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He is particularly interested in lipids and lipid disorders and he supervises the Lipid Clinic at the Johannesburg Hospital. He is currently researching lipid abnormalities in South African subjects with familial hypercholesterolaemia and completed his PhD thesis based on studies in these subjects.

Management of dyslipidaemia

As society becomes increasingly sedentary and obese, the management of dyslipidaemia becomes ever more important for the general practitioner.

Cardiovascular disease, particularly coronary artery disease (CAD), remains the leading cause of morbidity and mortality worldwide. Yet, despite compelling epidemiological and clinical data demonstrating conclusively that dyslipidaemia, particularly elevated low-density lipoprotein cholesterol (LDLC) levels, correlates with heightened CAD mortality and that lipid-lowering interventions with either lifestyle modification or drug therapy can reduce rates of cardiovascular events, we remain a 'hypercholesterolaemic, atherogenic society' who are becoming increasingly more sedentary and more obese.

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Although this review will concentrate mainly on currently available drug therapy for the management of dyslipidaemia, it must be emphasised that non-pharmacological therapy plays a vital role. Many patients with mild or moderate dyslipidaemia will be able to achieve optimum lipid levels with lifestyle modification alone and, if they are able to maintain a healthy lifestyle, will not require lifelong lipid-modifying therapy.

The management of a patient with dyslipidaemia depends on the type of lipid dis-

turbance, on whether the elevated lipid level is primary or secondary, and on the presence of other risk factors for CAD and absolute risk. The measurement of serum lipids should therefore form part of a full clinical examination.

The following serves as a check list that must be considered in each patient:

- Accompanying modifiable risk factors for CAD, e.g. hypertension, smoking, diabetes, should be sought and treated.
- Underlying secondary causes of dyslipidaemia, e.g. excess alcohol intake, hypothyroidism, should be identified and corrected.
- The goal of treatment should be clearly explained to the patient and the risks conferred by untreated dyslipidaemia should be emphasised.

NON-PHARMACOLOGICAL THERAPY (LIFESTYLE MODIFICATION)

Epidemiological and clinical trial evidence evaluating diet and CAD prevention shows that at least three dietary strategies are effective, namely

- substituting non-hydrogenated unsaturated fats (mono- and polyunsaturated fats) for saturated and trans-fats
- increasing consumption of omega-3 fatty acids from fish and plant sources
- consuming a diet high in fruits, vegetables, nuts and whole unrefined grains.

Such diets, together with regular physical activity, avoidance of smoking, and maintaining a healthy weight, will probably prevent or at least reduce the prevalence of CAD.

In a patient consuming a typical Western diet who complies well with a prudent lipid-lowering diet and achieves and maintains ideal body weight (BMI < 27 kg/m²), the average fall in LDLC could be up to 20% (i.e. a decrease in LDLC of 1 - 2 mmol/l). There is, however, considerable individual variation in responsiveness, and the average reduction in LDLC in response to a change in diet is usually more modest.

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INDICATIONS FOR DRUG THERAPY

Cardiovascular

The main indication for lipid-modifying medication is to reduce cardiovascular risk. Drug therapy should be considered when non-pharmacological means have failed to reduce the lipid levels to within the target range (Table I). When global risk for the individual is high lipid-lowering drugs are used. This is *always* in conjunction with ongoing lifestyle modification.

There are 3 main cardiovascular indications for lipid-modifying drug therapy:

- **Severe genetic dyslipidaemia**, e.g. familial hypercholesterolaemia, familial combined hyperlipidaemia and dysbetalipoproteinaemia. These subjects usually have a positive family history of

severe dyslipidaemia and premature CAD, together with clinical markers of genetic dyslipidaemia.

- **Secondary prevention.** Patients with manifest CAD, cerebrovascular disease or peripheral vascular disease. Diabetics are at high cardiovascular risk and type 2 diabetes is now considered a CAD risk equivalent in the USA (NCEP III).
- **Primary prevention.** Subjects at high risk for CAD (e.g. hypertensives) in whom the calculated 10-year risk for an acute coronary event is greater than 20% (or more than 30% in young patients if their risk is projected to 60 years of age). Recent evidence suggests that such high-risk patients will benefit from lipid-lowering (statin) therapy irrespective of baseline LDLC levels.

Non-cardiovascular

The most serious non-cardiovascular complication of dyslipidaemia is the development of acute pancreatitis. This is seen in subjects with severe hypertriglyceridaemia (triglyceride (TG) >15 mmol/l). Ideally such patients should be referred to a lipid specialist.

The basic principles are to control or reverse possible secondary factors (e.g. alcohol excess, diabetes), introduction of a very low-fat diet and lipid-modifying drug therapy. Statin therapy is not appropriate for the treatment of severe hypertriglyceridaemia and fibrates are the drugs of choice.

LIPID-MODIFYING DRUGS

Several drugs are currently available for the treatment of dyslipidaemia on the South African market.

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HMG CoA reductase inhibitors or statins – atorvastatin, fluvastatin, pravastatin, simvastatin

The HMG CoA reductase inhibitors or ‘statins’ have revolutionised the therapy of dyslipidaemia and are now the drugs of choice for the management of hypercholesterolaemia. Results from 6 major clinical trials involving over 30 000 subjects have documented a decrease in both CAD and total morbidity and mortality, reductions in myocardial infarctions, revascularisation procedures, stroke and peripheral vascular disease. These drugs act by competitively inhibiting the rate-limiting enzyme of cholesterol synthesis — HMG CoA reductase. Cholesterol is essential for normal intracellular metabolic processes. Therefore to compensate for the decreased availability of intracellular cholesterol, the cell increases its LDL receptor number, resulting in increased utilisation of circulating cholesterol and reducing the serum cholesterol level.

The statins are the most powerful of the cholesterol-lowering drugs available. Serum cholesterol is reduced by 20 - 45%. LDLC is decreased by 25 - 55%; TGs are moderately reduced by 10 - 30% and HDLC is elevated by 5 - 15%. It is important to remember that reductions in LDLC are log-linear, so that with each doubling of the dose of a statin one does not get a doubling of LDLC reduction. Rather, each doubling of the dose of any statin only results in a further 6% reduction in LDLC.

Cost effectiveness of the different statins can be determined by comparing prices of equivalent doses of statins as shown in Table II. The statins are equally effective in treating patients with familial and non-familial hypercholesterolaemia.

Table I. Optimal fasted lipid profile

Total cholesterol	5 mmol/l
Triglycerides	1.5 mmol/l
HDL cholesterol	1.2 mmol/l
LDL cholesterol	3 mmol/l

MAIN TOPIC

Age, gender, or body weight do not influence the response to the statins significantly. Tolerance does not develop, and the response is maintained indefinitely during therapy. The statins are mainly hepatically excreted and doses therefore do not have to be decreased in renal failure. The drugs are easily administered and are very well tolerated. They are best given at bedtime. However, atorvastatin can be administered at any time of the day because of its long half-life.

Hepatotoxicity (transient 3%, persistent 0.5%) and myopathy (< 0.5%) are the two major side-effects of the statins. The incidence of myopathy is increased in the elderly, in the presence of liver or renal disease, or with the concomitant administration of other drugs such as cyclosporine, fibrates, erythromycin and nicotinic acid.

Fatal rhabdomyolysis is however a very rare event with an incidence of less than one death per million prescriptions. Frequently rhabdomyolysis is the result of a potentially avoidable drug interaction.

Statins are therefore remarkably safe drugs. The ratio between saved and lost lives among statin-treated patients over 10 years of use can be estimated at about 100 000 to 1 — undoubtedly justifying lifelong clinical use of statins in those who warrant it.

Bile acid sequestrants (or anion exchange resins) – cholestyramine

This is a well-tried drug that is widely used in the treatment of familial hypercholesterolaemia. Cholestyramine is not absorbed and its function is to reduce intestinal reabsorption of bile acids. Increased production of bile acids by the liver therefore ensues, depleting liver cells of cholesterol, thereby inducing increased LDL receptor activity on the liver cells. As a result LDL catabolism is increased and plasma LDLC levels fall by 15 - 30%.

HDLC may increase by 3 - 5%. Because of increased hepatic lipoprotein synthesis stimulated by resin therapy, triglycerides may however increase moderately. Resins are therefore contraindicated as monotherapy in persons with hypertriglyceridaemia.

The sequestrants are not absorbed from the gastrointestinal tract and therefore lack systemic toxicity. They are particularly suitable for treating younger patients, especially children, and women considering pregnancy.

Unfortunately these agents are unpalatable, leading to poor patient compliance. Common side-effects include constipation (> 30%), gastrointestinal (GIT) discomfort (20%), nausea (8%) and bloating

(9%). More rarely diarrhoea, steatorrhoea, intestinal obstruction and hyperchloraemic acidosis can occur.

These agents also interfere with absorption of anionic drugs, e.g. warfarin, thyroxine and lipid-soluble vitamins. Antacids can ameliorate the dyspepsia, while increasing fluid intake and a high-fibre diet or stool softener can help counteract constipation.

Nicotinic acid (niacin)

Nicotinic acid, or niacin, a B-group vitamin, is a potent lipid-lowering agent which decreases LDL and VLDL production. Nicotinamide is not effective in lowering serum cholesterol (SC) and cannot substitute for nicotinic acid. Nicotinic acid appears to act by inhibiting lipolysis and by reducing the flux of free fatty acids to the liver, limiting VLDL and LDL production. Nicotinic acid may also reduce hepatic synthesis of apoB₁₀₀, an essential component of VLDL. The reduced hepatic synthesis of these lipoproteins leads to a reduction of the plasma concentrations of triglyceride, and to a lesser extent cholesterol (as LDL is derived mainly from VLDL). Serum cholesterol levels decrease by 20 - 30% and TGs by 20 - 60%. HDLC can increase by 20 - 30%. The dose needed is 2 - 6 g/day (100 mg tabs only are available in South Africa, therefore one would require 20 - 60 tabs/day in divided doses). Side-

Table II. Comparative efficacy of currently available statins (mg/day)

Atorvastatin	Simvastatin	Pravastatin	Fluvastatin	% reduction	
				TC	LDLC
	10	20	40	22	27
10	20	40	80*	27	34
20	40			32	41
40	80			37	48
80				42	55

TC = total cholesterol; LDLC = low-density lipoprotein cholesterol.
*Extended release.

effects at the doses needed to be effective are significant and the drug can often not be tolerated. The adverse effects include flushing (> 95%), pruritus, rash, acanthosis nigricans, toxic amblyopia, dizziness, GIT discomfort, hyperuricaemia with acute gout, impaired glucose tolerance and increased liver enzymes.

The incidence of side-effects can be decreased by taking the tablets with meals and by starting with small doses increasing the dose gradually over a 3 - 4-week period. Patients must be encouraged not to take the tablets intermittently as this aggravates the side-effects. Aspirin taken approximately an hour before can also ameliorate side-effects. Over 40% of patients are unable to remain on therapy due to side-effects. Sustained-release preparations of nicotinic acid have been used which cause fewer side-effects, but are unfortunately also less effective in lipid reduction. Rare cases of fulminant hepatitis have also been reported with sustained-release preparations.

Contraindications to the use of nicotinic acid include peptic ulceration, hepatic disease and gouty arthritis. It is also necessary to monitor blood glucose, liver function and uric acid levels during therapy.

Fibrates – fenofibrate, bezafibrate, gemfibrozil

These drugs appear to work mainly by increasing the activity of lipoprotein lipase (thereby increasing VLDL clearance) and may also decrease VLDL production. They act by stimulating the nuclear transcription factor peroxisome proliferator-activated receptor-alpha (PPAR- α). Their main effect is on plasma triglycerides which can decrease by 20 - 50%. HDLC can increase by 10 - 35%. SC can however also be decreased due to decreased VLDL synthesis and increased LDL clearance. LDLC is usually decreased modestly by 5 - 20%.

The fibrates are well tolerated and side-effects are uncommon (< 3% of patients). Side-effects include nausea, abdominal pain and rarely myopathy, impotence, raised liver function tests (LFTs) and alopecia. These drugs are renally excreted and therefore impaired renal function is a relative contraindication to fibrate drugs. Gemfibrozil is least reliant on the kidney for its excretion but its limiting effect on glucuronidation is thought to be the reason for its interaction with statins to promote rhabdomyolysis.

A summary of the lipid-modifying effects of the different drugs as well as the present drugs of choice for

the treatment of dyslipidaemia are shown in Tables III and IV.

Combination therapy

In patients with severe dyslipidaemia single drug therapy in combination with diet may fail to achieve an adequate reduction in the lipid levels. In these situations combination therapy may be warranted.

In patients with predominant hypercholesterolaemia the most effective combination currently available is a statin plus a resin. With this combination, a greater upregulation of LDL receptors occurs as a result of both a decrease in cholesterol synthesis and an increase in cholesterol elimination. Reductions in LDLC are therefore greater than with either agent alone. This combination can decrease serum LDLC by 50 - 60%. The triple combination of an HMG CoA reductase inhibitor + resin + nicotinic acid can reduce LDLC by up to 70%.

In patients with mixed hyperlipidaemia or predominant hypertriglyceridaemia, a combination of a statin plus a fibrate or nicotinic acid may be more effective.

While combination drug therapy may prove essential to achieve desirable lipid levels, it must be remembered that side-effects are

Table III. Summary of the effects of the major lipid-lowering agents

	% decrease TC	% decrease LDLC	% increase HDLC	% change TG	Reduced CHD risk	Long-term safety
HMG CoA reductase inhibitors	15 - 45%	25 - 55%	5 - 15%	10 - 30%	Yes	Yes
Bile acid resins	10 - 25%	15 - 30%	3 - 5%	0 - 10%	Yes	Yes
Nicotinic acid	5 - 20%	5 - 25%	15 - 35%	20 - 50%	Yes	Yes
Fibrates	0 - 15%	5 - 20%	10 - 35%	20 - 50%	Yes	Yes

TC = total cholesterol; LDLC = low-density lipoprotein cholesterol; TG = triglycerides; CHD = coronary heart disease; HDLC = high-density lipoprotein cholesterol.

Table IV. Present drugs of choice for the treatment of dyslipidaemia

Predominant hypercholesterolaemia

- Statin*
- Resin
- Fibrate
- Nicotinic acid

Combined hyperlipidaemia

- Statin or fibrate*
- Nicotinic acid

Predominant hyperglyceridaemia

- Fibrate*
- Nicotinic acid
- Statin (only effective in mild to moderate hypertriglyceridaemia)

*First choice.

more likely and that costs become substantial.

OTHER AGENTS

Plant stanol/sterols

These act to lower cholesterol absorption by interfering with cholesterol assimilation in micelles in the gut. They are added to margarines and at a dose of 2 - 3 g/day can lower LDLC by 6 - 15% with little or no change in HDLC or TG levels.

Policosanol

Policosanol is a mixture of higher primary aliphatic alcohols isolated from sugar cane wax; its main component is octacosanol. The exact mechanism of action of policosanol is unknown but at doses of 10 - 20 mg/day it can lower LDLC by 15 - 29%. Data on efficacy determined by clinical end-points such as cardiac mortality are however lacking.

WHAT'S ON THE HORIZON?

More potent statins

Two new statins, rosuvastatin and pitavastatin, are being developed. In clinical studies with rosuvastatin reductions in LDLC of 45 - 70% have been achieved.

Ezetimibe

Ezetimibe is the first in a new class of cholesterol absorption inhibitors

that potently and selectively inhibit dietary cholesterol absorption at the brush border of the intestinal epithelium without affecting the absorption of triglyceride or fat-soluble vitamins. Unlike resins, GIT side-effects are uncommon.

Ezetimibe at a dose of 10 mg/day can reduce LDLC by 15 - 25%. When used in combination with statins, ezetimibe produces significant additional reductions in LDLC ($\pm 20\%$) with no increase in adverse events.

CONCLUSIONS

Management of dyslipidaemia requires appropriate lifestyle modification and, where indicated, lipid-modifying drug therapy. Safe and effective drug therapy is now available for the management of most dyslipidaemias.

There is now substantial evidence to show that appropriately prescribed lipid-modifying drug therapy can lower morbidity and mortality from CAD and improve overall survival, both in subjects with established cardiovascular disease and in those at high risk for developing cardiovascular disease.

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FURTHER READING

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IN A NUTSHELL

Dyslipidaemia, particularly an elevated LDL-cholesterol level, is the major risk factor for cardiovascular disease.

Lifestyle modification is essential and must be applied to all patients with dyslipidaemia.

Patients with genetic dyslipidaemia, established cardiovascular disease, diabetes, and those at high cardiovascular risk warrant lipid-modifying drug therapy.

Appropriately prescribed lipid-modifying drug therapy can lower cardiovascular morbidity and mortality and improve overall survival.

Statins are the most effective agents for the treatment of predominant hypercholesterolaemia.

Fibrates are more effective for the treatment of hypertriglyceridaemia.

Combination therapy may be required for the treatment of severe dyslipidaemia but side-effects are more likely and costs become substantial.