Lipid therapy
an update on the evidence

Lipid-modifying therapy significantly reduces the risk of initial and recurrent cardiovascular disease and is generally safe. LDL-cholesterol below 2.5 mmol/L is an arbitrary goal, and recent trials support the benefit of achieving this or even lower levels.

LEON A. SIMONS
MD, FRACP

Dr Simons is Associate Professor of Medicine, University of NSW, Sydney; and Director, Lipid Department, St Vincent's Hospital, Sydney, NSW.

I began working in a lipid clinic in 1971 when GP interest in such therapy was already awakening. Thirty-five years on, lipid disorders and lipid therapy occupy practitioners on a daily basis, to the point that lipid-modifying drugs constitute the largest class of subsidised drugs in Australia.

Although dietary advice has been constant in the management of patients with lipid disorders, many of the drugs popular in the 1970s and '80s for these conditions have become obsolete. Therapy was originally offered on an empirical basis and relied on surrogate outcomes. Population studies such as Framingham (and others) had suggested that elevated blood cholesterol was important in the pathogenesis of cardiovascular disease (CVD). Hence, we assumed that diet and drug therapy to lower cholesterol would probably reduce the future risk of CVD and our patients might live longer.

Since 1994 we have witnessed a stream of landmark publications from controlled trials that indeed support our original assumptions. Randomised, placebo-controlled trials with 'statin' drugs have clearly shown prevention of coronary heart disease (CHD) and atherosclerotic stroke in subjects with or without a prior history of CVD. In terms of relative risk reduction, similar results have been obtained in those with highly elevated cholesterol levels[1] and in those with total cholesterol levels as low as 3.5 mmol/L.[2]

A new meta-analysis of statin trials

The lipid aspect of CVD prevention has now reached such a degree of maturity that we have witnessed the recent publication of a pre-planned meta-analysis of efficacy and safety of cholesterol-lowering therapy in more than 90,000 participants in 14 randomised trials using statin drugs.[3] This pooled analysis is capable of demonstrating outcomes not possible in individual trials.

IN SUMMARY

- **Lipid disorders and lipid therapy occupy GPs on a daily basis; lipid-modifying drugs comprise the largest class of subsidised drugs in Australia.**
- **Since 1994 controlled trials have supported original assumptions that diet and drug therapy to lower cholesterol would reduce patients' future risk of cardiovascular disease and mortality.**
- **A recently published meta-analysis of 14 randomised statin trials has reinforced the notion that the absolute benefit of therapy relates chiefly to an individual's absolute risk of CVD and the absolute reduction in LDL-cholesterol level achieved.**
- **Randomised comparisons of different statin regimens in patients with prior coronary disease indicate that achieving much lower levels of LDL-cholesterol will generate even further reductions in CVD risk.**
- **In patients with type 2 diabetes, fenofibrate has been shown to reduce the risk of nonfatal myocardial infarction, the need for revascularisation and the risk of microvascular disease.**

Overall, the trials demonstrate a significant 12% reduction in all-cause mortality for each 1 mmol/L reduction in LDL-cholesterol (Figure 1a). This reflects a 19% reduction in coronary mortality, a 23% reduction in myocardial infarction (MI) or coronary death, and a 17% reduction in fatal or nonfatal stroke for each 1 mmol/L reduction in LDL-cholesterol over a five-year period (Figure 1b). The relative risk reduction for major coronary events was similar in:

- the presence or absence of prior CHD
- those younger or older than 65 years
- men or women
- those with or without treated hypertension or a history of diabetes
- those with LDL-cholesterol under 3.5 mmol/L or greater than 4.5 mmol/L
- those with HDL-cholesterol under 0.9 mmol/L or greater than 1.1 mmol/L, or triglycerides under 1.4 mmol/L or greater than 2.0 mmol/L.

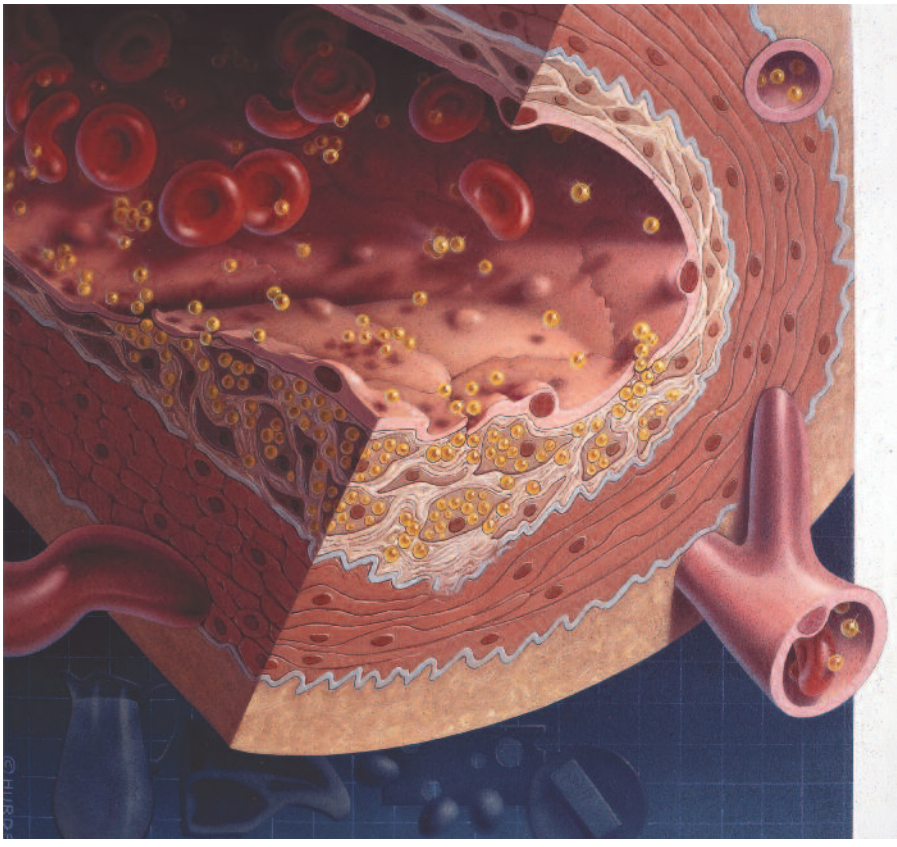
Over five-years' treatment, this translates into about 50 fewer participants having a major vascular event per 1000 participants with pre-existing CHD, compared with about 25 fewer events per 1000 participants with no such history. The analyses reinforced the notion that absolute benefit of treatment is related chiefly to an individual's absolute risk of CVD and to the absolute reduction in LDL-cholesterol achieved.

Most importantly, this large meta-analysis found no evidence that statins increased the risk of cancer overall or at any particular site. Nor was there any effect on the risk of haemorrhagic stroke.[3]

The latest clinical trials

The years 2004 and 2005 also witnessed the publication of several individual clinical trials that will gradually impact on the way we use lipid-modifying drugs. Randomised comparisons of different statin regimens in patients with prior CHD indicate that achieving much lower levels of LDL-cholesterol will generate even further reductions in CVD risk (Figure 3).[4-6]

In patients without established CHD, most international bodies recommend an approach of risk stratification. The patients at highest risk are those with other risk factors in addition to elevated LDL-cholesterol. These factors include hypertension, diabetes, low HDL-cholesterol level, cigarette smoking and family history of premature CHD. This approach is reflected in Australian PBS guidelines.



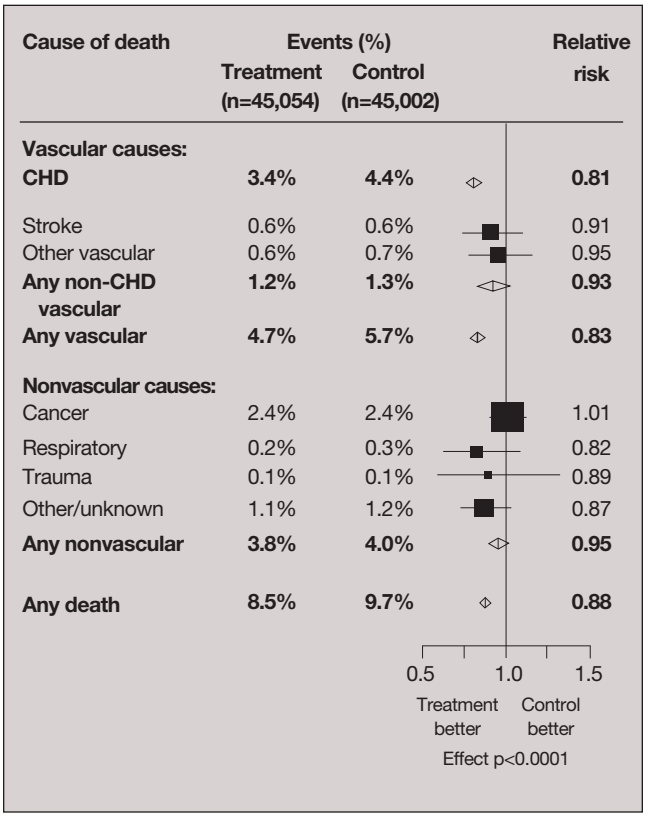
JANE HURD, SCIENCE PHOTO LIBRARY

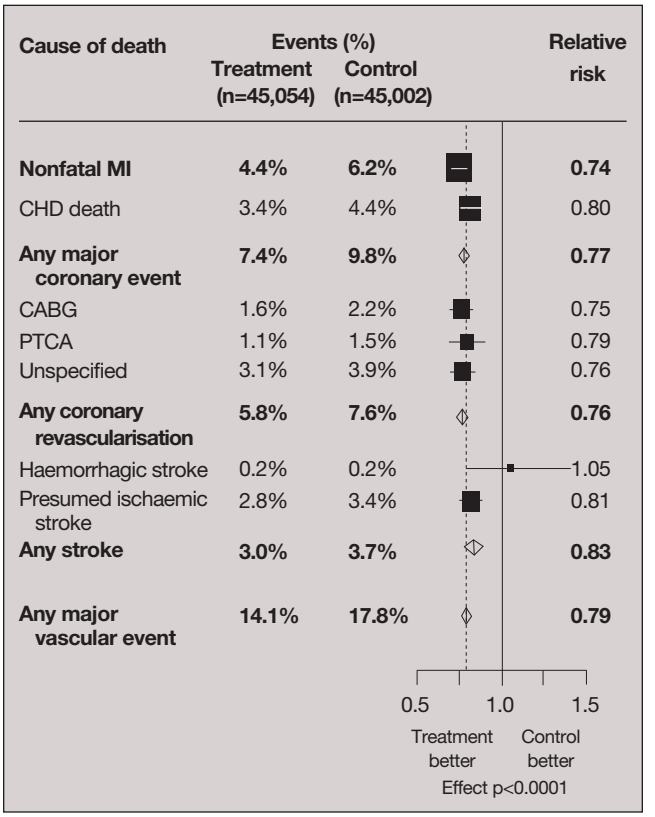
Results from the recently published Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) provide support for a multi-risk factor approach.[7] In this trial, patients with hypertension were randomised to one of two antihypertensive regimens and, simultaneously, to a low dose statin (atorvastatin 10 mg) or matching placebo. As shown in Table 1, patients receiving antihypertensive medication plus statin experienced about 50% fewer CVD events than did those on antihypertensive medication plus placebo.

Beyond statin drugs

Until now, I have discussed only trials of statin drugs. There has been suggestive evidence that the use of fibrate drugs (mainly gemfibrozil) might reduce future coronary risk, especially in patients with low HDL-cholesterol. In late 2005 we saw the publication of a placebo-controlled, randomised trial with fenofibrate given for at least five years to almost 10,000 patients with type 2 diabetes (the

continued





Figures 1a and b. a (left). Proportional effects on cause-specific mortality per mmol/L LDL-cholesterol reduction. b (right). Proportional effects on macrovascular events per mmol/L LDL-cholesterol reduction. Data from 14 randomised statin trials.[3] Diamonds = totals and subtotals. Squares = individual categories (horizontal lines are 99% CIs). Area of square is proportional to amount of statistical information in that category. Broken vertical line indicates overall relative risk for any type of major vascular event.

Abbreviations: CABG = coronary artery bypass graft; PTCA = percutaneous transluminal coronary angioplasty; CHD = coronary heart disease; MI = myocardial infarction.

FIELD study).[8] Although there was a nonsignificant reduction of just 11% in the primary outcome of MI plus coronary death, the treatment was associated with a significant 24% reduction in nonfatal MI and 21% reduction in the need for coronary revascularisation. Surprisingly, benefits were seen predominantly in those diabetic patients without prior CVD. Fenofibrate was also associated with a reduced risk of microvascular disease.

The high coronary risk status in patients with type 2 diabetes is well recognised, and a statin will continue to be the first choice of lipid drug to use in diabetes.[3] The FIELD trial did permit the concurrent use of a statin, and this was proportionately greater in the placebo arm of the study, possibly masking some of the treatment benefit of fenofibrate. Although not arising directly out of the FIELD trial, a key role for fenofibrate may yet be in combination therapy with a statin, where such is indicated by the lipid profile (see below).

Newer drugs

The advent of newer lipid-modifying drugs has yielded the possibility of achieving still greater improvements in lipid levels, especially in patients not currently achieving the arbitrary LDL-cholesterol goal of below 2.5 mmol/L. The National Heart Foundation has recently suggested a lower LDL-cholesterol goal of below 2.0 mmol/L in patients with existing coronary disease.[9]

Inevitably, we lack clinical trial evidence that newer therapies actually reduce CVD events. In the case of ezetimibe (Ezetrol), we have a drug that is not a statin but one that reduces cholesterol absorption. But since the effect of this drug is to reduce LDL-cholesterol, we can make the fairly reasonable assumption that improvement in the surrogate outcome will ultimately reduce the risk of a clinical event.

On the other hand, another new drug in development, torcetrapib, an inhibitor of the enzyme cholesteryl ester transfer

protein (CETP), may increase HDL-cholesterol by more than 50%. Unfortunately, we have no genuinely relevant evidence base from which we might extrapolate that this totally new approach will be effective or safe. Controlled trials with this drug are proceeding, and it is too early to judge whether it will become part of routine lipid therapy.

Clinical management

The pharmacological management of lipid problems requires the usual structured clinical approach, as summarised in Table 2. The predominant problem in the fasting lipid pattern should be characterised. Problems with diet, overweight, smoking, hypertension or diabetes should also be addressed.

In patients with the acute coronary syndrome (MI or unstable angina) it is becoming routine practice to prescribe high dose statin, unless a contraindication

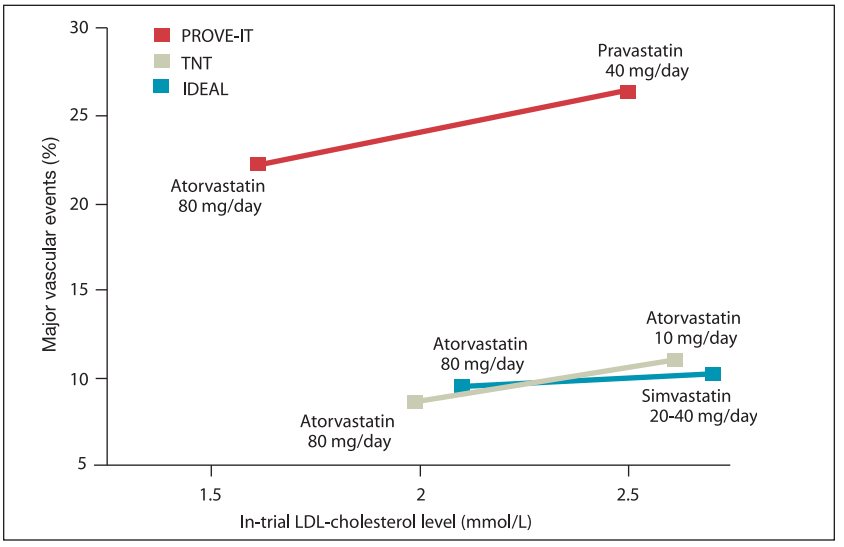


Figure 3. Major vascular event rates in recent trials comparing three different statin regimens in patients with CHD. Consider only the trend within an individual trial; event rates should not be compared between trials because of differences in trial design or patient selection.

Trial abbreviations: PROVE-IT = Pravastatin or atorvastatin evaluation and infection therapy; TNT = treating to new targets; IDEAL = incremental decrease in end points through aggressive lipid lowering.

Table 1. ASCOT: the combination of antihypertensive and lipid therapy[7]*

Endpoint	Amlodipine ± perindopril + atorvastatin	Atenolol ± thiazide + placebo	Relative risk differential
Nonfatal MI and fatal CHD	4.8/1000 patient-years	9.2/1000 patient-years	48%
Fatal and nonfatal stroke	4.6/1000 patient-years	8.2/1000 patient-years	44%

* Data also available at www.ascotstudy.org
Abbreviations: ASCOT = Anglo-Scandinavian Cardiac Outcomes Trial; MI = myocardial infarction; CHD = coronary heart disease.

Table 2. Lipid-modifying therapy for lipid disorders[10]

	Predominant hypercholesterolaemia	Predominant hypertriglyceridaemia	Combined hyperlipidaemia
First line therapy	Statin, or ezetimibe if patient is statin-intolerant	Fibrate, or fish oil if patient is fibrate-intolerant	Combination treatment is likely to be needed if TG or LDL-cholesterol is >4 mmol/L: statin plus fibrate or statin plus fish oil
Follow up	Monitor lipids, CK and LFTs,* and titrate dose as needed		Monitor for side effects*
Second line therapy	Add ezetimibe and/or resin to statin if patient is resistant	Monitor lipids, CK and LFTs*	

* Interrupt treatment if CK>5-10 times upper limit, if severe muscle symptoms are present, or if ALT >2-3 times upper limit.
Abbreviations: TG = triglycerides; CK = creatinine kinase; LFTs = liver function tests; ALT = alanine aminotransferase.

An individualised approach to elevated LDL-cholesterol

The multifactorial aetiology underlying CVD, as well as patient characteristics, means that there is not just one approach to managing LDL-cholesterol levels. Consider the following cases. Who would you treat and how?

Geoff – the gym goer

Geoff is a 38-year-old teacher who goes to the gym four times a week. He is reasonably health conscious, eating plenty of salads and vegetables, and has a reasonably high protein diet. He has a high intake of red meat and dairy products, and tries to include fish in his diet once or twice a week.

A screening blood test for insurance purposes shows a LDL-cholesterol level of 4.4 mmol/L, total cholesterol of 6.0 mmol/L and HDL-cholesterol 1.0 mmol/L. Fasting blood glucose is normal and blood pressure is 110/68 mmHg. He is a nonsmoker.

Comment. From the information that we have, Geoff's absolute risk of CVD is low (about 1% over the next five years). His only abnormality is a mild to moderately elevated LDL-cholesterol level. At this point it would be reasonable to defer treating the elevated LDL-cholesterol and monitor Geoff with annual blood lipid assays. However, dietary education would be useful because it appears that he could reduce his cholesterol intake with simple measures such as using low fat products. Geoff seems to be quite health conscious, so he is likely to follow your advice.

Fabian – with a family history

Fabian is a 47-year-old photographer in good health. After his 49-year-old brother had a heart attack last month, Fabian underwent several tests. His LDL-cholesterol level was 4.4 mmol/L, total cholesterol 6.0 mmol/L, HDL-cholesterol 1.0 mmol/L, fasting glucose 4.2 mmol/L and blood pressure 130/80 mmHg. He is slightly overweight (BMI 26 kg/m^2) and smokes about 10 cigarettes/day.

Fabian's father died in his 50s, but Fabian is uncertain of the cause. He reports a healthy diet but admits to being quite sedentary most days unless he is out on a 'shoot', which he does about twice per week.

Comment. According to the New Zealand Cardiovascular Risk Calculator (see *Medicine Today* 2004; 12: 20), Fabian's absolute five-year risk of a CV event is borderline at about 9%. However, he is at increased risk of CVD as he has a positive family history, an elevated LDL-cholesterol level and a sedentary lifestyle, and is a smoker and overweight. Hence, attempts should be made to lower his LDL-cholesterol to below 2.5 mmol/L and to help him cease smoking.

It would be reasonable to start Fabian with simple measures such as dietary education and advising him to increase his physical activity level. However, if a repeat blood test in a few months did not show improvement, it would be appropriate to start statin theory.

Dianne – who has diabetes

Dianne is a 49-year-old editor with type 2 diabetes that is not ideally controlled. She has no evidence of any micro- or macrovascular disease. Her most recent HbA_{1c} was 7.8%; her blood pressure is 125/80 mmHg, but her LDL-cholesterol level was 4.6 mmol/L, total cholesterol 7.2 mmol/L, HDL-cholesterol 1.0 mmol/L and triglycerides 3.5 mmol/L. Dianne is fairly conscientious with her diet, choosing fresh produce and low fat foods, and she is careful to go for a 45 minute brisk walk every day.

Comment. Generally, people with diabetes can be considered to be at a similar risk of a CV event to people with known CVD. Hence a target LDL-cholesterol of below 2.5 mmol/L would be appropriate in this case. Referral to a dietitian may be advisable, given Dianne's diabetes. She will quite likely need pharmacological treatment, and a statin would be a reasonable start. The later addition of fenofibrate may be necessary if her triglyceride levels do not improve sufficiently. This combination of fibrate and statin is relatively free of muscle problems, but she should still be warned about the theoretical risk of such effects.

is present. This might be a past history of adverse event with statin or the presence of highly elevated triglycerides.

In the nonacute situation, the full effect of drug therapy is generally apparent within six weeks, so it is prudent to review patients for side effects, lipid response and safety tests (e.g. liver and muscle enzyme levels) at this stage, and thereafter at regular intervals (say every six to 12 months for those on stable dosages). Encouragement of long-term compliance in patients (especially regarding diet and exercise) plus monitoring of weight and blood pressure is desirable. Review of possible drug interactions is required when other treatment adjustments are made, especially with the introduction of drugs that interfere with catabolic pathways such as cytochrome P450.

The box on this page summarises some suggested approaches to lipid management in individual patients. Additional practical details on lipid management may be found in a recent review by Simons and Sullivan.[10]

Conclusion

Lipid-modifying therapy significantly reduces the risk of initial and recurrent

CVD and is generally safe. LDL-cholesterol below 2.5 mmol/L is an arbitrary goal, and recent trials support the benefit of achieving this or even lower levels. Pharmacological treatment is warranted in patients with high absolute risk of CVD. Other randomised clinical trials are in progress and results will further refine treatment strategies and targets. MT

References

1. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease (the 4S). Lancet 1994; 344: 1383-1389.
2. 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.
3. Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005; 366: 1267-1278.
4. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004; 350: 1495-1504.
5. LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 2005; 352: 1425-1435.
6. Pedersen TR, Faergeman O, Kastelein JJP, et al. High-dose atorvastatin versus usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. JAMA 2005; 294: 2437-2445.
7. Dahlof B, Sever PS, Poulter NR, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required, in the Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet 2005; 366: 895-906.
8. FIELD study investigators. Effect of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet 2005; 366: 1849-1861.
9. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand. Position statement on lipid management – 2005. Heart Lung Circulation 2005; 14: 275-291.
10. Simons LA, Sullivan DR. Lipid-modifying drugs. Med J Aust 2005; 182: 286-289.

DECLARATION OF INTEREST: Associate Professor Simons has received consultancy fees or research grants from manufacturers of lipid-modifying drugs.