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SECONDARY PREVENTION OF CARDIOVASCULAR DISEASE IN GENERAL PRACTICE

SUMMARY

-  Secondary prevention involves (a) promotion of risk reduction (diet, weight, smoking and exercise), (b) active management of existing diseases and (c) use of specific drug regimens
-  After myocardial infarction all patients should receive aspirin, β -blocker, ACE inhibitor and statin therapy, unless specifically contraindicated
-  Optimal control of hypertension, diabetes and heart failure will improve outcome

INTRODUCTION

In 2001, 41% of all deaths in Ireland were due to cardiovascular disease (CVD), comprising coronary heart disease (CHD) 21%, stroke 9% and other diseases of the circulation 11%¹. By comparison, 26% of deaths were due to cancer. Although deaths from CVD in Ireland have been decreasing since 1985, they remain high (176/100,000 of the population) compared with the average EU figure of 108/100,000². Moreover, Ireland has the highest rate of premature deaths (<65 years) from CVD in the EU. The premature death rate of 46/100,000 is almost twice the EU average (25/100,000). Deaths from stroke are close to the EU average at 65/100,000¹.

Data on morbidity are more limited but it would appear that CVD accounts for approximately 10% of all hospital admissions. Furthermore, patients with vascular diseases have required more bed days than patients with any other group of diseases³. Therefore, CVD continues to pose a significant burden on the health services in Ireland.

In 1999, the Cardiovascular Health Strategy "Building Healthier Hearts" was launched with the aims of reducing mortality and morbidity associated with CVD in Ireland⁴. One of the cornerstones of this strategy is the implementation of a structure for the prevention and management of CVD in general practice. This initiative includes (a) promotion of risk reduction - smoking, diet, weight and exercise, (b) active management of existing diseases such as hypertension, diabetes and (c) prescribing of specific drug regimens. This bulletin will focus on secondary prevention in general practice, i.e. the drug management of patients with prior CVD (i.e. myocardial infarction (MI), coronary bypass surgery or angioplasty) in order to prevent disease progression.

PHARMACOLOGICAL INTERVENTIONS IN SECONDARY PREVENTION

Survivors of acute MI are at increased risk of recurrent MI or cardiac death – 10% death rate in the first year and 5% in subsequent years⁵. National and international guidelines recommend that these patients be given a combination of drugs to help prevent recurrences of symptoms and improve survival^{2,5,6,7}. Drugs include aspirin, β -blockers, angiotensin-converting enzyme (ACE) inhibitors and statin therapy. The guidelines also recommend that heart failure, hypertension and diabetes should be managed aggressively. For patients with other manifestations of CVD such as ischaemic stroke, antiplatelet therapy, such as aspirin, is recommended⁸.

ASPIRIN

Evidence. Aspirin produces an irreversible antiplatelet effect which lasts for 7-10 days after a single dose (i.e. until new unaffected platelets are produced). The ISIS-2 (second international study of infarct survival) study showed the benefits of aspirin⁹. For every 1,000 patients with acute MI receiving one month's treatment with aspirin, about 25 deaths and 10-15 non-fatal re-infarctions or strokes were avoided during the first month post MI. A follow-up of ISIS-2 showed that this survival advantage was maintained for at least 10 years¹⁰. **Low dose aspirin (75-150mg daily)** appears to be effective **for chronic use**⁸ but in the emergency/acute setting it is recommended that an initial loading dose of 150-300mg soluble aspirin be used, to produce a more rapid effect.

Side effects are dose-related and are primarily gastrointestinal (GI) – bleeding, perforation, GI upset. Studies have found that regular use of aspirin (< 300mg/day) results in a 2-fold increased risk of upper GI bleeding or perforation¹¹. Use of enteric-coated tablets may reduce the risk of GI side effects but onset of action may be delayed¹¹. This should not be a problem with chronic therapy.

Practical Advice. Aspirin therapy should be started while the patient is still in hospital, as there is evidence to support benefit following early initiation. Most will therefore commence therapy in hospital, but if not, aspirin should be initiated by the general practitioner¹². Aspirin at doses of 75-150mg daily has been shown to be protective against all other types of occlusive vascular events, including ischaemic stroke or cerebral ischaemia, transient ischaemic attacks, peripheral vascular disease, stable and unstable angina⁸.

BETA-BLOCKERS

Evidence. The efficacy of β -blockers in reducing mortality and morbidity in patients post-MI has been known for several decades. The beneficial effect has been shown to be independent of fibrinolysis or ACE inhibitor therapy¹³ and to last for as long as treatment continues¹⁴. The most commonly investigated β -blockers were propranolol and metoprolol, both of which achieved statistically significant reductions in mortality⁶. Other agents such as sotalol and atenolol showed beneficial effects, but the results did not reach statistical significance.

Side effects reported included dizziness, depression, cold extremities and fatigue, but in a review of randomised controlled trials involving over 50,000 patients, such reports were only marginally more common in β -blocker-treated patients, compared with placebo¹⁴. Withdrawal rates, due to side effects, were low in the long-term studies. Heart failure was previously a contraindication to use of β -blockers but recent studies have shown that β -blocker therapy reduces mortality in patients with heart failure caused by left ventricular systolic dysfunction¹⁵.

Practical Advice. Based on the initiation points in the trials, it is recommended that β -blockers (e.g. **metoprolol 100-200mg daily**) be started as soon as possible post-MI. Most will therefore commence therapy in hospital but if not, it should be initiated by the general practitioner¹². Treatment in patients with heart failure should be started only when the heart failure has been stabilised. Treatment in this group should be initiated using low doses and increased very slowly (e.g. at fortnightly intervals) over a period of 12 weeks¹². Initiation of β -blocker treatment in post-MI patients with heart failure may require specialist supervision. β -blocker therapy will also help in the management of hypertension, which is another element of the secondary prevention strategy in CVD.

ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS

Evidence. One of the major factors affecting long-term outcome following acute MI is the presence or absence of left ventricular dysfunction (LVD). Long-term treatment with ACE inhibitors is associated with a substantial reduction in all cause mortality in selected patients with signs of heart failure, including those who have recently experienced an MI⁶. A review of 3 large studies, involving almost 6,000 post-MI patients with LVD, showed that use of an ACE inhibitor (**captopril 75-150mg daily; ramipril 5-10mg daily; trandolapril 1-4mg daily**) within 2 weeks of an MI resulted in lower rates of mortality, re-infarction, and hospital readmission compared with placebo¹⁶. These benefits were maintained for the period of follow-up (range 15–42 months). In addition, the HOPE study evaluated the effectiveness of ramipril versus placebo in over 9,000 patients who had evidence of vascular disease or diabetes plus one other risk factor for CVD, but without known LVD¹⁷. Over half of each group had had a previous MI. In this study, **ramipril 10mg daily** significantly reduced overall mortality including CVD mortality as well as rates of MI and stroke.

Side effects. The main side effects reported with ACE inhibitor treatment in the 3 studies included in the review were hypotension and renal dysfunction¹⁶. Cough (7.3%), hypotension or dizziness (1.9%) and uncontrolled hypertension (2.3%) were the main reasons for discontinuation of ACE inhibitor therapy in the HOPE study¹⁷. Some investigators have suggested that aspirin therapy may blunt the benefits of ACE inhibitors by reducing the synthesis of various prostaglandins necessary for their effect. However, a review of trials involving 22,000 patients, with either heart failure or at high risk of developing cardiovascular events, has shown that ACE inhibitor therapy

significantly reduced the risk of developing major clinical outcomes (such as death, MI, stroke, hospital readmission) by 22% compared with placebo¹⁸ whether or not the patient was receiving concomitant aspirin therapy.

Practical Advice. It is recommended that ACE inhibitor therapy be started as soon as possible after MI. Most will therefore commence therapy in hospital, but if not, it should be initiated by the general practitioner¹². It is important to consider the risk of first dose hypotension. Although it is thought likely that the beneficial effects of ACE inhibitors post-MI relate to a class effect⁵, not all ACE inhibitors are currently licensed for such usage. ACE inhibitors (like β -blocker therapy) will also be of benefit in treating hypertension in this patient group.

STATINS

Evidence. The relationship between cholesterol and CVD risk has been shown in large epidemiological studies. The Framingham study¹⁹ noted that for every 1% reduction in cholesterol there was a 2% reduction in the occurrence of coronary heart disease. The MRFIT study²⁰ showed a direct relationship between serum cholesterol level, measured at initial screening and death from coronary heart disease, which persisted during the 12-year follow-up period.

Statins have been shown to be effective agents for reducing cholesterol. A meta-analysis of 3 major placebo-controlled statin trials²¹, evaluated the effect of **simvastatin 20-40mg daily** (n=4444) or **pravastatin 40mg daily** (n=13,173) in secondary prevention of coronary disease. Patients in the simvastatin study had raised low density lipoprotein (LDL) levels on admission (mean 4.87mmol/L), while patients with average levels of LDL (means of 3.59 and 3.88mmol/L) were enrolled in the 2 pravastatin studies. Follow up ranged from 5 – 6 years. Results showed a reduction in total cholesterol and LDL levels in all studies (reductions ranged from 25-36% for LDL levels in the groups). In addition, treatment significantly reduced cardiovascular and non-cardiovascular mortality and major cardiac events in each study.

More recently, the Heart Protection Study (HPS) evaluated the effects of long-term (5 years) treatment with **simvastatin 40mg daily** in over 20,000 high-risk patients²². Inclusion criteria included non-fasting blood total cholesterol levels of > 3.5mmol/L. A total of 8510 (41%) and 7150 (35%) had a history of MI or other CHD respectively. Results showed a highly significant reduction in cardiac-related mortality and marginally significant reduction in other vascular deaths, such as stroke, in the treated group compared with placebo. There were also significant reductions in non-fatal cardiac events and non-fatal stroke with treatment. These benefits were additional to those of other cardio-protective treatments used. This study was important because it showed that statin therapy produced substantial benefits that were not necessarily influenced by the initial concentrations of blood lipids, i.e. lowering LDL levels from below 3 mmol/L to below 2 mmol/L reduced vascular disease by the same proportion as that seen with 1 mmol/L reductions at higher starting LDL levels.

Another recent study (PROSPER) evaluated the effectiveness of **pravastatin 40mg daily** in older patients (70-82 years) in Ireland and Europe, who were treated for an average of 3.2 years²³. Results showed similar reductions in cardiovascular events, to those reported in the HPS.

Side effects were recorded for all of the trials. Non-specific muscle pains were reported equally in treatment and placebo groups. Elevations in liver enzymes and creatine kinase occurred rarely, even in the elderly age groups, with no significant difference in rate between treatment and placebo groups.

Practical Advice. Although there is no evidence of long-term benefit from the early initiation of statin therapy, i.e. prior to 12 weeks post-MI, many patients may have been taking statins prior to admission or may have had them prescribed prior to discharge. Otherwise treatment should be initiated by the general practitioner by 12 weeks post-MI¹². According to the results of the HPS, statin treatment should be beneficial to all post-MI patients, irrespective of their total cholesterol/LDL levels. However, some statins are restricted in their licence to use in patients with hypercholesterolaemia.

It is important to ensure that adequate dosage is used to lower cholesterol levels and hence achieve benefit from statin therapy. There is evidence to suggest that many patients in Ireland receive sub optimal doses of statins, i.e. doses which are below those used in the clinical studies (outlined above), resulting in failure to achieve the goal of total cholesterol levels of < 5mmol/L. Ongoing studies are evaluating whether even greater reductions in total cholesterol levels are associated with greater protection against CVD mortality and morbidity and results will be available in the near future.

Benefits of Treatment (based on treating 1,000 patients for one year) ⁶		
Drug	Reduction in deaths	Reduction in other events
Aspirin	7	8 MIs; 2 strokes
β -blocker	13	8 MIs
ACE inhibitor	4 (18 in heart failure)	Not available
Statin	4	6 MIs; 2 strokes

OTHER PHARMACOLOGICAL INTERVENTIONS

Although post-MI patients may suffer from arrhythmias, β -blockers are the only anti-arrhythmic drugs which have been shown to reduce mortality²⁴. Use of anti-arrhythmic agents is not routinely recommended, except for patients at high risk of sudden death (e.g. sustained ventricular tachycardia). Anti-arrhythmic usage in these patients (e.g. amiodarone) is likely to be under specialist supervision.

Calcium channel blockers are not recommended in secondary prevention as studies have suggested that their use is associated with a trend towards increased mortality and re-infarction⁵. Their use is restricted to post-MI patients who cannot tolerate β -blockers, providing there is no heart failure²⁴. In this case verapamil or diltiazem should be used²⁵.

Details on the pharmacological interventions used in the **management of obesity** and to aid **smoking cessation** are available in previously published NMIC bulletins (Vol 8 (2) 2002; Vol 7 (2) 2001).

MANAGEMENT OF CO-EXISTING DISEASES

Patients with concomitant diseases, such as hypertension, diabetes or heart failure, should be actively treated to ensure that disease control is optimum. All patients should also be offered cardiac rehabilitation.

Hypertension. Control of blood pressure is reported to improve outcome and therefore blood pressure should be regularly monitored⁵. Ideally blood pressure should be maintained at < 140/90mmHg. Patients should already be receiving ACE inhibitor and β -blocker therapy (see above), which will have a beneficial effect on blood pressure, but additional therapy such as diuretics may be used.

Diabetes is a major risk factor for heart disease. The European Task Force on the prevention of CVD⁷ has recommended that diabetic patients should have rigid blood glucose control (target of fasting levels 5.1-6.5 mmol/L; postprandial levels 7.6-9.0 mmol/L). The UK Prospective Diabetes Study²⁶ showed that strict blood pressure control significantly reduced diabetes-related morbidity and mortality during a median follow-up of 10 years – strokes and heart failure were reduced by 50% in the intensive treatment group. Many experts now recommend a target blood pressure of < 130/85mm Hg in diabetic patients. The DIGAMI study²⁷ compared the outcomes of MI patients, treated with strict blood glucose control post-MI (including use of subcutaneous insulin for a minimum of 3 months post MI) with patients managed by standard control procedures. Mortality at 1 year was reduced by 25% in the insulin group (rate of 33% compared with 44%). Therefore, the available evidence supports intensive control of blood glucose as well as aggressive management of co-existing conditions such as hypertension and high cholesterol levels.

Heart failure. ACE inhibitor and β -blocker therapy have been shown to prolong life in heart failure¹⁵. Patients may also require loop diuretics for symptom control and spironolactone (25mg/day) for management of severe heart failure²⁸. Full information on the management of heart failure is available in a previously published NMIC bulletin (Vol 7 (5) 2001).

CONCLUSION

Effective secondary prevention is a continuing challenge to both the physician and patient. Patients need to take at least 4 medications on a long-term basis and this raises problems with compliance²⁹. Moreover, the cost of implementing the recommended drug regimen (see below) represents a considerable investment in preventive health care. Optimal implementation of the other aspects of the secondary prevention programme (active management of existing diseases, guidance on diet, exercise, smoking cessation etc.) require regular medical review, all of which can be done effectively at primary care level²⁹. The initial implementation phase of the National Programme in General Practice for Secondary Prevention of CVD is currently underway, with the aim of reducing mortality and morbidity from CVD in Ireland.

Cost of Treatment (based on GMS costs July 2002)		
Drug Class	Daily Dose/Range	Daily Cost (€)
Aspirin (enteric coated)	75-150mg	0.07-0.14
Metoprolol	100-200mg	0.10-0.20
Ramipril	5-10mg	0.48-0.63
Simvastatin	20-40mg	1.51
Pravastatin	40mg	1.94

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