

The Heart Protection Study: implications for clinical practice

The benefits of statin therapy do not come without financial cost

THE AIM of the recently reported Heart Protection Study¹ in the United Kingdom, with over 20 000 participants aged 40–80 years, was to establish whether statin therapy is of benefit to people who are at high risk of cardiovascular disease (CVD) but have average-to-low levels of total cholesterol and LDL-cholesterol. High-risk patients (defined as those having previous coronary heart disease, diabetes, stroke, or peripheral vascular disease) were treated with simvastatin (40 mg daily), antioxidant vitamins (20 mg beta-carotene, 250 mg vitamin C and 600 mg vitamin E daily) or placebo in a 2 x 2 factorial design.

Among patients allocated to the antioxidant arm of the trial, there was no change in incidence of any prespecified endpoints, and there were small but significant increases in blood levels of LDL-cholesterol and triglycerides, which have the potential to increase CVD risk with long-term antioxidant use.² High-dose antioxidant therapy is therefore not recommended.³

Reductions in cardiovascular events (including myocardial infarction, stroke and either coronary or peripheral arterial revascularisation) occurred with simvastatin therapy in women, elderly people, and people with previous cerebrovascular disease, peripheral artery disease, renal impairment or diabetes (see Box).

Translating the results of the HPS into clinical practice, patients with an absolute overall CVD risk of more than 17% over five years (the lowest rate occurring in any subgroup of the HPS treated with placebo) should receive

- high-dose statin therapy, equivalent to 40 mg/day simvastatin, independent of baseline levels of total cholesterol; and
- other cardioprotective therapy, such as β -blockers and aspirin.

Overall CVD risk can be estimated with the National Prescribing Service charts,⁴ which refer to CVD rather than coronary heart disease risk — a strategy flowing from the HPS outcomes.^{1,4} These charts, based on the Framingham study, provide only an approximation of absolute risk, but serve as a useful guide. Examples of patients with five-year CVD risk above 17% include most men over 60 years who smoke and have diabetes, and a 60-year-old non-smoking, non-diabetic man with blood pressure of 160/95 mmHg and a total cholesterol/HDL-cholesterol ratio of 6:1.⁴

Benefits are likely to occur after 12 months of statin therapy, with greater benefits occurring the longer therapy is continued. Allowing for non-compliance, the HPS showed that about a third of major CVD events are likely to be prevented by statin therapy over five years. In the HPS, 23% of patients in the simvastatin group were smokers, 22% were being treated with antihypertensive agents, 20% with β -blockers, 25% with angiotensin-converting enzyme inhibitors (ACE inhibitors) and 21% with aspirin. Relative risk reductions in CVD incidence of up to 80% may be expected when statins are combined with standard cardioprotective

Absolute risk reductions and numbers needed to treat to prevent one cardiovascular event¹

Event	ARR (%)*	NNT [†]
All-cause mortality	1.8%	56
Mortality due to CHD	1.5%	83
Non-fatal myocardial infarction	2.1%	48
Coronary revascularisation	2.6%	38
Ischaemic stroke	1.2%	83
MVE without baseline CHD	4.7%	21
MVE with baseline CHD	5.7%	18
MVE with baseline creatinine >200 μ mol/L	9.0%	11
MVE in patient aged <65 years	5.2%	19
MVE in patient aged \geq 70 years	5.1%	20

CHD=coronary heart disease. MVE=major vascular event (includes CHD, stroke, revascularisation). *Absolute risk reduction (%), simvastatin therapy v placebo. [†]Number needed to treat with simvastatin 40 mg/day to prevent one event over 5.3 years.

agents (aspirin, β -blockers and ACE inhibitors) and stopping smoking.³

Given that CVD reduction in the HPS was independent of baseline cholesterol levels, it has been suggested that lipid levels need not be measured before commencing statin therapy in high-risk patients.³ However, fasting levels of triglycerides and HDL-cholesterol should be measured after 1–2 months, as therapy may need to be modified if these lipids are inadequately controlled by statin therapy alone. For example, gemfibrozil therapy may be considered for patients with low HDL-cholesterol levels.⁵

The HPS included about 6000 individuals with diabetes — the largest number in any statin trial reported to date. The CVD event rate for placebo-treated diabetics without coronary heart disease was 18.6%, compared with 22.5% for non-diabetics with coronary heart disease. Thus, the HPS confirms diabetes as a “coronary-equivalent” risk disorder for CVD.⁶ However, risk of CVD may vary from low to very high, depending on age and other risk factors, so it is still necessary to determine the global risk of CVD for an individual with diabetes when assessing the need to treat with a statin.⁴

Subjects at highest risk of CVD in the HPS had slightly elevated baseline serum creatinine levels (>200 μ mol/L), although only results of univariate analysis have been provided. The HPS confirms the high CVD risk in patients with impaired renal function and also supports the need for treatment of their dyslipidaemia.⁷ Caution is required in giving statin therapy to patients with more severe renal impairment, as they are at increased risk of myopathy.⁸

In the HPS, the safety profiles for statin and placebo therapy were similar. This finding may partly be a consequence of the exclusion of patients who showed adverse

reactions to simvastatin during a 4–6-week run-in period leading up to the trial. However, only 32% of 63 603 screened patients were allocated to receive simvastatin in the study, so the low adverse event rate in the study may not necessarily apply to an unselected population.

Of particular importance with regard to safety was the low incidence of myopathy (defined as serum creatine kinase levels exceeding 10 times the upper limit of normal), which occurred in only 11 simvastatin-treated patients and six placebo-treated patients. These results are reassuring, but muscle symptoms and creatine kinase levels should still be monitored periodically, and withdrawal of statin therapy should be considered if myalgia occurs or creatine kinase levels rise to more than three times the upper limit of normal.⁹

There were no apparent safety concerns in patients with low baseline LDL-cholesterol levels (<3 mmol/L), in whom average LDL-cholesterol levels during the trial were 1.8 mmol/L in the simvastatin-treated group and 2.7 mmol/L in the group receiving placebo. The association between low levels of total cholesterol and increased cerebral haemorrhage found in a study by Iso et al¹⁰ was not borne out by the HPS.

The safety and efficacy of treatment with 40 mg/day of simvastatin demonstrated by the HPS will probably result in a higher average dose being used in Australia, where the current average dose is 25 mg/day (Glen Godresse, Specialist/Hospital Product Manager, Merck Sharp and Dohme Australia Pty Ltd, personal communication). The benefits of statin therapy do not come without financial cost, although the long-term savings as a result of statin therapy are very likely to outweigh that cost.¹¹ As CVD remains the single most important cause of mortality in Australia, consideration should be given to extending the availability of statins under the Pharmaceutical Benefits Scheme to

include patients shown in the HPS to benefit from therapy: diabetics, women over 40 years, elderly people, and those with peripheral vascular disease, renal disease and low-to-average cholesterol levels, if their estimated global CVD risk exceeds 17% over five years.⁴

Ian Hamilton-Craig

Cardiologist, North Adelaide Cardiac Clinic
North Adelaide, SA
ihc@medped-aust.com

Competing interests: The author has served in an advisory capacity to government and non-government bodies, including pharmaceutical companies, and has received support for clinical research, presentations and attendance at scientific meetings from these bodies.

1. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; 360: 7-22.
2. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; 360: 23-33.
3. Yusuf S. Two decades of preventing vascular disease. *Lancet* 2002; 360: 2-3.
4. National Prescribing Service. Dyslipidaemia — background material. Sydney: National Prescribing Service Limited, 2002.
5. Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. *N Engl J Med* 1999; 341: 410-418.
6. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001; 285: 2486-2497.
7. Saltissi D, Morgan C, Rigby RJ, Westhuyzen J. Safety and efficacy of simvastatin in hypercholesterolemic patients undergoing chronic renal dialysis. *Am J Kidney Dis* 2002; 39: 369-375.
8. Masterson TM. Safety and efficacy of simvastatin in patients undergoing chronic renal dialysis: are we ready to treat hypercholesterolemia? *Am J Kidney Dis* 2002; 39: 419-421.
9. Hamilton-Craig I. Statin-associated myopathy. *Med J Aust* 2001; 175: 486-489.
10. Iso H, Jacobs DR Jr, Wentworth D, et al. Serum cholesterol levels and six-year mortality from stroke in 350,977 men screened for the multiple risk factor intervention trial. *N Engl J Med* 1989; 320: 904-910.
11. Prosser LA, Stinnett AA, Goldman PA, et al. Cost-effectiveness of cholesterol-lowering therapies according to selected patient characteristics. *Ann Intern Med* 2000; 132: 769-779. □

Caring for family carers in general practice

A more proactive approach by GPs would help to ease the burden on family carers

IN AUSTRALIA, up to 2.3 million people are involved in informal care of children, adults and older persons with disabling chronic and terminal conditions.¹ Their role includes managing medications, therapies and medical emergencies; providing supervision and emotional support; and assisting with personal care, mobility and household tasks.¹⁻³ While caring can provide considerable satisfaction and strengthen relationships, carers often feel exhausted, isolated and burdened by their responsibilities.^{1,3,4} In a recent survey of carers, 58% reported their physical health had been adversely affected, a third said they had sustained a physical injury, and over half reported depression, anxiety, high levels of stress and other impacts on their mental health.²

There have been many calls for general practitioners to be more proactive in addressing the support needs of carers,³⁻⁶

and carers have identified how this may be accomplished (see Box).

A 1998 editorial on family carers in Australia³ called for strategies to raise health professionals' awareness about carers, to keep them abreast of programs available to carers, and to encourage them to be more proactive in helping carers to obtain support. Since then, there has been limited apparent progress in Australia (unlike Britain, where there has been considerable interest in the primary care team's designated responsibility for addressing carer needs⁷).

Projects conducted through Divisions of General Practice to inform and educate doctors, to promote carer self-identification and discussion⁵⁻⁶ and to promote collaborative referral with regional carer respite services⁵ showed encouraging outcomes, but have failed to attract further funding from government.