

# Lipid-modifying drugs

Leon A Simons and David R Sullivan

Epidemiological studies have shown a continuous relationship between total serum cholesterol and the risk of coronary heart disease<sup>1</sup> (E1; based on NHMRC levels of evidence<sup>2</sup>). Because most serum cholesterol is transported in the low-density-lipoprotein cholesterol (LDL-C) fraction, this relationship with coronary heart disease (CHD) holds equally well with LDL-C. The relationship is continuous, but not linear — CHD risk rises more steeply at higher LDL-C concentrations.<sup>3</sup>

High-density-lipoprotein cholesterol (HDL-C), through mediation of reverse cholesterol transport from peripheral tissues to the liver, is also an important regulator of CHD risk. Below average HDL-C concentrations are associated with increased CHD risk (E1).<sup>1</sup> Elevated triglyceride concentrations, usually in association with a reduced HDL-C concentration, are related to increased CHD risk, although the evidence here is not as strong as for LDL-C.<sup>1</sup> A large international study recently concluded that the ratio of apolipoprotein B to apolipoprotein AI, a reflection of LDL-C and HDL-C, accounted for almost half the population-attributable risk of myocardial infarction.<sup>4</sup>

Risk factors may be equated with some degree of causality. However, not every person with an elevated LDL-C concentration will have premature CHD. Nor will everyone with premature CHD show a lipid concentration abnormality, although other risk factors such as hypertension, cigarette smoking, diabetes, family history or coagulopathy may be important in such cases.<sup>1</sup> The importance of lipid abnormalities in cardiovascular disease have become apparent to both doctors and the lay public following the publication of landmark studies of intervention with statins over the past 10 years.<sup>5</sup> The positive results from intervention studies show a high degree of concordance with predictions from observational studies.

The role of lipids in stroke causation has been potentially confounded by a single, large meta-analysis that did not divide stroke into its subtypes. This analysis of 45 cohorts, which included 450 000 people followed for an average of 16 years and 13 000 incident strokes, found no association between serum cholesterol concentrations and stroke.<sup>6</sup>

However, analysis of cohort studies by stroke subtype has shown that the risk of non-haemorrhagic (ie, ischaemic) stroke increases as LDL-C concentration increases (a 15% increase for each 1-mmol/L increase in LDL-C concentration) (E1).<sup>5</sup> The risk of haemorrhagic stroke increases as LDL-C concentration falls (a

## ABSTRACT

- An elevated concentration of low-density-lipoprotein cholesterol (LDL-C) plays a causal role in the development of coronary heart disease and ischaemic stroke.
- Placebo-controlled intervention studies of statin drugs for lowering LDL-C provide clear evidence of cardiovascular disease prevention.
- LDL-C concentration below 2.5 mmol/L is an arbitrary goal, and recent trials support the benefit of achieving this goal, or even lower levels.
- Pharmacological treatment is warranted in patients with high absolute risk of future cardiovascular events.
- Effective monotherapy is available for predominant hypercholesterolaemia and predominant hypertriglyceridaemia, but combination therapy may be required for severe cases or in those with mixed hyperlipidaemia.
- Side-effects are infrequent and usually mild, but widespread use of lipid-modifying medication demands caution because of the possibility of muscle or liver dysfunction or drug interactions.

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19% increase for each fall of 1 mmol/L in LDL-C concentration).<sup>5</sup> There is increased risk of haemorrhagic stroke at concentrations of total cholesterol below 5.2 mmol/L.<sup>7</sup> The absence of a relationship with total stroke probably relates to these opposite relationships, and to an age-selection bias in the selected cohorts.<sup>5,8</sup> Elevated LDL-C concentration is an important risk factor for ischaemic stroke. Several studies show that elevated HDL-C is a protective factor in ischaemic stroke (E2).<sup>9,10</sup>

## Intervention studies

Placebo-controlled trials with statins (including simvastatin, pravastatin, atorvastatin and fluvastatin) have now been included in a number of independent meta-analyses, all of which have come to the same broad conclusions that statins reduce coronary events by about 25%–30% over 5 years of treatment, and reduce ischaemic stroke risk by about 10%–15% (E1).<sup>5,11</sup> In the context of secondary heart disease prevention, this translates into the need to treat about 20–30 patients to prevent one coronary event, and the need to treat about 80–100 patients to prevent one stroke over 5 years. Intervention studies show no increase in the risk of haemorrhagic stroke with the use of statins. Adverse events attributable to statin therapy in these trials have been at very low rates.<sup>5</sup>

Statin were used in some of these studies for secondary prevention and in some for primary prevention; the relative risk reduction in CHD was broadly similar in both clinical categories.<sup>11</sup> However, a similar relative risk reduction translates into a much higher absolute

University of New South Wales Lipid Research Department,  
St Vincent's Hospital, Sydney, NSW.

Leon A Simons, MD, FRACP, Associate Professor of Medicine, and  
Director.

Department of Clinical Biochemistry, Royal Prince Alfred Hospital,  
Sydney, NSW.

David R Sullivan, FRACP, FRCPA, Clinical Associate Professor, and  
Senior Staff Specialist.

Reprints will not be available from the authors. Correspondence:  
Associate Professor Leon A Simons, Lipid Research Department,  
St Vincent's Hospital, Darlinghurst, NSW 2010.

L.Simons@notes.med.unsw.edu.au

risk reduction in the context of secondary CHD prevention, and hence a lower number needed to treat to prevent one coronary event (about 20–30 compared with about 50–60).

One report presents the results of meta-analysis in a helpful manner.<sup>5</sup> In 58 statin trials, an average reduction in LDL-C concentration of 1 mmol/L reduced the risk of a CHD event by 11% in the first year of treatment, 24% in the second year, 33% in years 3–5 and by 36% thereafter. After several years of treatment, a reduction in LDL-C concentration of 1.8 mmol/L reduced CHD events by an estimated 61%! A reduction of 1 mmol/L in LDL-C concentration reduced the risk of stroke by 10% and a reduction of 1.8 mmol/L reduced the risk of stroke by 17% (E1).<sup>5</sup>

Three studies — the UK Heart Protection Study of simvastatin (40 mg/day),<sup>12</sup> and ASCOT-LLA<sup>13</sup> and CARDS<sup>14</sup> of atorvastatin (10 mg/day) — show the reduction in the rate of CHD event with statins from middle age onwards, in both sexes, and in the presence of other major coronary risk factors such as hypertension or diabetes. The LIPID trial of pravastatin (40 mg/day)<sup>15</sup> and these more recent studies<sup>12–14</sup> suggest that a similarly improved coronary event rate, in relative risk terms, occurs in both those with above-average and below-average LDL-C concentrations; that is, benefit is observed across the whole range of cholesterol levels (E2).

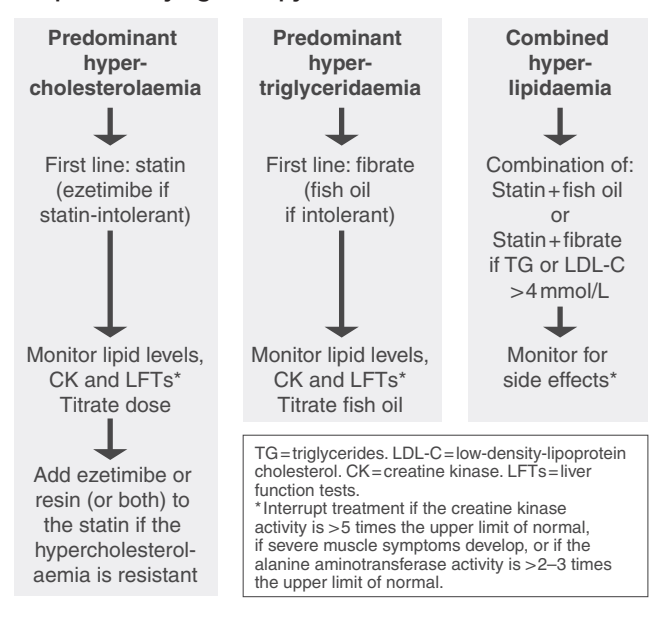
Recent randomised, controlled intervention studies have taken a new approach by comparing the clinical benefits of two statins. The PROVE-IT trial compared atorvastatin (80 mg/day) with pravastatin (40 mg/day) in patients with acute coronary syndrome.<sup>16</sup> Atorvastatin showed an incrementally better cardiovascular outcome overall, associated with a greater reduction in LDL-C concentration (sub-group analysis showed statistical significance only for those with baseline LDL-C concentration > 3.2 mmol/L). The REVERSAL study used similar treatments in patients with proven CHD (not acute coronary syndrome) and used coronary intravascular ultrasound; it showed that progression of coronary lesions was arrested if an LDL-C concentration below 2.3 mmol/L was achieved (this occurred only in those taking atorvastatin).<sup>17</sup>

High-grade clinical trial evidence of the benefit of raising HDL-C concentration and reducing triglyceride concentration is limited. Post-hoc analyses of several trials of fibrate drugs (especially the VA-HIT trial<sup>18</sup> of gemfibrozil) indicate that they reduce the risk of CHD in patients with elevated triglyceride concentrations and low HDL-C concentration, especially in those who have diabetes or the metabolic syndrome.<sup>18,19</sup> Post-hoc analysis of the LIPID trial confined to patients with the same entry criteria as VA-HIT also showed that pravastatin had a similar benefit to gemfibrozil in preventing recurrent vascular disease.<sup>20</sup>

## Clinical management

The pharmacological management of lipid problems requires a structured clinical approach (see Box 1). The predominant problem in the fasting lipid pattern should be characterised as either a predominant increase in LDL-C concentration, a predominant increase in the concentration of triglycerides (usually accompanied by low HDL-C concentration), or a combination of both. Treatable secondary causes of lipid disturbance should be identified and managed. Absolute cardiovascular disease risk, which also depends on the presence of other major risk factors, can be estimated with the assistance of algorithms or charts.<sup>1</sup> In the presence of high absolute risk (eg, > 10%–15% risk over the next 5 years), long-term pharmacological treatment should be considered. Problems with

## 1 Lipid-modifying therapy



diet, overweight, smoking, high blood pressure or diabetes should also be addressed.

## LDL-C goals and targets

Some clinical trials have achieved relatively low LDL-C concentrations (around 2.4 mmol/L in the Heart Protection Study<sup>12</sup> and around 1.6 mmol/L in PROVE-IT<sup>16</sup>). This has been possible through the use of potent drugs in patients with “average” LDL-C concentrations at baseline. On this basis, the United States National Cholesterol Education Program has recently suggested that their goal LDL-C concentration in people at very high risk (those with prior CHD and multiple risk factors, especially diabetes) be lowered from the present 2.6 mmol/L to 1.8 mmol/L.<sup>18</sup> While a new LDL-C concentration target is a theoretical consideration at this time, the above data strengthen the case for treating as many high-risk patients as possible to the existing Australian target of below 2.5 mmol/L.<sup>1</sup> (Although less clearly supported by clinical trial evidence, the target LDL-C concentration may be < 3.0 mmol/L in lower-risk patients — those without prior cardiovascular disease, diabetes, or those who have an absolute risk in the next 5 years of < 10%–15%).<sup>1</sup>

## Predominant elevation of LDL-C concentration (hypercholesterolaemia)

**First-line therapy:** HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme-A) reductase inhibitors (statins) are the first-line treatment for hypercholesterolaemia (Box 2). They inhibit cholesterol synthesis, resulting in increased low-density-lipoprotein (LDL) receptor activity with enhanced clearance of LDL particles and precursors. Statins reduce LDL-C concentration by up to 60%, while the associated reduction in triglyceride concentrations and increase in HDL-C concentration are relatively modest, but potentially useful.

A patient presenting for the first time with acute coronary syndrome (myocardial infarction or unstable angina) will usually be under specialist care, and may be prescribed 80 mg/day of atorvastatin (unless a contra-indication is present), plus other drugs. This is

## 2 Clinical application and effectiveness of statin medications for reducing low-density-lipoprotein cholesterol concentrations

Drug	Clinical trial evidence	Usual starting dose (mg/day)	Maximum dose (mg/day)	Relative LDL-C reduction*	CYP 3A4 excretion†
Simvastatin	Primary and secondary prevention	20–40	80	--	Yes
Pravastatin	Primary and secondary prevention	40	80	–	No
Fluvastatin	Secondary prevention	40	80	–	No
Atorvastatin	Primary and secondary prevention	10–20	80	---	Yes
Rosuvastatin†	Not available	10–20	40	----	No

LDL-C = low-density-lipoprotein cholesterol. CYP 3A4 = cytochrome P450 subtype.

\*More minus signs indicate greater reduction for same dose (in mg) of drug. †Not yet marketed in Australia, but already widely used in Europe and North America.

Note: dose titration is not usual in acute coronary syndrome.

based on clinical trial evidence of cardiovascular disease prevention, and does not emphasise dose titration or target LDL-C levels in the acute setting.<sup>16,21</sup> This treatment will be continued on a permanent basis. In less acute settings, it is more usual to initiate treatment with a submaximal dose of statin and then titrate the dose upwards, according to LDL-C concentration, at intervals of 6–8 weeks. Each dose increment will be a doubling, as this will produce only about a further 6% reduction in LDL-C concentration.

Serious side-effects are rare<sup>22</sup> and statin therapy is usually well tolerated. Important adverse events include myalgia, asymptomatic increase in creatine kinase (CK) concentration, myositis, and (very rarely) rhabdomyolysis, as well as elevation in liver enzyme concentrations. Caution should be exercised in patients who are elderly, debilitated or receiving other drugs that interfere with statin excretion by cytochrome P450 3A4 or other pathways.

In animals fed very high doses of statins, some evidence of carcinogenesis was suggested. Placebo-controlled trials in humans generally lasting about 5 years show no credible evidence of increased carcinogenesis.<sup>5</sup> Statin drugs cross the blood-brain barrier to a limited extent (much less so in the case of pravastatin). Nervous system complaints, such as insomnia, mood and personality changes, memory loss, paraesthesiae and peripheral neuropathy (see product information of the respective drugs) have occasionally been noted. However, the frequency of these side effects is low and causality cannot be assumed in every case.

**Alternative therapy:** This includes a drug that inhibits intestinal cholesterol absorption. The recently introduced drug, ezetimibe, appears to interact with the intestinal mucosal transporter, NPC1L1 (Niemann-Pick type C1 like 1 protein), that absorbs dietary and biliary cholesterol.<sup>23</sup> The standard 10 mg/day dose in monotherapy reduces LDL-C concentration by 15%–20%, while beneficial effects on triglyceride and HDL-C concentrations are marginal. The addition of ezetimibe to statin therapy achieves an additional reduction in LDL-C concentration of up to 24%.<sup>24</sup> Ezetimibe is well-tolerated, but long-term experience is limited and its effect on cardiovascular outcomes remains to be determined. There remains a limited role for the use of resins (cholestyramine, colestipol) or high dose nicotinic acid in reducing LDL-C concentration.<sup>1</sup>

In general, drugs for lowering LDL-C concentration should be given in sufficient doses to achieve target LDL-C concentrations below 2.5 mmol/L. In a high-risk patient with initial LDL-C concentration around 2.5 mmol/L, a still lower LDL-C target concentration may be desirable. In primary prevention, selection of cases for drug treatment will be based on absolute risk assessment and will still use standard targets.

Definite myalgia or muscle weakness, elevation of CK activity beyond five times the upper limit of normal, or sustained elevation of alanine aminotransferase concentration beyond 2 to 3 times the upper limit of normal (and not accounted for by fatty liver) are indications for interruption or cessation of statin therapy. Occasionally a reduction in dose or a switch in statin drugs may be helpful. Myalgia is less frequent with pravastatin, but may still occur in susceptible patients. Patients who are intolerant of statins may receive ezetimibe or resins. These agents may also be used as supplementary therapy when patients do not reach LDL-C target concentrations on the highest tolerated statin dose.

### Predominant elevation of triglyceride concentration (with low HDL-C concentration)

**First-line therapy:** Statin therapy alone is unlikely to normalise lipid levels in patients in whom low HDL-C concentration and fasting concentrations of triglycerides in excess of 4 mmol/L persist after diet and lifestyle advice. In such patients, specific triglyceride-lowering treatment with fibrates such as fenofibrate or gemfibrozil is required. These drugs stimulate peroxisome proliferator activated receptor- $\alpha$  (PPAR $\alpha$ ), a nuclear transcription factor that controls the expression of genes mediating triglyceride metabolism. This treatment reduces synthesis of fatty acids and triglyceride-rich lipoproteins, and increases synthesis of apolipoprotein AI and lipoprotein lipase, thus promoting high-density lipoprotein (HDL) production and triglyceride catabolism. Fenofibrate (160 mg once daily) or gemfibrozil (600 mg twice daily) reduce triglyceride concentrations by up to 50% and increase HDL-C concentration by up to 20%, but changes in LDL-C concentration are variable and usually small. Fibrate therapy is generally well tolerated, but myalgia or raised liver enzymes may occasionally occur. Fibrates slightly increase the risk of cholelithiasis and do potentiate the action of warfarin.

**Alternative therapy:** Fish oil n-3 fatty acids can be used to reduce triglyceride concentrations. Fish oils contain highly poly-unsaturated long-chain n-3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid). A daily intake of 2–5 g of n-3 fatty acids (6–15 g of fish oil) lowers triglyceride concentrations by up to 50%. Changes in LDL-C and HDL-C levels are small and variable. Platelet aggregation is inhibited by fish oil. Dietary and pharmacological trials suggest that n-3 fatty acids reduce CHD mortality,<sup>25</sup> possibly because of a reduction in ventricular arrhythmias (E2). Fish oils are safe and most patients can tolerate the required doses.

Hypertriglyceridaemic patients who do not achieve target levels during monotherapy with fibrate or fish oil (or nicotinic acid) can

### 3 Important messages for patients

- Cholesterol plays a key role in the onset of coronary heart disease, alongside other causes such as cigarette smoking, hypertension, diabetes and adverse family history
- Controlled trials have shown that statin drugs are effective in preventing heart disease
- Treatment with statins is strongly indicated in those with a past history of heart disease or stroke, and in other patients at high risk by virtue of the presence of diabetes or other risk factors
- Lipid-modifying drugs must be taken over the long term and are generally safe

proceed to a combination of these agents. Massive triglyceride level elevation ( $>10\text{ mmol/L}$ ) may require more aggressive limitation of dietary fat intake ( $<10\text{--}20\%$  energy as fat). The short-term objective is to lower triglycerides to well below  $10\text{ mmol/L}$  to reduce the risk of acute pancreatitis.

### Mixed or combined hyperlipidaemia

When patients have a modest increase in both triglyceride and LDL-C concentrations, *monotherapy* with statins, fibrate or nicotinic acid may just suffice. If concentrations of triglycerides or LDL-C or both exceed around  $4\text{ mmol/L}$ , *combination therapy* with statin plus fish oil is a relatively safe and effective option. Statin (in low dose) plus fibrate, or statin plus nicotinic acid, is also effective, but the risk of myopathy is increased, and careful monitoring is required.

### General principles of therapy

The full effect of drug therapy is generally apparent within 6 weeks, so side-effects, lipid response, liver and muscle enzymes should be reviewed at this stage, and at regular intervals thereafter (much longer intervals at stable dose). Long-term compliance (especially diet and exercise) should be encouraged, and weight and blood pressure should be monitored. Deterioration in control should prompt renewed attention to diet, weight control, alcohol use and drug compliance; it may also be necessary to re-investigate for the onset of secondary causes such as diabetes or hypothyroidism. Possible drug interactions should be reviewed when other treatment adjustments are made, especially with the introduction of drugs that interfere with catabolic pathways such as cytochrome P450.

### Conclusions

Lipid-lowering therapy significantly reduces the risk of initial and recurrent cardiovascular disease. LDL-C concentration below  $2.5\text{ mmol/L}$  is an arbitrary goal, and recent trials support the benefit of achieving this goal, or even lower levels. Pharmacological treatment is warranted in patients with high absolute risk of future cardiovascular events. Other randomised clinical trials are in progress and their results will further refine treatment strategies and targets. Important messages for patients are shown in Box 3.

### Competing interests

The authors have received consultancy fees or research support from manufacturers of lipid-modifying drugs.

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