Lipid management – what's hot and what's not?

Statin therapy reduces the risk of cardiovascular disease, but significant residual cardiovascular risk remains. This may be addressed, in part, by more intensive statin therapy. We should continue to use supplementary ezetimibe in patients who are not achieving relevant target LDL-C levels on maximum doses of statin, pending the availability of further outcome data. Fibrates may be indicated, as a supplement to statins, in patients with high triglyceride levels.

LEON A. SIMONS
MD, FRACP

Professor Simons is an Associate Professor of Medicine at the University of New South Wales and Director, Lipid Department at St Vincent's Hospital, Sydney, NSW.

Lipid drug therapy, mostly statin therapy, consumes the largest proportion of PBS expenditure by cost and prescription volume – $1.208 billion in 2006 to 2007 and almost 20% of the PBS budget. This heavy usage is fully justified, given that numerous controlled trials have demonstrated highly beneficial effects on cardiovascular disease (CVD) outcomes – a relative risk reduction of 20 to 30% over a typical five-year period in the context of secondary or primary prevention.[1]

However, we must now accept that a 20 to 30% reduction in CVD risk, significant though it may be, is quite inadequate in terms of societal expectations. One of the biggest challenges in clinical medicine today is to find a way of delivering perhaps a 50 to 60% reduction in CVD risk. Two approaches outlined below have been suggested to solve this problem, both of which offer a realistic expectation of benefit, but neither has been proven to do so so far.

- The first suggestion is better overall management of all cardiovascular risk factors simultaneously (e.g. hypertension, cigarette smoking and diabetes).

IN SUMMARY

- **Statin therapy reduces the risk of cardiovascular disease (CVD) by 20 to 30% (relative risk reduction), but significant residual cardiovascular risk remains. This may be addressed, in part, by more intensive statin therapy.**
- **Supplementary ezetimibe should continue to be used in patients who are not achieving relevant target low density lipoprotein cholesterol (LDL-C) levels on maximum tolerated doses of a statin, pending the availability of further outcome data.**
- **Compliance should be confirmed in patients who are not at goal LDL-C levels after use of a statin and ezetimibe in proper dosage. A third drug such as fenofibrate 145 mg daily or low-dose cholestyramine 8 g daily could then be prescribed to reduce LDL-C levels further. This approach should be reserved for high-risk patients who are strongly motivated.**
- **In patients with triglyceride levels of 2.3 mmol/L or more, fibrates can be prescribed as a supplement to statins.**

- The second suggestion, in reality part of the first, is a more comprehensive management of the lipid profile.
  This article will focus exclusively on this area.

Goals and targets

The Australian Heart Foundation and many other specialist bodies have recommended goal low density lipoprotein cholesterol (LDL-C) levels of less than 2.0 mmol/L in the context of secondary CVD prevention and goal LDL-C levels of less than 2.5 mmol/L in the context of primary prevention. We will be able to achieve these goals more regularly in patients by the use of more potent statin drugs such as atorvastatin (Lipitor) and rosuvastatin (Crestor).

In the primary prevention setting it is prudent to commence with 10 mg daily of a potent statin, doubling the dose every six to eight weeks according to the LDL-C response. The maximum approved dose is 80 mg daily for atorvastatin and 40 mg daily for rosuvastatin. The product information for rosuvastatin recommends specialist guidance for doses of more than 20 mg daily, but this may be no more than a phone call to a consultant.

In regards to LDL-C lowering, statins produce a similar relative risk reduction across the full spectrum of LDL-C readings. But those patients who have the highest LDL-C readings will have the greatest CVD risk reduction in absolute terms and they will belong to the group with the lowest 'number needed to treat' (NNT) to prevent one CVD event (Figure 1).

Although statins have a modest triglyceride-lowering effect (about 20%), these drugs mainly reduce LDL-C levels and this reduction in LDL-C is highly correlated with the reduction in CVD events. LDL-C should be treated aggressively – with LDL-C it is genuinely 'the lower the better'.

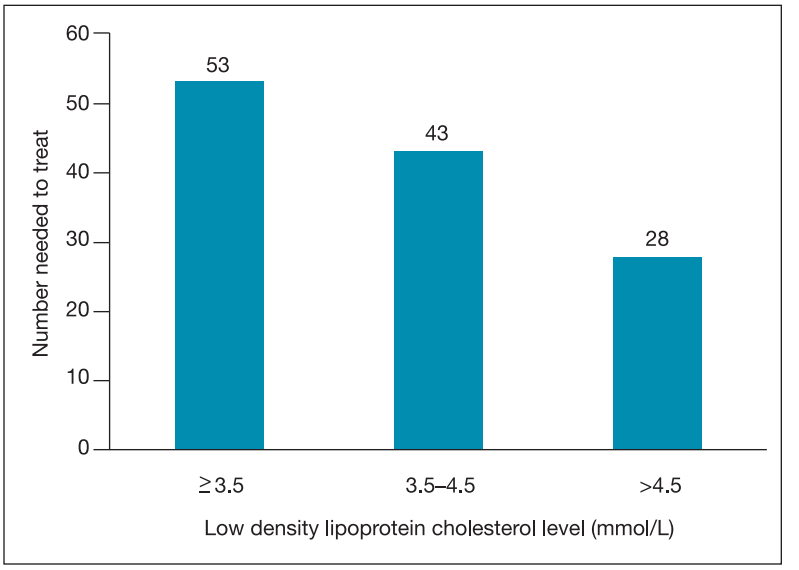

Figure 1. The number needed to treat with statins over five years to prevent one cardiovascular disease event according to entry LDL-C level. This is based on a meta-analysis in 90,056 patients in 14 trials.[1]

What will be the future use of ezetimibe?

There is no doubt that the addition of ezetimibe (Ezetrol) 10 mg daily to any ongoing statin therapy will yield a further 20 to 25% reduction in LDL-C levels and many more patients will thus achieve target LDL-C levels. However, a recent study comparing simvastatin with or without supplementary ezetimibe (Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression [ENHANCE] study) failed to show any improvement in carotid wall thickness by ultrasound – a 'surrogate' outcome.[2] This apparent lack of benefit in artery wall thickness was both surprising and disappointing.

A separate study investigating simvastatin and ezetimibe combination therapy (Vytorin) versus placebo in patients with aortic stenosis (the Simvastatin and Ezetimibe in Aortic Stenosis [SEAS] study) has just been completed.[3] Although this study showed a modest improvement in ischaemic cardiovascular events, a small but significant increase in cancer was noted (10.7% *v.* 7.0%). Analysis of cancer rates in other large cohorts using this same treatment has shown no evidence of increased cancer risk.

It remains uncertain whether ezetimibe is a clinically effective drug (i.e. whether it adds further clinical benefit to statin therapy) or whether the clinical trials reported thus far have been inappropriate models to define clinical benefit for this drug. The ultimate clinical role of ezetimibe will not be resolved until the completion of large clinical outcome studies, which are now in progress.

In the meantime we need a policy on the use of ezetimibe and ezetimibe/statin combinations. Ezetimibe products represent second-line choices in lipid therapy after the use of statins, unless a statin cannot be tolerated by a patient. Most authorities

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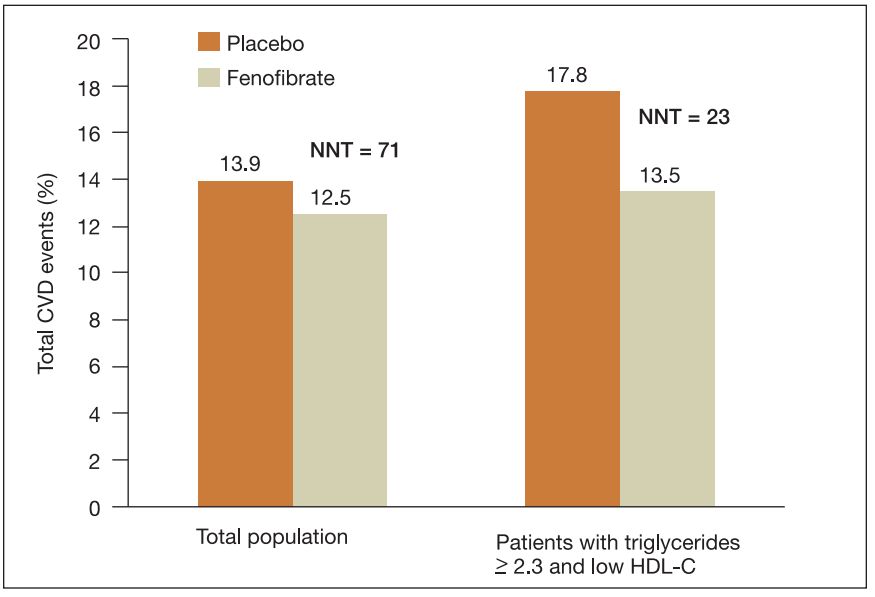

Figure 2. Cardiovascular disease events in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial using fenofibrate in patients with type 2 diabetes in the total study population and in those with triglyceride levels of 2.3 mmol/L or more and low HDL-C (<1.0 mmol/L in men and <1.3 mmol/L in women).[7]

ABBREVIATIONS: CVD = cardiovascular disease; HDL = high density lipoprotein cholesterol; NNT = number needed to treat to prevent one CVD event.

have expressed the view that we should continue to use ezetimibe in patients who are not achieving relevant target LDL-C levels on maximum tolerated doses of statin, pending the availability of further outcome data.

How do we manage a patient whose LDL-C level is not at goal after use of a statin and ezetimibe in proper dosage? Firstly, one needs to confirm that such a patient is taking his or her medication faithfully, then in the presence of good compliance:

- you can reassure the patient that a minimum 30% reduction in LDL-C levels, even if not at goal, will still translate into substantial CVD prevention
- alternatively, in high-risk patients who are strongly motivated, you could prescribe a third drug such as fenofibrate (Lipidil) 145 mg daily or even low-dose cholestyramine (Questran Lite) 8 g daily to reduce LDL-C levels further.

What should I do about HDL-C or triglycerides?

Low levels of high density lipoprotein cholesterol (HDL-C) are strongly associated with an increased risk of coronary heart disease (CHD), as are elevated levels of triglycerides. However, adjustment for established cardiovascular risk factors, especially HDL-C, substantially attenuates the magnitude of the association for triglycerides.[4]

High levels of HDL-C are clearly protective for CHD and it has seemed logical that therapy to raise HDL-C levels might provide future CVD benefit. Statins have a modest HDL-C raising effect, but fibrates and high-dose nicotinic acid have larger effects (10 to 30% and 15 to 30% elevations, respectively). Unfortunately, the formulation of nicotinic acid currently available has very poor patient acceptability because of cutaneous flushing and other side effects. We await the future availability of extended-release nicotinic acid products, especially those in combination with inhibitors of the flushing reaction.

Meanwhile a new class of drugs has been developed that inhibit the enzyme cholesterol ester transfer protein (CETP), a key enzyme in HDL-C metabolism. The first member of this class, torcetrapib, raises HDL-C levels by 60 to 100% and theoretically this should have been the next major breakthrough in CVD prevention. Unfortunately, in a major out - come study this drug actually increased all-causes mortality and its further clinical development has now been halted.[5]

Other research has revealed that torcetrapib has an unexpected, off-target effect, stimulating the release of aldosterone and raising blood pressure. This may have contributed to the adverse outcomes in the study described above. Other CETP inhibitors free of this off-target effect are now undergoing clinical trials. So it is very much 'watch this space' for CETP inhibitors in the future.

Triglycerides and fibrate therapy

Since fibrates effectively reduce triglyceride levels by 40 to 50% and raise HDL-C levels by 10 to 30%, there was a logical expectation that cardiovascular benefits in trials investigating fibrates would follow from these lipid responses. However, intervention trials investigating fibrates have produced somewhat inconsistent outcomes in terms of CVD prevention, possibly due to selection of study population as well as statin drop-ins in one major study. Furthermore, the benefits that have been observed have not been correlated with a reduction in triglyceride levels and any relation to the raising of HDL-C levels has been weak.[6] However, the degree of triglyceride-lowering achieved may still be an indicator of good compliance.

What is beginning to emerge from these studies is the notion that triglyceride levels of 2.3 mmol/L or more are a 'marker' for those patients who are most likely to benefit from CVD prevention

Table 1. Possible anti-atherogenic mechanisms of fibrates[6]

- Reduce levels of plasma triglycerides
- Reduce levels of chylomicron and very low density lipoprotein remnants
- Increase size of low density lipoproteins
- Increase levels of high density lipoprotein cholesterol
- Facilitate reverse cholesterol transport
- Direct anti-inflammatory effects in the artery wall
- Direct anti-inflammatory effects in visceral fat

with fibrate therapy.

Clinical trials have shown that elevated triglyceride levels remain predictive of CVD events in the presence of statin therapy, indicating a potential treatment avenue. Recent data from the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study investigating fenofibrate in patients with type 2 diabetes indicate that those with triglyceride levels of 2.3 mmol/L or more and low HDL-C levels (<1.0 mmol/L in men and <1.3 mmol/L in women) show the greatest CVD risk reduction and belong to the group with the lowest NNT to prevent one CVD event (Figure 2).[7] This study has also shown a reduction in microvascular disease with fenofibrate (reduction in rate of progression to albuminuria, reduced need for laser treatment for retinopathy and a reduction in the number of nontraumatic amputations).

It has been reported that fibrates have many potentially beneficial anti-atherogenic effects beyond triglyceride reduction (Table 1). Fibrates also remain indicated for the prevention of pancreatitis if triglyceride levels are highly elevated (e.g. >10 mmol/L).

This emphasis on the potential benefit of fibrate therapy should probably be viewed as benefit supplementary to the use of statins. Trials designed to answer this specific question are now in progress. Meanwhile we should give serious consideration to supplementing statin therapy with fibrates when triglyceride levels are 2.3 mmol/L or more. Finally, a combined tablet formulation of a statin plus fenofibrate is now under development.

Combining statins with fibrates immediately raises the issue of muscle problems. This appears to be a more serious issue when using gemfibrozil and is less problematical when using fenofibrate. Hence, I recommend that fenofibrate be used in preference to gemfibrozil in patients taking a statin. Fenofibrate is generally used in a fixed dose of 145 mg once daily with no special relationship to food and it is my personal practice to avoid maximum doses of statin in this setting. For the few patients who are unable to tolerate fibrates, high-dose fish oil capsules may be helpful (e.g. Maxepa omega-3 capsules twice daily).

Adverse events with statins

Serious adverse events are uncommon with statins, yet perhaps 5 to 10% of patients will experience less severe but annoying side effects – for example, myalgia, arthralgia and raised liver enzymes (transaminases). Recent study experience has suggested that patients currently experiencing such problems may sometimes be helped by a switch to fluvastatin (Lescol-XL) 80 mg daily, an extended-release preparation of an older statin. Another approach, now gaining some credence, is a switch to low-dose rosuvastatin on

Table 2. Principles of lipid therapy for different patient groups

Patient group	Treatment	
	Most patients	Patients with triglyceride levels of 2.3 mmol/L or more and low HDL-C*
Patients requiring secondary CVD prevention	Statin	Consider addition of fenofibrate to statin
Patients at risk requiring primary CVD prevention	Statin	Consider addition of fenofibrate to statin
Patients whose LDL-C level is not at target	Statin plus ezetimibe	Fenofibrate plus statin
Patients experiencing adverse event(s)	Consider fluvastatin (extended release), or low-dose rosuvastatin on alternate days with or without the addition of ezetimibe	Consider solo fenofibrate therapy

* Low HDL-C is <1.0 mmol/L in men and <1.3 mmol/L in women.
ABBREVIATIONS: CVD = cardiovascular disease; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol.

alternate days (e.g. half a 5 mg tablet every other day, with or without the addition of ezetimibe). There may also be a limited role in this situation for solo fenofibrate therapy.

We have to accept that there will be some patients who will experience adverse events with statins or other drugs, whatever measures we have offered with the best of intentions. On the grounds of quality of life issues and the principle of *primum non nocere*, these patients should not be coerced into continuing drug therapy that causes ongoing problems or discomfort.

A modified approach to lipid therapy

The general principles of prioritising patients in the primary prevention category have not changed. Drugs should be reserved for those patients at higher absolute CVD risk, after standard global risk assessment. Virtually all patients in the secondary prevention category will be treated with a statin. Statins should still be used for reducing cholesterol and LDL-C levels and fibrates predominantly for triglyceride problems. Given the proven value of statin therapy, very few patients will be managed on solo fibrate therapy. It should be noted that, under PBS guidelines, the qualifying criteria for statins and fibrates are the same. Table 2 indicates how this may be applied in practice.

Summary

Statins reduce the risk of CVD by 20 to 30% but significant residual cardiovascular risk remains. This may be addressed, in part, by more intensive statin therapy. We should continue to use supplementary ezetimibe in patients who are not achieving relevant target LDL-C levels on maximum doses of statin, pending the availability of further outcome data. Fibrates may be indicated, as a supplement to statins, in patients with triglyceride levels of 2.3 mmol/L or more. MT

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