Lipid therapy
a 2007 update

Lipid modifying therapy reduces the future risk of cardiovascular disease, but significant vascular risk remains despite statin therapy. Those patients not reaching target LDL cholesterol levels on statin treatment may benefit from the addition of ezetimibe; those with low HDL cholesterol/high triglyceride levels may benefit from the use of fenofibrate or a combination of a statin and fenofibrate.

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.

In the year ending June 2005, prescription volume for lipid modifying drugs under the Australian Pharmaceutical Benefits Scheme (PBS) numbered 16.2 million units.[1] If we assume one prescription per month per person, this would suggest that more than 1.3 million adult Australians were taking a lipid drug at any one point in time. The cost of these 16.2 million prescriptions to the Australian Government was $919 million, creating a total cost of $1063 million after allowing for patient co-payments. This represented 17% of total expenditure through the PBS.

It is known that around 30% of patients will have discontinued lipid therapy within six months.[2] As the prescription volume has not fallen over recent times, we thus have indirect evidence that patients are starting or returning to lipid drugs in great numbers. The predominantly used lipid modifying drugs are the statins (96% by volume); others are fibrates (2%), inhibitors of cholesterol absorption and sundry others (the balance).

Although controlled clinical trials with atorvastatin essentially used 10 mg or 80 mg daily, and

IN SUMMARY

- **Lipid and lipoprotein levels are key risk factors in coronary heart disease (CHD) and ischaemic stroke.**
- **Prescription of lipid therapy is likely to remain or even increase as a key daily activity for GPs.**
- **The predominant lipid pattern in an individual patient is a factor in selecting the most appropriate lipid therapy choice.**
- **LDL cholesterol reduction by statins reduces the future risk of cardiovascular disease in patients with and without a prior history of CHD.**
- **There remains significant residual coronary risk in patients despite statin therapy.**
- **Those patients not reaching target LDL cholesterol levels on statin therapy may be better managed by the addition of ezetimibe to the statin therapy, or a switch to the combined ezetimibe–simvastatin preparation.**
- **Patients with low HDL cholesterol and high triglyceride levels may be better managed with fenofibrate or a combination of statin and fenofibrate.**
- **As a general rule, combination lipid therapy is a second step treatment rather than an initiating therapy.**

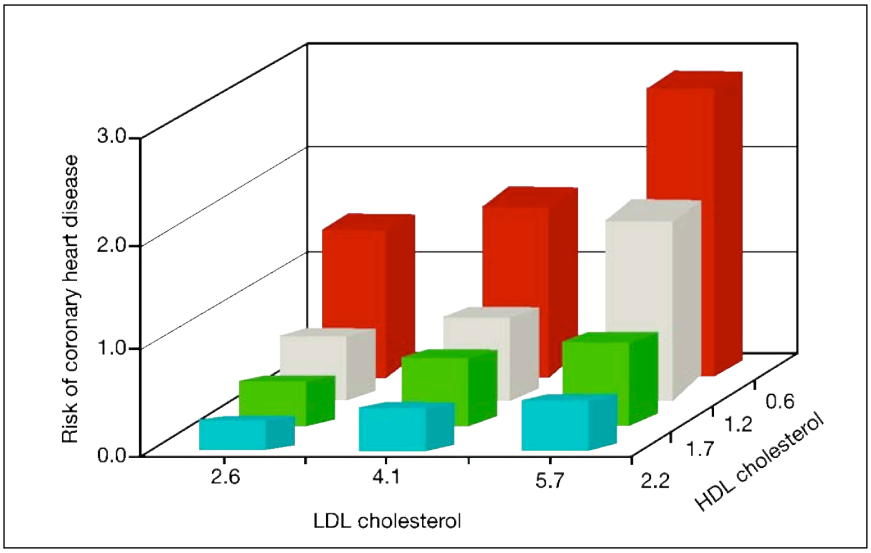

Figure 1. The interaction of LDL and HDL cholesterol in predicting coronary heart disease (the Framingham Study).[3]

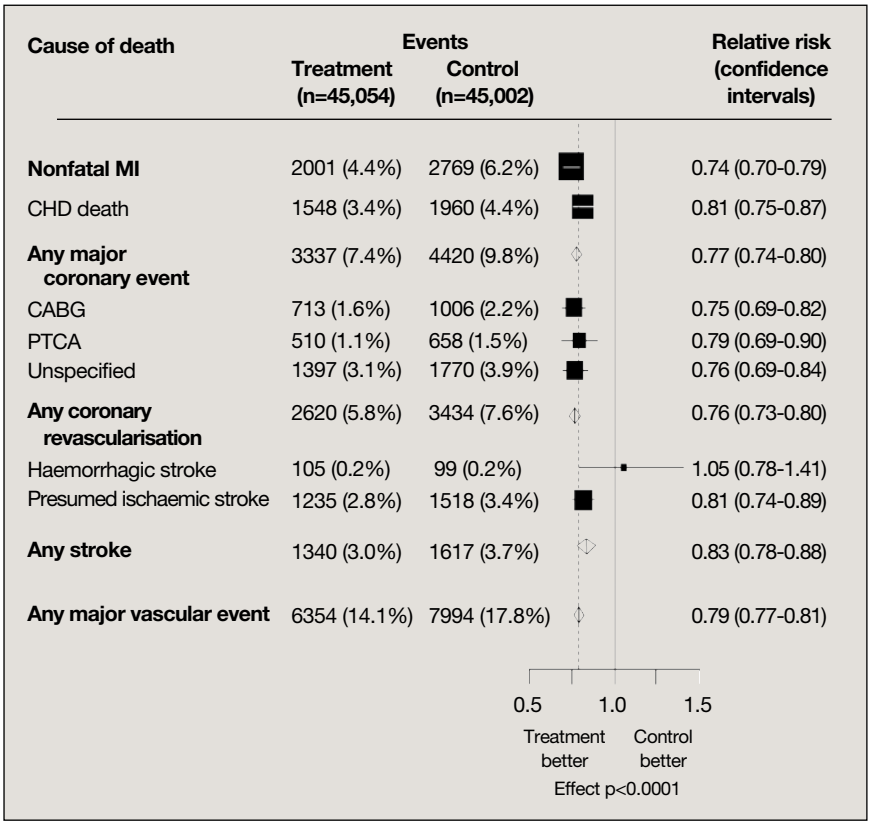

Figure 2. Proportional effects on vascular events per mmol/L LDL cholesterol reduction. Data from 14 randomised statin trials.[5] Relative risk <1.0 indicates that statin therapy is superior to placebo, while confidence intervals excluding 1.0 indicate a statistically significant outcome.

Abbreviations: CABG = coronary artery bypass graft; CHD = coronary heart disease; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty. Key: Diamonds = totals and subtotals; squares = individual categories; horizontal lines across squares are 99% confidence intervals. 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.

with simvastatin mainly 40 mg daily, this 'evidence' is not faithfully reflected in doses prescribed under the PBS. For example, the respective proportions of patients on 10, 20, 40 and 80 mg daily of atorvastatin were 26, 38, 27 and 9%. Comparable proportions for simvastatin were 14, 39, 38 and 9%. The doses in use do not necessarily imply poor choice of therapy if patients were being 'treated to target'.

Why are we treating so many people?

Why are so many Australians, around 10% of the adult population, receiving these drugs? The answer to this question is relatively simple:

- lipids and lipoproteins, alongside other major risk factors, are key players in the pathogenesis of coronary heart disease (CHD) and ischaemic cerebrovascular disease
- lipid drugs (predominantly statins, to a much lesser extent fibrates) have been shown to reduce the future risk of cardiovascular disease in the context of primary or secondary prevention
- significant disease prevention is achieved with an acceptably low rate of adverse events.

Management of patients on lipid therapy is, therefore, likely to remain or even increase as a key daily activity for all GPs.

Regarding observational studies, the opposite yet interacting prediction of CHD by higher LDL cholesterol and lower HDL cholesterol is well known (Figure 1).[3] Elevated triglycerides are also important, particularly in the context of the so-called metabolic syndrome (low HDL cholesterol, central abdominal obesity, hypertension and glucose intolerance).[4] Regarding controlled intervention studies in patients with prior CHD or at high cardiovascular risk, a meta-analysis covering 14 randomised trials showed that statins reduced the relative risk of CHD by 23% and ischaemic stroke by 19% (Figure 2).[5]

A major study has now been completed exclusively in patients with prior stroke or transient ischaemic attack (TIA) but no known CHD – the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study.[6] Compared with placebo over five years of treatment, high dose atorvastatin (80 mg daily) reduced the risk of fatal or nonfatal stroke by 16%, TIA by 26% and coronary events by 35%. Thus, a role is emerging for statins in the secondary prevention of stroke or TIA.

Controlled interventions with fibrates (gemfibrozil, fenofibrate) have been fewer and findings less robust. Of recent note has been the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, specifically in patients with diabetes.[7] Fenofibrate therapy reduced CHD events by only 11%, but this outcome was confounded by non-study use of statins. Microvascular disease in the eye and kidney was significantly reduced by fenofibrate.

Placebo-controlled trials with statin and fibrate drugs confirm the overall safety of these therapies: the drugs do not increase the risk of cancer or other serious diseases. On the other hand, these drugs are not free from side effects. Patients are becoming increasingly informed in these matters from media sources and they need to be counselled about the low risk of usually minor side effects.

High residual coronary risk despite lipid therapy

Even if CHD event rates are reduced by 20 to 30%, this still indicates that around 70 to 80% of patients treated will suffer a CHD event despite their lipid (and other) therapy over, say, a five-year period. (This is not the same as stating that 70 to 80% of the whole population will suffer an event.)

There could be many reasons for this high level of residual CHD risk. Two key, and potentially modifiable, reasons are:

- many patients do not achieve target lipid or lipoprotein levels (see the National Heart Foundation targets in Table 1)[8]
- other risk factors may need additional attention.

Although there is much evidence underpinning the clear benefits of statin therapy in relevant patients, it is still essential to examine the overall lipid profile as there will be some instances where a non-statin choice may be more appropriate.

Clinical management

All pharmacological management should be accompanied by standard diet and lifestyle advice, including attention to all coronary risk factors. Following direct measurement of total cholesterol, triglycerides and HDL cholesterol, the pathologist will calculate the patient's LDL cholesterol level (note that this calculation is not valid when triglycerides exceed 4 to 4.5 mmol/L). The patient's predominant lipid pattern is characterised from these results.

The appropriate lipid modifying therapies for each of the three main lipid disorders are discussed below and summarised in Table 2. A lipid modifying drug will be strongly indicated in the context of secondary prevention or in those at increased absolute risk, notably in patients with multiple coronary risk factors. The box on page 26 summarises suggested approaches to lipid management in two patients.

Table 1. National Heart Foundation lipid and lipoprotein targets, revised 2005[8]

- LDL cholesterol:
  - in high risk patients with existing CHD: <2.0 mmol/L
  - in others: <2.5 mmol/L
- HDL cholesterol: >1.0 mmol/L
- Triglycerides: <1.5 mmol/L
- Total cholesterol: no target specified

Predominant hypercholesterolaemia

In patients with predominant hypercholesterolaemia, statins remain the first choice treatment. Statins primarily work by reducing cholesterol synthesis, but they

Table 2. Principles underpinning lipid modifying therapy

	Predominant hypercholesterolaemia	Predominant hypertriglyceridaemia	Combined hyperlipidaemia
First line therapy	Statin (or ezetimibe if patients is statin-intolerant)	Fibrate (or fish oil if patient is fibrate-intolerant)	Statin or fibrate (monotherapy)
Follow up	Monitor lipids, CK and LFTs;* titrate dose as needed	Monitor lipids, CK and LFTs*	Monitor lipids, CK and LFTs*
Second line therapy	Add ezetimibe to statin if patient is resistant	Possible role for extended release nicotinic acid	Combination treatment is likely

* Interrupt treatment if CK >5 to10 times upper limit, if severe muscle symptoms are present, or if transaminases >2 to 3 times upper limit.
Abbreviations: CK = creatine kinase; LFTs = liver function tests.

Lipid management: tailoring treatment

There is not just one approach to managing dyslipidaemia. Consider the following cases.

Mark: multiple risk factors

Mark, a 45-year-old builder, has been sent to you for a cardiovascular work-up by the company for which he works.

On questioning you find that Mark smokes 20 to 30 cigarettes per day, and has done so for almost 20 years. His father died of heart disease in his 60s and Mark thinks his older brother has had a heart attack. Examination shows a blood pressure of 130/80 mmHg, a body mass index of 26.1 kg/m^2 and a normal ECG. His fasting plasma glucose is 4.0 mmol/L, total cholesterol 6.0 mmol/L, LDL cholesterol 4.2 mmol/L, HDL cholesterol 0.9 mmol/L and triglycerides 1.9 mmol/L.

Comment. In the context of primary prevention, it is necessary to calculate the absolute risk of cardiovascular disease (CVD).* Mark's five-year risk of CVD is calculated to be around 10%, this result largely being driven by his smoking, elevated LDL and lowish HDL. National Heart Foundation guidelines suggest that a five-year risk exceeding 10% in someone with this family history is a 'high risk' situation, and certainly worthy of intervention. His smoking and lipid problems both merit intervention and the difficult decision of where to begin first will have to be made. Ultimately, the lipid therapy will consist of dietary advice and, if the problem persists, the prescription of a statin.

Olga: only elevated cholesterol

Olga, now 67 years old, had a heart attack last year – it was minor. She had no apparent risk factors at the time and had coronary angioplasty to one vessel. Currently she is taking aspirin. She has been symptom free since the infarction.

An annual blood test reveals her total cholesterol is 6.0 mmol/L, LDL cholesterol 4.4 mmol/l, HDL cholesterol 1.0 mmol/L and triglycerides 1.3 mmol/L. Blood pressure and fasting blood glucose are normal. Olga is resistant to taking any more medication.

Comment. Olga should be informed that patients surviving a heart attack generally have improved survival and lower risk of re-infarction in the immediate future if they take a statin, and that this is irrespective of their current cholesterol levels. It is not too late for her to start statin therapy.

Case histories provided by Dr Audra Barclay, Medicine Today, comments by Professor Simons.

* Cardiovascular risk calculators for men and women with no history of cardiovascular disease include the National Prescribing Service's version of the New Zealand Cardiovascular Risk Calculator (www.nps.org.au) and the UKPDS Risk Engine (www.dtu.ox.ac.uk)

differ in potency and pharmacokinetics. Table 3 lists some key properties of the statins available in Australia. The most potent statin, mg for mg, is rosuvastatin (Crestor), which has been available under PBS subsidy since December 2006. As with all newer drugs, the results of definitive mortality and morbidity studies with this drug are awaited.

A combined formulation of atorvastatin and amlodipine (Caduet) has also been available under PBS subsidy since December 2006. This formulation may prove helpful in patients who also have hypertension.

For patients not reaching target LDL cholesterol, ezetimibe (Ezetrol) 10 mg daily added to a statin will produce a further LDL cholesterol reduction of approximately 25%. This may be achieved by dual therapy of any statin with ezetimibe or use of the combined formulation of simvastatin and ezetimibe (Vytorin). Ezetimibe reduces intestinal cholesterol absorption.

A combination of extended release nicotinic acid with a statin should be available in mid-2007.

If statins are contraindicated, some patients can be safely managed with a combination of ezetimibe and fenofibrate (Lipidil), or with a bile acid sequestrant (cholestyramine [Questran Lite]).

Predominant hypertriglyceridaemia

In patients with predominant hypertriglyceridaemia, fibrates are a first choice therapy after attention to glucose intolerance, obesity and alcohol sensitivity. Fenofibrate offers the convenience of once daily dosing and a much lower potential for drug interactions (myopathy) with statins.[9] The usual daily dose of fenofibrate is 145 mg, but reduced doses may be required because of renal impairment.

If fibrates are contraindicated, fish oil capsules may be considered in a dose delivering at least 2 g of omega-3 fatty acids daily.

Combined hyperlipidaemia

Some patients with combined hyperlipidaemia, may require a combination of a statin and fenofibrate. As mentioned above, the likelihood of a myopathic problem with this combination is very much lower than that with gemfibrozil, but caution is still required.[9]

The following approach is a personal recommendation:

- monotherapy is the first step, either a statin or fenofibrate, depending on the magnitude of the background lipid problem
- generally limit the statin dose to 10 to 20 mg daily in combination therapy, and do not exceed 40 mg daily; adjust the dose of statin later, as required
- monitor creatine kinase levels and muscle symptoms (myalgia), noting that minor elevations in creatine kinase may be nonspecific

Table 3. Key properties of statin drugs

Generic name	Trade name	Usual starting dose (mg/day)	Max. dose (mg/day)	Relative LDL cholesterol reduction*	CYP 3A4 excretion†
Atorvastatin	Lipitor	10-20	80	+++	Yes
Fluvastatin	Lescol, Vastin	40	80	+	No
Pravastatin	Cholstat, Lipostat, Liprachol, Pravachol	40	80	+	No
Rosuvastatin	Crestor	10	40	++++	No
Simvastatin	Lipex, Simvabell, Simvahexal, Simvar, Zimstat, Zocor	20-40	80	++	Yes

* More + signs indicate greater reduction for same mg dose; † excretion through CYP 3A4 pathway in the liver for any drug indicates a greater potential for drug interactions.

- warn patients about the low probability of myalgia; tell them that any problem will be followed by complete recovery with early cessation of treatment.

Some patients can be managed with a combination of a statin and high dose fish oil capsules, others with a combination of a statin and extended release nicotinic acid (when available). If statins are contraindicated, some patients can be safely managed with a combination of ezetimibe and fenofibrate.

Conclusion

Lipid modifying therapy reduces the future risk of cardiovascular disease, but significant vascular risk remains despite statin therapy. Those patients not reaching target LDL cholesterol levels on statin therapy may benefit from the addition of ezetimibe; those with low HDL cholesterol/high triglycerides may benefit from the use of fenofibrate or by a combination of a statin plus fenofibrate. It should be noted that PBS subsidy guidelines for lipid drugs were substantially revised in October 2006. MT

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DECLARATION OF INTEREST: Associate Professor Simons has received consultancy fees and research grants from manufacturers of lipid modifying drugs. The views expressed in this article are personal opinions and depart at times from official Product Information.

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