Cardiovascular disease, cholesterol and statin drugs

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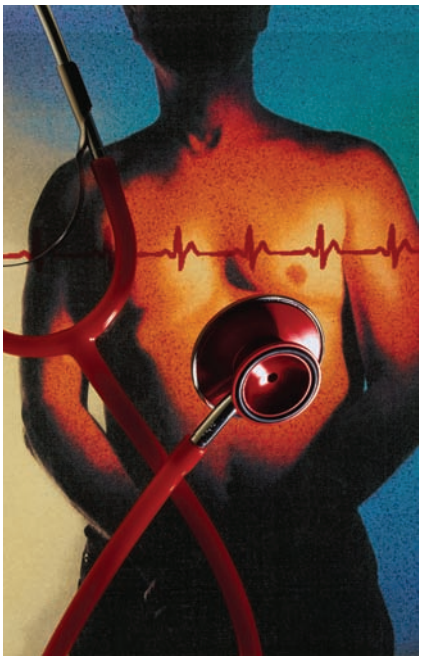
Randomised placebo-controlled trials have clearly shown that the use of statins prevents heart disease and stroke in patients with and without prior cardiovascular disease.



The pivotal role of elevated blood cholesterol in the pathogenesis of cardiovascular disease has been established over a long period. Advances in our knowledge of cell biology and biochemistry have led to the discovery and now widespread use of statin drugs. Statins inhibit the rate-limiting step in cholesterol biosynthesis, thereby initiating a series of reactions that lower levels of serum cholesterol, or more specifically LDL cholesterol.

Randomised, placebo-controlled trials have clearly demonstrated that statins prevent heart disease and stroke in patients with and without a history of cardiovascular disease (see the box on page 49)[1-7]. The recent UK Heart Prevention Study has created new interest by showing that statins prevent cardiovascular disease in high risk patients with baseline cholesterol readings as low as 3.5 mmol/L.[4] This is a far cry from a few years back when cholesterol levels were regarded as probably deserving treatment only when they were greater than 6.5 mmol/L.

Patients with established coronary artery disease

A patient presenting for the first time with an acute coronary syndrome (myocardial infarction or unstable angina) will usually be under specialist care, and he or she will be prescribed 40 or 80 mg a day of statin (unless a contraindication is present), together with other drugs. This treatment will be continued on a permanent basis.

When selecting a statin and dose to prescribe in the acute setting, cardiologists rely on general trial evidence of cardiovascular disease prevention; dose titration and target LDL cholesterol levels are not the priority in acute disease.[8] During long term follow up, the GP may need to address goals as outlined by the National Heart Foundation of Australia (see lipid management guidelines on www.heartfoundation.com.au).

Patients without established coronary artery disease

GPs can prescribe statins with Government subsidy to patients without coronary artery disease who are at high cardiovascular risk and have a serum cholesterol level above a given threshold, if dietary therapy has been tried, typically for at least six weeks. High risk patients are those with multiple risk factors, which include hypertension, diabetes, low HDL cholesterol, cigarette smoking, and family history (refer to current PBS guidelines).

A practical approach recommended by the National Heart Foundation and other national bodies is to calculate absolute cardiovascular disease risk by applying risk factors to Framingham risk equations and tables. (Tools to calculate absolute cardiovascular risk can be found in the December 2004 issue of *Medicine Today* and on the New Zealand Guidelines Group website – www.nzgg.org.nz). An absolute cardiovascular disease risk of heart attack or stroke exceeding 10 to 15% in the next five years is deemed unacceptably high by the National Heart Foundation and Cardiac Society of Australia and New Zealand and should be a trigger for considering prescription of statin drugs.

In the primary care situation, it is usual to initiate treatment with a submaximal dosage of statin (Table) and then titrate the dosage upward according

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to the LDL cholesterol level, at intervals of six to eight weeks. Each increment in daily dose should be a doubling, which will produce about a further 6% reduction in LDL cholesterol level. The target LDL cholesterol for high risk patients is below 2.5 mmol/L.

These comments apply also to patients with established coronary disease who are not already receiving statins or whose LDL cholesterol levels are not in the target range. In these patients, absolute risk calculations are unnecessary.

Diabetes mellitus

There is accumulating evidence that the presence of diabetes implies future coronary risk almost equivalent to that of a patient with established heart disease. Subjects with diabetes in the UK Heart Protection Study (and in other studies) achieved the expected heart disease prevention when using a statin drug. Patients with diabetes may need to receive statins as readily as those with established heart disease, and standard targets and dose titration may be applicable.

Stroke prevention

Controlled trials with statins in high risk patients demonstrate significant prevention of ischaemic stroke. This should be regarded as an additional bonus of statin therapy. The benefit of statin therapy in the secondary prevention of stroke requires further confirmation.

Hypertriglyceridaemia

Generally, patients with highly elevated triglycerides (e.g. above 8 mmol/L) have been excluded from placebo-controlled statin trials. These patients often have very low levels of HDL cholesterol. There is evidence of heart disease prevention from the use of fibrates (e.g. gemfibrozil or fenofibrate [Lipidil]) in such patients.

Monitoring

Before initiating statin therapy, baseline assessment of liver transaminases and total creatine kinase is essential. Liver enzymes and creatine kinase should be reassessed whenever lipids are measured again, or when clinically indicated (e.g. reported onset of nausea or myalgia).

Patient compliance

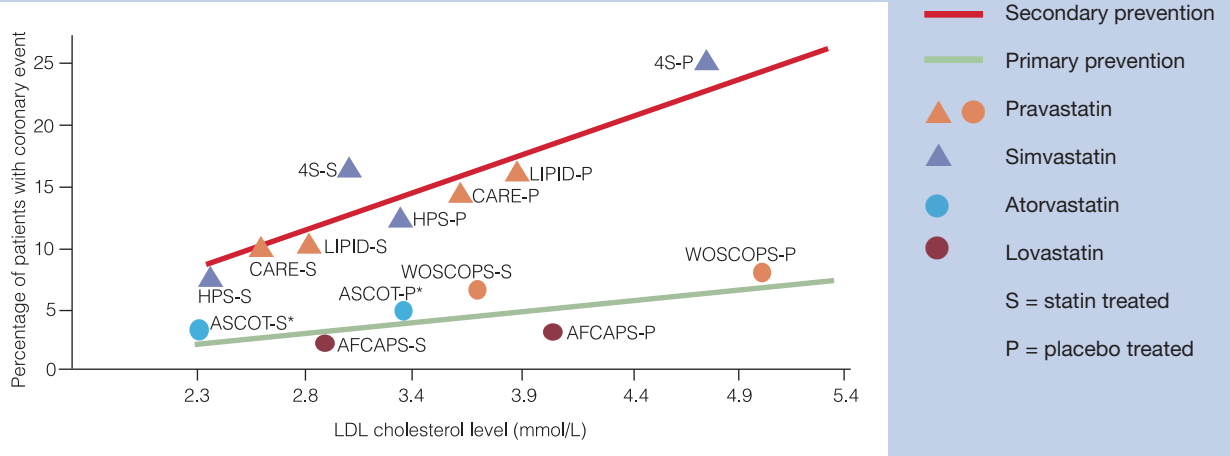
Monitoring patient compliance is also important. As with the therapy of all chronic asymptomatic conditions, there are practical difficulties in getting patients to continue statins on a permanent basis. Around 30% of Australians who were newly prescribed a statin in 1999 had discontinued the treatment within about six months.[9] Education and support are essential to help counter this situation.

Side effects

Side effects from statins are uncommon, occurring perhaps in 1 to 3% of patients. The more common examples include myalgia, arthralgia and fatigue. Less common are liver dysfunction and bowel symptoms. Clinicians should consult the relevant Product Information for more details.

Myalgia is of note because this often occurs in the absence of an impressive rise in creatine kinase, such as with an increase to only twice the upper limit of

Statin trials: LDL cholesterol levels and primary and secondary prevention of coronary events



Abbreviations: AFCAPS = Air Force Coronary Atherosclerosis Prevention Study;[1] ASCOT = Anglo-Scandinavian Cardiac Outcomes Trial;[2] CARE = Cholesterol And Recurrent Events trial;[3] HPS = Heart Protection Study;[4] LIPID = Long-term Intervention with Pravastatin in Ischaemic Disease study;[5] WOSCOPS = West Of Scotland Coronary Prevention Study;[6] 4S = the Scandinavian Simvastatin Survival Study.[7]

*Results extrapolated to five years.

Table. Guide to using statins outside the acute coronary syndrome setting

Statin	Usual starting dosage	Maximum dosage	Relative LDL cholesterol reduction*	CYP 3A4 excretion†
Simvastatin (Lipex, Zocor)	20 to 40 mg once daily	80 mg once daily	++	Yes
Pravastatin (Pravachol)	40 mg once daily	80 mg once daily	+	No
Fluvastatin (Lescol, Vastin)	40 mg once daily	40 mg twice daily	+	No
Atorvastatin (Lipitor)	10 to 20 mg once daily	80 mg once daily	+++	Yes
Rosuvastatin‡ (Crestor)	10 to 20 mg once daily	40 mg once daily	++++	No

* More + signs indicate greater reduction for the same dose in mg. † CYP 3A4 refers to a cytochrome P450 subtype. ‡ Rosuvastatin is not yet marketed in Australia but is already used in Europe and North America.

normal. (In myopathy and myositis, the creatine kinase generally rises to above 10 times normal limits.) Conversely, minor rises in creatine kinase may occur in the absence of muscle symptoms and may be clinically unimportant.

Two of the currently available statins – atorvastatin and simvastatin – are metabolised in the liver via the CYP 3A4 pathway and the potential for drug interaction exists. However, some drug interactions arise through other mechanisms. Of note is an interaction between statins and gemfibrozil, which may lead to muscle problems. This combination is not absolutely contraindicated but it should be approached with caution, and patients must be counselled to report myalgia immediately.

Conclusion

Statin drugs have revolutionised cardiovascular medicine. They will be offered to most patients with established coronary artery disease. GPs should consider prescribing statins to other patients at high risk of developing cardiovascular disease, such as those with multiple cardiovascular risk factors. MT

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This article is for general information purposes only, and the full product information should be consulted before prescribing the aforementioned medication(s).

DECLARATION OF INTEREST: Professor Simons has received research grants or lecture fees from several manufacturers of statin drugs.