentially, a more effective method for reducing cardiovascular deaths and other cardiac events than primary prevention, which is aimed at a lower risk, asymptomatic population. However, chapter 2 of the National Service Framework for CHD emphasises the importance of appropriate management of both patients with established disease (ie, secondary prevention) and those at high risk of developing heart disease (ie, primary prevention in high risk populations). Appropriate management requires routine risk assessments to identify target subjects and robust follow-up to ensure they are, and continue to be, treated according to current best knowledge and practice.

Cardiovascular risk assessments involve reviewing the modifiable and non-modifiable (see Panel 1) risk factors that apply to an individual and calculating the risk of that person having a cardiac event over the next 10 years. All patients with established CHD require secondary prevention interventions. Primary prevention will be discussed in a later article.

Chapter 3 of the NSF describes standards for the management of acute MI and recommends after-treatments known to improve outcome. The National Institute for Clinical Excellence has issued a guideline on prophylaxis for patients who have experienced an MI, which covers drug treatment, cardiac rehabilitation and dietary manipulation. Treatment guidelines are also available in the form of the British5 and European3 recommendations on the prevention of CHD in clinical practice, with similar messages. There are two aspects of secondary prevention: lifestyle changes and drug treatment.

LIFESTYLE CHANGES

Examples of lifestyle changes to reduce cardiovascular risk include stopping smoking, increasing exercise, losing weight (if obese or overweight), improving diet (eg, reducing total and saturated fat intake; increasing fruit, vegetable and fibre intake) and moderating alcohol consumption.

EVIDENCE-BASED TREATMENT OPTIONS

Unless there are contraindications, all patients who have had an MI should be prescribed a combination of secondary prevention drugs, which will include all of the following: an antiplatelet agent, a beta-blocker, a statin and an angiotensin converting enzyme inhibitor (ACEI).

Aspirin and other antiplatelet agents

An overview of all antiplatelet randomised trials shows that use of antiplatelet agents can reduce non-fatal infarction and strokes by about one third and mortality by 25 per cent. Aspirin is the first line antiplatelet agent in the majority of patients because it is effective, generally safe and inexpensive. A dose of 75mg daily is recommended because it is proven to be equally effective as higher doses and is associated with a lower incidence of side effects. Patients should be reminded to dissolve soluble aspirin and take it with or after food.

In the CAPRIE trial6 (over 19,000 patients), clopidogrel was shown to be as effective as aspirin in the secondary prevention of coronary, peripheral and cerebro-occlusive disease. Clopidogrel is a suitable alternative for patients intolerant of aspirin due to allergy but, like aspirin, it is associated with gastric side effects. There is no evidence to support the use of dipyridamole, alone or in addition to aspirin, in CHD although it probably has a role in the secondary prevention of stroke.

Beta-blockers

There is strong evidence that beta-blockers reduce the risk of overall mortality, coronary mortality, recurrent non-fatal MI and sudden cardiac death in patients post infarction. Beta-blockers have a number of beneficial features including rate control,
Recent evidence from the HPS study further extends the benefit of beta-blockers beyond the traditional threshold of 3.5mmol/L, or by 25 per cent, whichever is greater. However, beta-blockers should be given to all patients following an MI, unless there are contraindications (e.g., unresolved heart failure). The beneficial effects of beta-blockers were studied in the early 1980s, before thrombolitics and ACE inhibitors became the gold standard treatments for MI. At this time, heart failure was considered a contraindication to beta-blockade but, in 2001, the CAPRICORN study reported a 23 per cent mortality reduction with carvedilol in patients with left ventricular dysfunction (LVD) after MI. Symptomless LVD or controlled heart failure are no longer contraindications to beta-blockade, and are indeed indications, but careful, slow dose titration is needed.

Treatment post-infarction should continue for at least one year because this was the usual follow-up period of many of the studies. Moreover, continuing treatment over one year is strongly recommended because the benefits of beta-blocker therapy appear to last for as long as treatment continues, up to at least six years.

The benefits of beta-blockers post-MI can be extrapolated to those patients with established coronary disease, and therefore beta-blockers are the first choice anti-anginal in patients with ischaemic symptoms (PJ, 14 September, pp163–4).

Lipid lowering agents Statins have been shown to be the most effective agents for reducing cholesterol. They work by inhibiting the action of the enzyme HMG-CoA reductase, which is responsible for the production of cholesterol in the liver. Lowering cholesterol in people at high risk of ischaemic coronary events substantially reduces the risk of overall mortality, cardiovascular mortality and non-fatal cardiovascular events. A meta-analysis of the three major secondary prevention statin trials confirms that reducing low density lipoprotein (LDL) cholesterol decreases coronary mortality in these patients by 29 per cent. Furthermore, there is increasing evidence to support the use of statin therapy in a wide range of clinical contexts, including in all ages and in both sexes. All patients with CHD should have a full lipid profile performed, receive dietary advice and, if their total cholesterol or LDL cholesterol is raised, should be prescribed a statin. According to the NSF, treatment goals in post-MI patients are either to reduce total cholesterol to less than 5.0mmol/L (or by 30 per cent, whichever is greater) or to reduce LDL cholesterol to less than 3.0mmol/L (or by 25 per cent, whichever is greater). However, the aim of treatment is to reduce absolute cardiovascular risk. Recent evidence from the HPS study further extends the boundaries of lipid-lowering by indicating benefits from statin therapy in a population with established CHD and cholesterol levels above 3.5mmol/L.

Occasionally there may be circumstances when an alternative cholesterol modifying drug, such as a fibrate, anion-exchange resin or ispaghula, is appropriate. Choice may be based on a patient’s inability to tolerate statins or the type of hyperlipidaemia and are usually prescribed on specialist advice.

Angiotensin converting enzyme inhibitors One of the major factors affecting long-term outcome following MI is LVD. ACEIs have been shown to prevent the development of LVD by altering the remodelling process (the process by which the heart repairs itself in response to an MI) following an infarction, resulting in a reduction in mortality. This effect is not believed to be specific to individual agents, although not all ACEIs are licensed for secondary prevention.

Many trials have investigated the use of ACEIs in post-MI patients. One meta-analysis of three such trials which included 6,000 patients and had a mean follow up of three years, showed that ACEIs reduced mortality by 23 per cent compared with placebo.

Participants in a similar study with ramipril (AIRE) were followed up at five years (AIREX) and it was found that a large mortality benefit (36 per cent) was sustained.

The Heart Outcomes Prevention Evaluation (HOPE) study looked at ramipril in patients at high risk for cardiovascular events (e.g., ischaemic heart disease or diabetes plus at least one other risk factor). Eighty per cent had CHD and more than half had an MI, although recent MIs (within four weeks), symptomatic heart failure and LVD were excluded. Ramipril was found significantly to reduce the rates of cardiovascular death (26 per cent), MI (20 per cent) and stroke (32 per cent). This landmark trial has increased the number of patients now considered eligible for ACEI treatment, ie, patients with IHD as well as those with heart failure. Therefore, except where there is a contraindication, ACEIs should be considered for:

- All post-MI patients, with or without symptoms of congestive heart failure or known LVD
- All patients with symptoms of congestive heart failure or known LVD
- All patients with established CHD
- All patients at high risk of developing CHD, such as those with diabetes (a primary prevention strategy)

Additional therapies

Treatment for heart failure A previous article in this series (PJ, 7 September, pp325–327) discusses the management of heart failure in detail. Adjunctive therapies for the management of heart failure post MI should be initiated where indicated. Briefly, in addition to ACEIs, this will include a loop diuretic for symptomatic relief, spironolactone for patients with moderate to severe heart failure and low dose beta-blockade, increased cautiously.

Blood glucose control Diabetes is a major risk factor for heart disease and can be described as a manifestation of cardiovascular disease in itself. It is well known that hyperglycaemia is associated with adverse outcomes. The benefits of good glucose control (HbA1c <7% per cent) and blood pressure control (<140/80mmHg) in patients with diabetes are well-documented.

For people with diabetes, the acute and one-year mortality of MI is greater than for non-diabetic patients. The DIGAMI study investigated acute MI patients with raised blood glucose (>11mmol/L) on admission, to compare intensive blood sugar control using insulin/glucose infusions with normal coronary care unit treatment. Patients treated intensively were continued on a subcutaneous insulin regimen for a minimum of three months. Mortality in the intensive treatment group at one year was 33 per cent compared with 44 per cent in the standard care group (a 25 per cent relative risk reduction). The improved MI prognosis in patients with elevated blood glucose receiving insulin therapy was maintained over the follow-up of three years. Rigorous control of blood glucose is therefore essential and this is best achieved with insulin. The available evidence supports treatment with insulin post MI for three months, but there is no rationale for stopping at this time and, patient permitting, it should be continued indefinitely.

Anti-arrhythmics Although arrhythmias are common post MI, anti-arrhythmic agents (except beta-blockers) have not been shown to confer any significant benefit on mortality. Class I anti-arrhythmics (quinidine, procainamide, disopyramide, encainide, flecainide, moracizine) should not be used because they have been shown to increase cardiovascular morbidity and mortality. The class III anti-arrhythmic amiodarone significantly reduces mortality in selected post MI patients at high risk of sudden death from cardiac arrhythmias.

Calcium channel blockers Calcium channel blockers are useful for control of angina symptoms but there is little evidence to support their use in post-MI patients. The rate-controlling calcium channel...
Optimising doses (For example, encouraging dose titration of

Advising on choice of agents

Ensuring evidence-based prescribing

Dietary supplements Despite public misconception, there remains no evidence that vitamin supplementation is beneficial for the secondary prevention of CHD. However, increasing polyunsaturated fatty acid (PUFA) intake, by dietary modification or supplementation, has been shown to reduce cardiac events. The GISSI-P study\(^1\) reported a 15 per cent relative reduction in the risk of death, non-

at MI and non-fatal stroke in a group randomised to receive omega-3 fatty acid ethyl ester supplements at 3.5 years follow-up. The American Heart Association recently issued a recommendation that people with CHD should increase omega-3 fatty acid intake (by eating fish) but conceded that this may not be achievable in all patients. In such cases, the use of a PUFA supplement may be considered (PJ, 23 November, p736).

Conclusion

Strategies to minimise cardiovascular risk in patients with CHD can be effective. It is essential to ensure that all relevant secondary prevention therapies are initiated, optimised and maintained in individuals at high risk of further cardiac events. The care of patients with established CHD offers many opportunities for pharmaceutical input. Key areas include:

- Identification of patients who have had or who are at high risk of an MI
- Ensuring evidence-based prescribing
- Advising on choice of agents
- Optimising doses (For example, encouraging dose titration of ACEIs and statins, with the aim of achieving doses that have demonstrated significant impact of cardiovascular events in clinical trials. ACEIs should be titrated to the maximum dose tolerate

ated by the patient [within the confines of the drug licence] Statins should be titrated to achieve target cholesterol levels.)

- Counselling patients on the aims and benefits of therapy and encouraging long-term compliance with treatments
- Ensuring patients know what to do if they experience chest pains (eg, people with angina should use glyceryl trinitrate spray or tablets, repeat, then dial 999 if the pain is not relieved)
- Giving advice on managing side effects

These actions must be instituted in conjunction with measures to assess and manage coexisting risk factors, eg, control of hypertension, tight diabetic control (preferably with insulin), health education, promoting a healthy lifestyle and support for stopping smoking.

References