The ultimate aim of lipid-modifying therapy is cardiovascular risk reduction for most patients, while patients with severe hypertriglyceridaemia are primarily treated to reduce the risk of acute pancreatitis. Patients and doctors are pleased to see improved lipid parameters, but without accompanying risk reduction this would be a somewhat hollow victory. Treatment decisions are therefore based on an assessment of risk, rather than on lipid levels alone. The article titled ‘A clinical approach to dyslipidaemia’ (p. 108) provides more information on risk assessment and indications for lipid-modifying therapy.

Lipid-modifying therapy

Hydroxymethylglutaryl co-enzyme A (HMG CoA) reductase inhibitors (statins)

Statins are the most potent and effective drugs for decreasing low-density lipoprotein cholesterol (LDLC) and are the drugs of first choice in patients in whom LDLC reduction is the primary goal of therapy. There is very extensive evidence confirming their clinical utility and safety. They are competitive inhibitors of HMG-CoA reductase, the rate-limiting step in cholesterol synthesis. Statins decrease intracellular cholesterol, leading to increased cell surface LDL receptor expression. This results in accelerated removal of LDL, until a new steady state at lower plasma LDL levels is established. There is a modest reduction in triglycerides with statins, as the LDL receptor can also bind triglyceride-rich lipoproteins. A mild increase in high-density lipoprotein (HDLC) also occurs.

The statins that are available in South Africa and their potency are shown in Table I, and the effects of the major lipid-modifying agents are summarised in Table II.

Statins interact with other metabolic pathways (isoprenoid synthesis) and so affect physiological functions beyond LDLC lowering. These effects are referred to as pleiotropic effects and may influence the biology of atherosclerosis by modulating immunoregulation, inflammation, coagulation and vasomotor responsiveness independent of changes in LDLC. Whether non-lipid effects of statins are of clinical significance and whether the differences in non-lipid effects among the various statins matter, is controversial.

Selection of a statin should be based on the required LDLC reduction, the cost of the drug, the potential for interactions with other drugs the patient is taking and its ability to reduce cardiovascular events.

Statins are well tolerated by most patients and have an excellent safety record. The two major side-effects are hepatotoxicity with transient increases in liver enzymes and muscle toxicity. Muscle toxicity may manifest with muscle pain affecting proximal muscles (myalgia) and/or release of muscle enzyme (creatinine kinase (CK) elevation). Myalgia and CK elevation may occur independently or in combination.

Rhabdomyolysis is a very rare complication of statin therapy. It is characterized by a marked elevation of CK (>10 times the upper limit of normality) and renal dysfunction secondary to rhabdomyolysis. Hyperkalaemia, metabolic acidosis and renal failure may lead to death. Muscle weakness may be present. The

Table I. Lipid-lowering effects of statins at their starting dose*$

<table>
<thead>
<tr>
<th>Statin</th>
<th>LDLC % change</th>
<th>HDLC % change</th>
<th>TG % change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin (10 mg)</td>
<td>-52</td>
<td>+14</td>
<td>-10</td>
</tr>
<tr>
<td>Atorvastatin (10 mg)</td>
<td>-38</td>
<td>+6</td>
<td>-19</td>
</tr>
<tr>
<td>Simvastatin (10 mg)</td>
<td>-28</td>
<td>+8</td>
<td>-19</td>
</tr>
<tr>
<td>Pravastatin (10 mg)</td>
<td>-19</td>
<td>+2</td>
<td>-11</td>
</tr>
<tr>
<td>Fluvastatin (20 mg)</td>
<td>-22</td>
<td>+3</td>
<td>-12</td>
</tr>
<tr>
<td>Lovastatin (20 mg)</td>
<td>-29</td>
<td>+5</td>
<td>-8</td>
</tr>
</tbody>
</table>

*$LDLC lowering increases by approximately 6% for every doubling in the statin dose.

Table II. Summary of the effects of the major lipid-modifying agents

<table>
<thead>
<tr>
<th></th>
<th>% decrease LDLC</th>
<th>% change HDLC</th>
<th>% change TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMG CoA reductase inhibitors</td>
<td>25 - 60</td>
<td>↑5 - 15</td>
<td>↓10 - 35</td>
</tr>
<tr>
<td>Bile acid resins</td>
<td>15 - 25</td>
<td>↑3 - 8</td>
<td>↑10 - 10</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>15 - 20</td>
<td>↑3 - 5</td>
<td>↓3 - 5</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>10 - 25</td>
<td>↑15 - 30</td>
<td>↓20 - 50</td>
</tr>
<tr>
<td>Fibrates</td>
<td>5 - 20</td>
<td>↑10 - 35</td>
<td>↓20 - 50</td>
</tr>
</tbody>
</table>

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risk of rhabdomyolysis is increased in patients with severe renal disease, when statins are combined with fibrates (esp. gemfibrozil) and when drugs that interfere with statin metabolism are prescribed concurrently with statins. The mechanism for most statin drug interactions involves the cytochrome p-450 system. Lovastatin, simvastatin and atorvastatin undergo metabolism by the CYP3A4 isozyme. Lovastatin and simvastatin are highly reliant on CYP3A4 for elimination, whereas only about 20% of atorvastatin is metabolised by this isozyme. Many drugs may potentially interact with statins, but commonly implicated drugs (examples are given in brackets) are macrolides (erythromycin), azole antifungals (ketoconazole), cyclosporin, amiodarone, verapamil and antiretroviral protease inhibitors (ritonavir). Pravastatin and rosuvastatin do not undergo significant metabolism.

Statins are best given at bedtime because cholesterol synthesis peaks at night. Atorvastatin and rosuvastatin can be administered at any time of day because of their long half-lives.

**Bile acid sequestrants**

Bile acid sequestrants (BAS) are also called resins. They have been available for many years and are very safe lipid-modifying agents as they are not absorbed systemically. Cholestyramine and colestipol are usually prepared as powders mixed with water or orange juice. Colesipol is also formulated as a tablet. A newer, specifically engineered BAS, colesvelam HCl, is a hydrophilic polymer taken as a tablet. Cholestyramine is the only resin available in South Africa. Resins are positively charged and bind the negatively charged bile acids. Approximately 95% of bile acids are reabsorbed by enterohepatic recycling. Resins interfere with this process, depleting the endogenous bile acid pool. This leads to increased bile acid synthesis from cholesterol, thus reducing the hepatic cholesterol pool. LDL receptor expression then increases, which lowers LDLc. Hepatic lipoprotein synthesis (mainly very-low-density lipoprotein (VLDL)) may also increase, leading to hypertriglyceridaemia in susceptible individuals. Resins are therefore contraindicated in patients with pre-existing hypertriglyceridaemia. Resins reduce levels of LDLc by 15 - 25%. They have little effect on HDLc and, as noted above, may increase triglycerides significantly in susceptible individuals.

Side-effects frequently include constipation, gastrointestinal discomfort, nausea and bloating. Rarely diarrhoea, steatorrhoea and intestinal obstruction may occur. Compliance is a huge problem because of unpalatability and gastrointestinal side-effects. Resins may bind other drugs such as warfarin, thyrroxine, digoxin and tetracyclines, to name a few only. Cholestyramine should not be taken at the same time as other medications.

Historically resins have been seen as the agents of choice in children and during pregnancy as they are not absorbed from the gut. However, the limited efficacy of resins in combination with frequent gastrointestinal side-effects and generally poor compliance has led to a changed recommendation that statins should be considered in children who require LDLc reduction. Resins provide effective further LDLc reduction if the LDLc remains high despite maximal doses of statins or if patients are unable to tolerate statins. Ezetimibe (see below) is easy to take and has few side-effects, and has therefore become the drug of first choice when a statin ‘boost’ is required.

**Niacin (nicotinic acid)**

Nicotinic acid or niacin is a B-group vitamin available as a nutritional supplement in South Africa. Extended and sustained-release formations are available by prescription in other countries. It is indicated for the treatment of low HDLc and for the reduction of triglyceride and LDLc.

The mechanism of action was previously unknown but recent research has now characterised and cloned a plasma membrane receptor that mediates the effects of niacin. The niacin receptor is a member of the large family of G-protein coupled receptors and is localised in adipose tissue where niacin causes a decrease in intracellular cyclic AMP, leading to inactivation of protein kinase A and suppression of hormone-sensitive lipase. This limits the lipolysis of triglyceride and reduces the transport of free fatty acids to the liver, thereby reducing the hepatic synthesis of triglyceride.

A decrease in triglyceride synthesis increases proteolysis of apolipoprotein B, leading to a reduction in the hepatic production and secretion of VLDL. Because VLDL is a precursor of intermediate-density lipoprotein (IDL) and LDL, reduction in VLDL results in decreased levels of both IDL and LDL.

The mechanism by which niacin increases plasma HDLc is unclear, but it appears to reduce hepatic clearance of apoA1 (the main apolipoprotein of HDL). Niacin can decrease LDLc by 10 - 25% and triglycerides by 20 - 50% and increases HDLc by 15 - 30%.

Niacin in its crystalline form has a half-life of about 1 hour. Large doses (greater than 1 g/day) several times a day are required to achieve maximal effect. Flushing is the most common side-effect, occurring in more than 50% of patients. Flushing may be exacerbated if niacin is taken with alcohol or hot beverages. Flushing can be reduced by taking aspirin 1 hour before niacin. Other side-effects include pruritus, rash, dizziness, gastrointestinal discomfort, hyperuricaemia, hyperglycaemia and impaired liver enzymes. Niacin should not be used in pregnancy. Other contraindications include peptic ulcer disease, gouty arthritis, and liver disease. It should be used with caution in patients with diabetes mellitus.

Numerous trials have demonstrated the benefits of niacin therapy in the management of dyslipidaemia, particularly in combination with a statin to reduce the residual risk observed on statin treatment. See the article on new therapeutic developments in lipidology for more information on niacin (p. 104).

**Fibrates**

There are currently 3 fibric acid derivatives, viz. bezafibrate, gemfibrozil and fenofibrate. Fibrates are agonists at the nuclear peroxisome proliferator activated receptor α (PPAR-α), where they mediate the transcription of multiple target genes involved in lipoprotein homeostasis. Fibrates upregulate the lipoprotein lipase and apo-A1 genes and downregulate the apo C-III gene, among others. This results in a reduction in triglycerides due to improved lipolysis and an increase in HDLc. Plasma triglycerides are decreased by 20 - 50%, HDLc can increase by 10 - 30% and there is a modest decrease in LDLc by 5 - 20%.

Fibrates are generally well tolerated. Side-effects include elevated liver enzymes, myalgia and myopathy, nausea, abdominal discomfort, impotence and alopecia. They are contraindicated in patients with severe liver and renal disease. Dosages need to be adjusted, using the estimated glomerular filtration rate in patients with impaired renal function.

Fibrates are indicated in patients with hypertriglyceridaemia, or combined dyslipidaemia where an elevated triglyceride is the predominant abnormality.

Recently, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study showed that using a micronised fenofibrate 200 mg/day in a randomised fashion...
versus placebo was associated with reduced coronary heart disease (CHD) events only in diabetics without pre-existing clinically overt atherosclerosis. Intriguingly, patients in the fenofibrate arm had fewer microvascular events (progression to albuminuria, diabetic retinopathy requiring laser therapy). This finding clearly requires further study and explanation.

Cholesterol absorption inhibitors
Ezetimibe is the only member of this drug class. It selectively inhibits a newly discovered transporter that moves cholesterol from the bile acid micelles into enterocytes. The transporter is a Niemann-Pick C1 like 1 (NPC1L1) protein localised at the brush border of enterocytes.

Ezetimibe reduces the delivery of cholesterol to the liver, decreasing hepatic cholesterol and promoting the upregulation of LDL receptors, leading to a decrease in plasma LDL. It can reduce LDL by 15 - 25% as monotherapy at a dose of 10 mg/day.

Ezetimibe is conjugated to its active glucuronide form, which undergoes enterohepatic circulation. This increases its elimination half-life to about 22 hours. It is usually indicated as a combination agent in patients who are on statin therapy and not reaching target LDL goals. When combined with a statin, there is an additional LDL reduction of approximately 20%. It is a safe drug and does not have gastrointestinal side-effects.

Omega-3 fatty acids
Docosahexanoic (DHA) and eicosapentanoic acids (EPA) are omega-3 fatty acids which are derived from marine sources. Studies have shown benefit with reductions in sudden cardiac death or CHD death.

The protective effects of these fatty acids are due to prevention of arrhythmias, decreased thrombogenicity, improved endothelial function, and reduced triglyceride levels. The American Heart Association (AHA) recommends that two or more servings of fish per week should be part of the CHD risk-reduction diet.

One gram of fish oil per day provides cardioprotection, but higher doses of 3 - 5 g per day reduce triglycerides (30%) by reducing VLDL production.

Plants sterols/stanols
These ‘cholesterol-like’ molecules inhibit intestinal absorption of dietary and biliary cholesterol and when given in a dosage of 2 - 3 g/day reduce LDL by 6 - 15% without any effect on HDL or triglycerides. They are available as soft margarines.

Treatment paradigms

Hypercholesterolaemia (LDLC)
Statins are the first choice for lowering LDL. Doses should be titrated at 4 - 6-weekly intervals. Doubling the dose of statin will reduce the LDL by a further 6%.

If target LDL is not achieved and increasing the dose is not feasible, combination with other drugs should be considered. Further reductions in LDL of about 10% can be achieved by adding plant stanol/stereol margarine, 15% by adding bile acid sequestrants and approximately 20% by adding ezetimibe.

Hypertriglyceridaemia
Treatment of hypertriglyceridaemia should include lifestyle changes, exclusion and control of secondary factors and fibrate therapy. Omega-3 fatty acids may be used to reduce triglyceride levels in patients with moderately severe hypertriglyceridaemia, but high doses are required. Niacin may be an additional useful treatment option in moderately severe hypertriglyceridaemia.

Severe hypertriglyceridaemia may be complicated by acute pancreatitis. These patients need urgent assessment and treatment. Referral to a specialist is strongly advised. Strict control of dietary fat intake (<30 g of dietary triglyceride per day) and secondary factors is essential.

Mixed dyslipidaemia (combined hyperlipidaemia)
Treatment depends on the predominant abnormality: elevated triglyceride or elevated LDL. Initial treatment is directed at the predominant abnormality, using a fibrate for patients with predominant hypertriglyceridaemia and a statin if high LDL is the major problem. If lipid control remains inadequate despite optimally dosed monotherapy combination therapy with a statin and a fibrate may be necessary. There is an increased risk of toxicity with combination therapy and specialist consultation is advised before starting combination therapy.

The treatment gap
Despite knowledge of the risk factors for cardiovascular system (CVS) disease and the availability of therapy to modify these factors, CVS disease remains a leading cause of death. There are several explanations for this phenomenon. Currently available therapies cannot prevent all atherosclerotic events, risk assessment is an imperfect science and atherosclerosis is often advanced once treatment is started (‘too little, too late’). However, often there is simply a failure to implement evidence-based medicine in clinical practice. This is most obvious when reviewing the treatment prescribed to patients with previous cardiovascular events. These patients are at very high risk and require aggressive multifactorial intervention, yet few receive all recommended interventions at adequate dosages. Various factors may account for this failure to utilise proven therapies:

- insurance reimbursement may be inadequate
- cost of the medication
- formularies may be restrictive
- patient and physician perceptions
- adverse effects of the drugs, especially when combination treatment is required.

If the treatment gap is to be narrowed, adherence and compliance programmes must take the patient’s as well as the patient’s perspectives into account. Clearly novel anti-atherosclerotic therapies are desirable, but we also need to utilise what we have optimally. Unfortunately this is not as simple as it seems.

Further reading


**Lipid modification**

### In a nutshell

- Lifestyle modification should be initiated before starting lipid-modifying drugs.
- Exclude secondary causes of dyslipidaemia.
- Optimal total and LDL cholesterol goals will depend on CVS risk stratification and Framingham risk charts.
- HDL cholesterol and triglyceride levels are important secondary targets to reduce CVS disease further.
- Statins are the drugs of choice for hypercholesterolaemia.
- Statins may be used in combination with ezetimibe, resins, fibrates and nicotinic acid if target LDL cholesterol is not achieved.
- Hypertriglyceridaemia should be treated with lifestyle modification in combination with fibrates, nicotinic acid or omega-3 fatty acids.
- Severe hypertriglyceridaemia needs specialist referral, as the complication of pancreatitis can be lethal.
- Although lipid-modifying drugs are reasonably safe, biochemical monitoring should include urea, creatinine, liver enzymes and CPK prior to, and during, therapy.
- The inertia displayed by doctors and patients to reach targets should be countered with education.

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### Single Sutures

**No link between vaccines and autism**

The US Court of Federal Claims has found no basis for claims made by three families that the MMR vaccine, combined with a mercury-based vaccine preservative, was responsible for their children's autism.

More than 5,500 claims have been filed by US families seeking compensation through the government’s Vaccine Injury Compensation Program. This ruling means that those families making the same claim will not receive compensation. Apparently the ruling does not affect those making slightly different claims, such as that the preservative thimerosal alone is to blame.

However, Paul Offit of the Children’s Hospital in Philadelphia, expects a similar outcome for all the cases because he believes the ruling clearly supports the science.

*New Scientist, 21 February 2009: 7.*

**Rare syndrome provides clues to the origins of sociability**

Children with William's Syndrome (WS) find it easy to make eye contact with complete strangers, even though they struggle to form lasting relationships. A team led by Julie Korenberg of the University of Utah wondered whether people with WS may shed some light on how sociability developed.

The team identified a girl with WS who, unusually, wasn’t overly friendly to strangers, but was good at forming lasting relationships. They compared her genome with that of people who had typical WS and found that she has the *GTF2I* gene, which most people have, but that other children with WS lack this. This suggests that this gene may play a role in governing normal social behaviour.

The next step is to find out whether *GTF2I*, which regulates other genes, helps determine brain function of controls the production of hormones that moderate trust and empathy.

*New Scientist 21 February 2009: 14.*