

A review of available cholesterol-lowering medicines in South Africa

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Abstract

Hypercholesterolaemia (high cholesterol) is one of the major risk factors that contribute to the vast number of deaths caused by cardiovascular disease. The *South African dyslipidaemia guideline consensus statement* (2012) provides strategies to ensure the appropriate diagnosis and management of hypercholesterolaemia. This article provides a review of various available cholesterol-lowering medicines in South Africa, and can assist healthcare providers to select the most appropriate treatment option.

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Introduction

Cardiovascular disease (CVD), which includes heart attacks, angina and strokes, is one of the most common causes of premature mortality and morbidity worldwide.¹ In 2008, CVD resulted in 17.3-million deaths, of which 80% occurred in low- and middle-income countries.¹ In South Africa, despite infectious diseases accounting for the majority of deaths, CVD follows closely because of the increasing adoption of an urbanised culture characterised by unhealthy lifestyle habits.²⁻⁴

Cholesterol is a fat-like substance that is produced by the body and obtained from a diet that is primarily of animal origin.⁵ The body requires some cholesterol to build cell membranes, synthesise hormones and produce substances that aid in fat digestion.⁵ Cholesterol travels via the bloodstream in small particles called

lipoproteins.⁶ Two types of lipoproteins are responsible for transporting cholesterol throughout the body: low-density lipoproteins (LDL) and high-density lipoproteins (HDL).⁶ High levels of LDL cholesterol, known as “bad” cholesterol, lead to a build-up of plaque in the arteries. Plaque causes narrowing of the blood vessels, and a subsequent decrease of blood flow to the vital organs.⁴ Conversely, HDL cholesterol is regarded as “good” cholesterol because of its function of carrying the cholesterol from other parts of the body back to the liver for elimination.⁶

After 20 years of age, cholesterol screening should be performed every five years.⁷ Total plasma cholesterol should be below 5 mmol/l and LDL cholesterol below 3 mmol/l.⁸ The target cholesterol level should be lower (LDL cholesterol < 1.8 mmol/l or 50% reduction) in high-risk patients with CVD or diabetes.⁸

Table 1: Treatment intervention strategies in relation to the Framingham total cardiovascular risk score and low-density lipoprotein cholesterol levels⁸

LDL cholesterol levels	Framingham total cardiovascular disease risk score*			
	Low risk (< 3%)	Moderate risk (3 -15%)	High risk (15-30%)	Very high risk (> 30%)
< 1.8 mmol/l	No intervention	Lifestyle modification	<ul style="list-style-type: none"> Lifestyle modification Consider pharmacotherapy** 	<ul style="list-style-type: none"> Lifestyle modification Consider pharmacotherapy**
1.8 to < 2.5 mmol/l	No intervention	Lifestyle modification	<ul style="list-style-type: none"> Lifestyle modification Consider pharmacotherapy** 	<ul style="list-style-type: none"> Lifestyle modification Immediate pharmacotherapy
2.5 to 4.9 mmol/l	Lifestyle modifications	<ul style="list-style-type: none"> Lifestyle modification Consider pharmacotherapy if uncontrolled 	<ul style="list-style-type: none"> Lifestyle modification Immediate pharmacotherapy 	<ul style="list-style-type: none"> Lifestyle modification Immediate pharmacotherapy
> 4.9mmol/l	<ul style="list-style-type: none"> Lifestyle modification Consider pharmacotherapy if uncontrolled 	<ul style="list-style-type: none"> Lifestyle modification Consider pharmacotherapy if uncontrolled 	<ul style="list-style-type: none"> Lifestyle modification Immediate pharmacotherapy 	<ul style="list-style-type: none"> Lifestyle modification Immediate pharmacotherapy

LDL: low-density lipoprotein

*: Based on the Framingham cardiovascular disease risk tables⁸

**:: Statin therapy should be considered in patients with myocardial infarction, regardless of low-density lipoprotein cholesterol levels

Treatment of hypercholesterolaemia

The *South African dyslipidaemia guideline consensus statement* (2012) provides strategies to ensure the appropriate diagnosis and management of hypercholesterolaemia.⁸ Table I describes the proposed treatment strategies according to the percentage risk calculated from the Framingham risk score, a gender-specific algorithm used to estimate the 10-year cardiovascular risk of an individual, and the LDL cholesterol levels obtained from cholesterol screening.⁸

Lifestyle modification

Lifestyle modification is the cornerstone of any treatment intervention aimed at lowering LDL cholesterol levels and reducing the risk of CVD.⁸ Several lifestyle changes have been proposed by the South African Heart Association/Lipid and Atherosclerosis Society of Southern Africa for the South African population.⁸ These guidelines highlight the need for a heart-healthy diet, a reduction in alcohol consumption, smoking cessation and regular exercise.⁸

Pharmacotherapy

Statins

Statins are generally regarded as the treatment of choice for hypercholesterolaemia.⁹ They are cost-effective agents and are commonly prescribed in South Africa.⁹ Currently available statins include atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin and rosuvastatin. The statins are known to be potent inhibitors of LDL cholesterol synthesis. Some beneficial effects have been reported regarding HDL cholesterol levels and triglyceride concentrations.¹⁰

The profile for statins is as follows:

- **Mechanism of action:** Statins decrease the synthesis of cholesterol in the liver by competitively inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This decrease in the synthesis of cholesterol is accompanied by upregulation of the LDL cholesterol receptors, whose primary function is extracting LDL cholesterol from the bloodstream.¹⁰
- **Clinical efficacy:** In 2005, the Cholesterol Treatment Trialists' Collaboration conducted a meta-analysis of 14 randomised controlled trials with 90 056 participants who had used statins for five years. The study reported that statin therapy could safely reduce the five-year incidence of cardiovascular events by approximately one fifth per mmol/l reduction in LDL cholesterol, irrespective of the initial lipid profile.¹¹ In 2010, a meta-analysis of data in 26 randomised control trials conducted on 170 000 participants reported a significant reduction in LDL cholesterol levels, together with a 40-50% decrease in cardiovascular events, when higher doses of statin therapy were utilised.¹² More intense statin therapy appears to be well tolerated and can be prescribed to patients with coronary artery disease.¹³
- **Side-effects and drug interactions:** At the pharmacokinetic level, statins differ in their solubility, absorption, bioavailability, plasma protein binding and excretion.¹³ They are generally well tolerated, with few serious side-effects.¹⁰ Factors such as advanced age, a small body size, being of the female gender, and having renal

and hepatic dysfunction, hypothyroidism, multisystem disease, as well as engaging in alcohol abuse, increase the possibility of side-effects.¹⁰ The most serious side-effect is myopathy, which may progress to rhabdomyolysis, and ultimately, renal failure or death.¹⁰ The mechanism by which statins injure skeletal muscle is unknown. The incidence of myopathy is < 1/1 000 in patients treated with statins, and < 1/10 000 in placebo-treated patients in clinical trials.¹⁰ Myopathy is most likely to occur in patients experiencing complex medical problems, those taking numerous medications and in the elderly, and in particular, in female patients.¹⁰ Myalgia may also occur and it is important to instruct patients to immediately report unexpected muscle pain or weakness.¹⁰ Liver transaminase levels may increase with the use of statins, although progression to liver failure is rare.¹⁰ Dose reduction can restore transaminase levels to normal, but if the increase is threefold in the upper limit of normal, therapy should be stopped immediately.¹⁰

Concurrent use of statins and other drugs metabolised by cytochrome (CYP) isoenzymes may result in interference in statin metabolism and a greater side-effect profile.⁹ Fibrates, erythromycin, ketoconazole, human immunodeficiency virus protease inhibitors, warfarin, some calcium-channel blockers, nefazodone, sildenafil and ciclosporin are examples of medicines that inhibit statin metabolism via CYP3A4, and can increase the blood levels of statins.¹³ An increase in statin-related side-effects is also seen with the intake of grapefruit juice.¹⁴ Pravastatin and rosuvastatin are metabolised via alternative routes, and are therefore less likely to result in these drug interactions.¹³

Bile acid sequestrants

Bile acids are made in the liver from cholesterol and are released into the intestinal lumen, where they are reabsorbed via enterohepatic recycling, then transported back to the liver.¹⁰ A disruption in bile acid reabsorption results in a decrease in cholesterol levels, particularly LDL cholesterol.^{9,10}

The profile for bile acid sequestrants is as follows:

- **Mechanism of action:** Cholestyramine is a bile acid sequestrant. It is a basic anion-exchange resin that binds to bile acids in the intestinal lumen, preventing enterohepatic recycling. This results in upregulation of LDL cholesterol receptors to absorb cholesterol from the blood.⁹ The bound bile acid resin is excreted via the faeces.⁹ Bile acid sequestrants are not absorbed systemically, and are not influenced by digestive enzymes.¹⁰ They also reduce glucose levels in patients with diabetes, but the exact mechanism of action by which this reduction occurs is unknown.¹⁰
- **Clinical efficacy:** At a maximum daily dose of 24 g of cholestyramine, a 18-25% reduction in LDL cholesterol has been observed.¹⁰ No major effect on HDL cholesterol has been reported, while triglyceride levels may increase in some predisposed patients.¹⁰
- **Side-effects and drug interactions:** The most commonly encountered side-effects are associated with the digestive system, and include constipation, bloating, nausea and vomiting.⁹ Adverse effects can be reduced by decreasing the

starting dose and implementing gradual dose increments thereafter.⁹ It is recommended that patients drink an adequate amount of water when taking this medicine.

Concurrent administration of bile sequestrants and many commonly prescribed medicines results in interactions.¹⁰ Ideally, bile sequestrants should be administered either four hours before, or one hour after, other medicines.¹⁰ A reduction in the absorption of fat-soluble vitamins has also been reported, especially with the long-term use of bile sequestrants.⁹

Cholesterol absorption inhibitors

Ezetimibe is the first of a novel class of drugs that selectively inhibits the absorption of biliary and dietary cholesterol from the small intestines without affecting the absorption of triglycerides, fat-soluble vitamins and bile acids.¹⁵

The profile for cholesterol absorption inhibitors is as follows:

- *Mechanism of action:* Ezetimibe inhibits a specific protein receptor (Niemann-pick C1-like protein) at the brush border of the intestinal wall, resulting in decreased absorption of dietary and biliary cholesterol.¹⁶ Ezetimibe differs from bile acid sequestrants in that it does not affect the levels of pancreatic lipase and bile acids.¹⁵
- *Clinical efficacy:* Phase 3 clinical trials have investigated the efficacy of ezetimibe as monotherapy and in combination with statins or fibrates.¹⁵ Results indicate a reduction of 15-20% in LDL cholesterol and a 2.5-5% increase in HDL cholesterol when used as monotherapy, or in combination with fenofibrate or a statin.¹⁵
- *Side-effects and drug interactions:* Minimal side-effects have been reported in clinical trials with ezetimibe, both as monotherapy, and in combination with statins.¹⁷ Reported side-effects in more than 2% of patients were fatigue, abdominal pain, diarrhoea, viral infections, pharyngitis, sinusitis, arthralgia, back pain and coughing. The incidence of these effects was similar for ezetimibe and placebo.¹⁷ However, there is evidence that a combination of ezetimibe and statins may result in a threefold increase in transaminase levels. When combined therapy is administered, it is important for liver function tests to be carried out to monitor any abnormalities in transaminase levels.¹⁷ Concurrent use of ezetimibe and fibrates may result in increased ezetimibe concentrations and an increased risk of cholelithiasis (gallstones).¹⁷ It is recommended that fibrates, other than fenofibrate, should be avoided when taking ezetimibe.¹⁷ Use of ezetimibe in patients on warfarin therapy should be carried out with caution.¹⁷

Nicotinic acid

Niacin or nicotinic acid is a B-complex vitamin that has cholesterol-lowering properties.¹⁸ Recent evidence indicates that therapeutic doses of nicotinic acid induce a profound change in the plasma levels of various lipids and lipoproteins, resulting in a greater ability to increase HDL cholesterol.¹⁹ Nicotinic acid is mainly used in patients with low levels of HDL cholesterol.¹⁰ Evidence suggests that nicotinic acid administered alone or in combination with other cholesterol-lowering medicines can reduce the risk of cardiovascular events and the progression of atherosclerosis.¹⁹

The profile for nicotinic acid is as follows:

- *Mechanism of action:* The precise mechanism of action of nicotinic acid is unknown.¹⁸ Recent studies have reported that nicotinic acid may act on multiple tissues, and beneficially modulate the lipid and lipoprotein profile. The liver is the major target organ.²⁰
- *Clinical efficacy:* Nicotinic acid is primarily administered as an extended-release dosage form. A daily dose of 2 g provides several therapeutic outcomes, including a 20-40% reduction in triglycerides, a 15-18% reduction in LDL cholesterol, and a 15-35% increase in HDL cholesterol.²⁰ In the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies in Atherosclerosis (ARBITER 6-HALTS) trial, conducted on 315 participants, it was found that extended-release niacin provided greater reduction in carotid intima-media thickness (CMIT), a predictor of cardiovascular events, whereas ezetimibe showed a progression in CMIT.²¹ Nonetheless, the extended-release niacin product, Tredaptive[®] was recalled worldwide after it failed to prevent cardiovascular events in a large clinical trial and raised safety concerns.
- *Side-effects and drug interactions:* In practise, the most commonly encountered side-effects are flushing (88%), nausea (4-9%) and vomiting (2-9%).¹⁸ Other less common, but serious, side-effects of niacin, include hepatic necrosis, hepatotoxicity and rhabdomyolysis.¹⁸ Concurrent use of nicotinic acid and statins, particularly simvastatin, may result in increased risk of myopathy or rhabdomyolysis.¹⁸

Fibrates

Fibrates are associated with a substantial decrease in plasma triglycerides, a moderate decrease in LDL cholesterol and an increase in HDL cholesterol.²² The newer fibrates, bezafibrate, fenofibrate and gemfibrozil, are suitable for the treatment of moderate hypercholesterolaemia, especially in patients with low HDL cholesterol and increased triglycerides.⁹

The profile for fibrates is as follows:

- *Mechanism of action:* Recent evidence indicates that fibrates act at several points through alterations in the transcription of genes encoded for proteins that control lipid and lipoprotein metabolism.^{9,22} These include an enhanced breakdown of triglyceride-rich particles, reduced secretion of very low-density lipoproteins and changes in HDL apolipoprotein expression.²²
- *Clinical efficacy:* The newer fibrates are similar in their cholesterol-lowering properties and potency. They reduce total plasma cholesterol by 15-20%, triglycerides by as much as 40% in predisposed patients, and increase HDL cholesterol by 15-20%.⁹ A recent meta-analysis reported that fibrate therapy reduced CVD by approximately 13%. The greatest benefit was seen in patients with elevated triglyceride levels.²³
- *Side-effects and drug interactions:* Fibrates are generally well-tolerated with the following mild side-effects: headaches, back pain, nasopharyngitis, nausea, myalgia, diarrhoea and upper respiratory tract infections.²⁴ An increase in liver transaminase is also common in the early stages of fibrate therapy. However, with time, the levels tend to normalise.⁹

Gemfibrozil inhibits glucuronidation, and consequently increases the risk of rhabdomyolysis with statin therapy.⁹ Fenofibrate does not share the same pharmacokinetic pathway as that of gemfibrozil, and so the risk of rhabdomyolysis is much less using combined therapy. Concurrent warfarin and fibrate therapy can result in a significant increase in anticoagulant activity.⁹ As a result, the warfarin dose should be halved and the international normalised ratio constantly monitored.⁹ Concomitant administration of sulphonureas and fibrates can result in hypoglycaemia.⁹ Cholestyramine should be administered at least two hours before, or two hours after, fibrate therapy.⁹

Combination treatment

Hypercholesterolaemia may not be adequately controlled using monotherapy and combination therapy is frequently required. In practise, the most commonly prescribed combination is a statin with a fibrate, which raises HDL and decreases triglycerides.¹⁵ However, the use of statins in combination with fibrates, other than fenofibrate, results in an increased risk of muscle effects and rhabdomyolysis.¹⁵

Alternatively, statin therapy and ezetimibe is known to be a potent combination for lowering LDL cholesterol.⁹ The mechanism of action by which ezetimibe lowers cholesterol complements the inhibitory mechanism of statins, with minimal side-effects and drug interactions.¹⁵ Ideally, this combination should be given to patients who are unable to tolerate high statin doses, and who thus require an additional agent to assist in lowering LDL cholesterol levels.¹⁵

Over-the-counter cholesterol-lowering agents

Although several nutritional supplements have been identified as potential cholesterol-lowering agents, they should not be replaced with those prescribed by the doctor.

Table II lists some over-the-counter cholesterol-lowering agents.

Conclusion

There are a number of available cholesterol-lowering medicines on the market in South Africa. Healthcare providers have a pivotal role to play in selecting an appropriate and effective treatment option. Statins remain the gold standard in the treatment of hypercholesterolaemia. However, since the beneficial effect varies among patients, it may be necessary to consider alternative or combined therapy.

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Table II: Over-the-counter cholesterol-lowering agents⁹

Omega-3 fatty acids	These come in the form of flaxseed oil, salmon oil and other dietary supplements. Ingestion of 0.9 g per day of omega-3 fatty acids may be recommended as a cardioprotective measure.
Phytosterols	These include natural fats, such as beta sitosterols, campesterols and stigmasterols, which inhibit the absorption of cholesterol. In South Africa, the new margarine spread, Flora Proactive [®] , contains 2 g of phytosterol per 20 g, which when eaten daily, can result in a 5-7% reduction in low-density lipoprotein cholesterol.
Policosanol	This is a group of long-chain alcohol that has been shown to reduce cholesterol levels by 10-30% in some trials. Some studies dispute the lipid lowering-effect.

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