Dyslipidaemia is defined as a clinically significant alteration in the circulating lipids and lipoproteins. In practice, the most important and common is hypercholesterolaemia, with hypertriglyceridaemia or a mixed phenotype in which both cholesterol and triglycerides are more or less equally elevated, occurring less frequently. Lipid lowering is beneficial in patients with dyslipidaemias for both primary and secondary prevention of coronary heart disease.\(^2\)

In general, total plasma cholesterol should be below 5 mmol/l and LDL-cholesterol should be below 3 mmol/l. For patients with clinically established cardiovascular disease or diabetes mellitus, the cholesterol goals should be lower i.e. total cholesterol < 4.5 mmol/l and LDL-cholesterol < 2.5 mmol/l.\(^3\) American and Canadian guidelines for secondary prevention (i.e. in the patient who has suffered a cardiovascular event), now recommend target LDL-cholesterol levels below 2 mmol/l in patients with coronary artery disease.\(^3\)

Hydroxymethylglutaryl coenzyme A (HMG CoA) reductase inhibitors or ‘statins’ are the medicines of first choice in patients with pure hypercholesterolaemia and in those with mixed hypercholesterolaemia and hypertriglyceridaemia.\(^2\) In addition to reducing low-density lipoprotein (LDL)-cholesterol levels (i.e. the ‘bad’ cholesterol), they variably elevate high-density lipoprotein (HDL)-cholesterol (i.e. the ‘good’ cholesterol) and lower triglyceride concentrations.\(^2\) Several clinical trials have confirmed the efficacy of the statins in reducing the risk of cardiovascular morbidity and mortality in patients with or at high risk of coronary heart disease (CHD).\(^4\) For every 1 mmol/l reduction in serum LDL-cholesterol achieved by statin therapy, the relative risk of cardiovascular events and mortality are reduced by 21% and 12% respectively.\(^4\)

Statins vary in potency, as defined by the capacity to lower plasma cholesterol level per unit mass of the statin.\(^2\) They also differ in terms of their clinical pharmacokinetics, medicine interactions and side effect profiles.\(^5\) In this context, it should be remembered that as a result of several cases of fatal rhabdomyolysis, cerivastatin was withdrawn from the market, underscoring the risk of therapeutic interchangeability and relying on a class effect to influence medicine selection.

This article provides a brief overview of the differences between the various statins, which may help health care professionals in selecting the most appropriate statin for individual patients.

### Statins – Potency and efficacy

Currently available statins include lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin and rosuvastatin. These agents are all competitive inhibitors of the enzyme HMG Co-A reductase, the rate-limiting step in cholesterol biosynthesis.

The statins are the most powerful medicines for lowering cholesterol, with reductions in the range of 20 to 63%.\(^5\) See

**Cardiovascular disease is a leading cause of death and disability with 80% of total deaths occurring in the developing world.\(^1\)** Cardiovascular disease is generally due to a combination of several risk factors. Nonetheless, dyslipidaemia is the most important modifiable risk factor for myocardial infarction worldwide and serum cholesterol levels are directly related to mortality from coronary artery disease.\(^1\)**

**See Expand your Portfolio on page 60**
More intensive statin therapy (i.e., using statins in the higher dose ranges), reduces LDL-cholesterol by a further 0.72 mmol/l, providing incremental benefits over lower-intensity statin therapy in the secondary prevention of myocardial infarction and stroke in patients with known coronary heart disease. These benefits are at the expense of small increases in the frequency of drug discontinuations and adverse events, although only elevations in liver enzyme levels are statistically significant. More intensive statin regimens appear to be safe and well-tolerated and may be prescribed for patients with established coronary artery disease, particularly among those with acute coronary syndromes.

Most of the statins have modest HDL-cholesterol raising properties (about 5%), although rosuvastatin has a larger effect (about 10%). Triglyceride concentrations fall by an average of 20 to 40%, depending on the statin and the dose used. Atorvastatin and rosuvastatin are more effective at lowering triglycerides (14 – 33%), than other statins.

Statins – Clinical pharmacokinetics and drug interactions

The available statins have important differences at the pharmacokinetic level i.e. lipophylicity, bioavailability, protein binding, metabolism, presence of active metabolites, half-life and excretion routes.

See Table 2.

The liver biotransforms all statins, which accounts for their overall low systemic bioavailability. The clearance of statins is high, because of a significant hepatic first-pass effect. With the exception of pravastatin, all statins undergo extensive microsomal metabolism by the cytochrome P450 enzyme systems. Rosuvastatin is also not extensively metabolised, but has some interaction with the CYP2C9 enzyme. These differences can affect the potential for drug interactions with the statins. Furthermore, part of the variability in the response, drug interactions and side effects with statins may be related to genetic differences in the rate of drug metabolism.

Concomitant use of certain medicines, which inhibit statin metabolism by CYP3A4, such as the fibrates, erythromycin, itraconazole, ketoconazole, HIV protease inhibitors, warfarin, some calcium channel blockers, nefazodone, sildenafil and immunosuppressive agents such as ciclosporin, can increase blood levels of statins. This may lead to a higher risk of adverse events, such as myopathy in patients taking these medicines concurrently. Fluvatatin, pravastatin and rosuvastatin, which are eliminated by other metabolic routes, are less subject to these drug interactions.

Pravastatin is the statin of choice in patients taking ciclosporin and pravastatin or fluvasatin are preferred in patients taking a fibrate such as gemfibrozil. Statin-fibrate combination therapy, however, should be undertaken cautiously and reserved for patients with severe or refractory hypercholesterolaemia and hypertriglyceridaemia.

Advanced age, small body size, female gender, renal and hepatic dysfunction, perioperative periods, hypothyroidism, multi-system disease (especially diabetes) and alcohol abuse increase the potential for interactions and side effects associated with increased blood levels of statins. Although it is important to keep these potential drug interactions in mind, it is important to emphasise that myopathy is an extremely uncommon side effect.

Statins – Safety

Adverse reactions occur less frequently with statins than with other classes of lipid-lowering agents. More than 50 000 patients have been randomised to a statin or placebo in clinical trials and no serious morbidity or increase in mortality has been reported. The statins effectively reduce the risk of essentially every clinical manifestation of the atherosclerotic process, are easy to administer, with good patient acceptance. Although there is less experience with the statins outside of clinical trials and it is reasonable to expect a higher incidence of side effects in routine clinical practice, statin therapy is generally well-tolerated, with a low frequency of adverse events. There has been some data that the more lipophytic statins (simvastatin, lovastatin, atorvastatin and fluvastatin) may be associated with more adverse events than the more hydrophilic statins (pravastatin and rosuvastatin).

The American College of Cardiology/American Heart Association/National Heart, Lung and Blood Institute have issued a joint clinical advisory on statin therapy. This document addresses muscle toxicity and provides recommendations for the appropriate use of statins.

<table>
<thead>
<tr>
<th>Statin</th>
<th>Dose range (per day)</th>
<th>Reduction in LDL-cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluvatatin</td>
<td>20–80 mg</td>
<td>20–35%</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>10–40 mg</td>
<td>20–30%</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>20–80 mg</td>
<td>21–42%</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>10–80 mg</td>
<td>30–50%</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>10–80 mg</td>
<td>35–55%</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>10–40 mg</td>
<td>45–63%</td>
</tr>
</tbody>
</table>

Table 1: Dosages and average responses to statins

Figure 1: Comparison of the efficacy of statin drugs in terms of the percent reduction in LDL-cholesterol levels
• Myopathy

The term ‘myopathy’ designates a general disorder of skeletal muscle that causes muscle weakness. Statin-associated myopathy represents a broad clinical spectrum of disorders:6

- Myalgia – muscle aches or weakness without creatine kinase (CK) elevation.8
- Myositis – muscle symptoms with increased CK levels.
- Rhabdomyolysis – muscle symptoms with marked CK elevation (typically substantially greater than 10 times the upper limit of normal) and with creatinine elevation (usually with brown urine and urinary myoglobin).8

Myositis is most likely to occur in people who have complex medical problems and/or who are taking multiple medications. It may rarely occur with statin monotherapy, but occurs more frequently when used in combination with a variety of medicines.8

All patients taking a statin should be advised to report muscle discomfort or weakness or brown urine immediately. This should prompt a CK measurement.8

- If myositis is present or strongly suspected, the statin should be discontinued immediately.
- If the CK is greater than 10 times the upper limit of normal, discontinue the statin in a patient with muscle soreness, tenderness or pain.
- If the CK level is not elevated or if the elevation is moderate (3 to 10 times the upper limit of normal), follow the patient’s symptoms and repeat the CK test every week until there is no longer a medical concern or symptoms worsen and require the discontinuation of therapy.

- For patients who develop muscle symptoms and also have progressive elevations of CK on serial measurements, either a reduction of statin dose or a temporary discontinuation may be prudent. A decision can later be made as to whether or when to reinstate statin therapy.

• Hepatic dysfunction

Elevated hepatic transaminases have been reported in 0.5% to 2% of patients receiving statins in clinical trials. This has primarily occurred during the first three months of therapy and is dose-dependent. Progression to liver failure specifically due to statins is exceedingly rare. Reversal of transaminase elevation is frequently noted with a reduction in dose and elevations often do not recur with either re-challenge or the selection of another statin.6,9

• Behavioural and cognitive effects

Although concerns have been raised about increased suicide in patients treated with some lipid-lowering therapies, statins do not appear to be associated with an increased risk of suicide or depression.6 There have been case reports of patients developing severe irritability and aggression with the use of statins, but it has not been established whether the statin caused these symptoms.6

Contd on p. 63