Evidence-based Pharmacy Practice (EBPP):

DYSLIPIDAEMIA

Angelene van der Westhuizen, BPharm
Department of Pharmacology, University of Pretoria

Abstract

Dyslipidaemia is a disorder of lipoprotein metabolism that alters the concentration or composition of lipoproteins. Atherosclerosis and pancreatitis are the two major complications of dyslipidaemia. The most common dyslipidaemia is hypercholesterolaemia, which is one of the major risk factors for coronary heart disease (CHD) and cerebrovascular morbidity and mortality. Severe hypertriglyceridaemia can cause acute pancreatitis. Initial therapy for any lipoprotein disorder is lifestyle changes which include smoking cessation, a diet low in saturated fats, weight loss if indicated and regular aerobic exercise. Correction of any precipitating factors such as uncontrolled diabetes, alcohol abuse or medications should be undertaken. If lifestyle changes are not effective, then drug therapy should be considered. The choice of drug therapy is dependent on the type of lipoprotein disorder. The most effective cholesterol lowering drugs are the statins (HMG CoA reductase inhibitors). They work by inhibiting the rate-limiting step in cholesterol synthesis. They are the most potent form of monotherapy as well as being the most cost effective. Patients not responding to statin monotherapy can be treated with combination therapy, which may include bile acid resins, fibrates, nicotinic acid or ezetimibe. Dietary supplements such as plant sterols and fish oils can also assist in lowering cholesterol levels. Lipid lowering is beneficial in patients with dyslipidaemias for both primary and secondary prevention of CHD.

Definitions

Cholesterol, triglycerides, and phospholipids are transported in the bloodstream as complexes of lipids and proteins known as lipoproteins.[1] The three major classes of lipoproteins found in the serum are low-density lipoproteins (LDLs), high-density lipoproteins (HDLs), and very low-density lipoproteins (VLDLs).[1] Intermediate-density lipoprotein (IDL) is between LDL and VLDL, and is included in the LDL measurement in routine clinical measurements.[1] Chylomicrons, the largest plasma lipoproteins, have the highest fat content of all the lipoproteins (98% to 99%), of which 85% is dietary triglyceride.[2]

Dyslipidaemia is defined as elevated total cholesterol, low-density lipoprotein (LDL) cholesterol, or triglycerides; a low high-density lipoprotein (HDL) cholesterol; or a combination of these abnormalities.[1] The most common dyslipidaemia is hypercholesterolaemia also known as hyperlipidaemia.

Lipoprotein disorders are classified into six categories known as the "Fredrickson-Levy-Lees Classification of Hyperlipoproteinaemia" (I, IIa, IIb, III, IV, V).[1] Refer to Table I for examples.

Epidemiology

Dyslipidaemias including hypercholesterolaemia and low levels of high-density lipoprotein (HDL) cholesterol are major causes of increased atherogenic risk leading to CHD, ischaemic cerebrovascular disease and peripheral vascular disease. Both genetic disorders, metabolic disorders and lifestyle contribute to dyslipidaemias seen around the world.[2] Familial hypercholesterolaemia (FH) (IIa) is highly prevalent in South Africa in Afrikaners, Ashkenazi Jews and Indians with Guajarati ancestory.[3] The worldwide prevalence of FH is 1:500 but in the above mentioned populations the prevalence approaches 1:70.[3]

Severe hypertriglyceridaemia (TG > 10–15 mmol/l) can cause acute pancreatitis which, unlike atherosclerosis which develops over several years, may set in suddenly and is associated with high short-term morbidity and mortality.[3] Patients with severe hypertriglyceridaemia must be evaluated quickly and treated rapidly.[3] Cholesterol and triglyceride levels increase throughout life until about the fifth decade for men and sixth decade for women. Past these ages, total cholesterol and LDL plateau and fall slightly. HDL tends to fall slightly with time and more rapidly after menopause in women.[1]

Table I: Lipoprotein disorders[1]

Lipoprotein disorder	Phenotype
Familial LPL deficiency	I, V
Familial apo CII deficiency	I, V
Familial hypercholesterolaemia	IIa
Familial defective apo B100	IIa
Polygenic hypercholesterolaemia	IIa
Combined hyperlipidaemia	IIb
Dysbetalipoproteinaemia	III
Familial hypertrigylceridaemia	IV

LPL = lipoprotein lipase

The results from clinical trials suggest that CHD risk is reduced by 1% for every 1% reduction in LDL cholesterol.[2]

Aetiology/pathophysiology

The normal function of lipoproteins is to distribute and recycle cholesterol.[4]

Primary causes of dyslipidaemia include major identifiable single-gene mutations and multiple genetic factors (which are also influenced by secondary and lifestyle mechanisms).[5] There are five primary inherited lipoprotein disorders:[4]

1. Familial hypertriglyceridaemia
2. Familial combined hyperlipidaemia
3. Remnant removal disease (Familial dysbetalipoproteinaemia)
4. Familial hypoalphalipoproteinaemia
5. Familial hypercholesterolaemia

Secondary dyslipidaemias occur in patients with a normal genetic constitution or when only minor gene defects are present but the environment or an underlying disease brings out the dyslipidaemia.[5] Refer to Table II for the most common causes of secondary dyslipidaemia.

HDLs are protective lipoproteins that decrease the risk of CHD, so high levels of HDL are desirable.[2] HDL cholesterol may be elevated by moderate alcohol ingestion (10 g per day), physical exercise, smoking cessation, weight loss, oral contraceptives, phenytoin and terbutaline.[1] HDL cholesterol may be lowered by smoking, obesity, a sedentary lifestyle, and drugs such as ß-blockers.[1]

Table II: Common causes of secondary dyslipidaemia[6]

Drugs
Amiodarone Anabolic steroids Antiretrovirals (especially protease inhibitors) Beta blockers Glucocorticoids Ciclosporin Retinoids Androgens, oestrogens Thiazide diuretics
Endocrinopathies
Acromegaly Cushing's syndrome Diabetes mellitus Metabolic syndrome and obesity Hypothyroidism
Gastrointestinal disease
Acute intermittent porphyria Cholestatic liver disease Intestinal malabsorption
Lifestyle
Anorexia nervosa, bulimia Cigarette smoking Diet Excessive alcohol consumption Stress
Miscellaneous
HIV Pregnancy Systemic lupus erythematosus
Renal disease
Nephrotic syndrome Chronic renal failure

Diagnosis

A random total cholesterol test is sufficient for screening patients for dyslipidaemia, but if the total cholesterol is > 5 mmol/l a fasting lipoprotein profile should be undertaken.[7] A complete history and physical examination should also be undertaken. A full fasting lipogram should be the initial investigation in patients with existing CHD, clinical signs of dyslipidaemia (e.g. tendon xanthomata), or a family history of premature CHD (men < 55 years, women < 65 years).[7] The assessment of dyslipidaemic patients should begin with exclusion of secondary disorders or causes e.g. drugs, global evaluation of cardiovascular risk, lifestyle evaluation and identification of any genetic lipid disorders.[3] Patients with clinical CHD, type 2 diabetes or type 1 diabetics with microalbuminuria, or severe monogenic hyperlipidaemia do not need a risk assessment and LMDs are required even if the lipids are not elevated.[3] Patients who are not at high risk need a risk assessment using an algorithm.[3] The European guidelines on cardiovascular disease prevention in clinical practice recommend a new model for total risk estimation based on the SCORE (Systematic Coronary Risk Evaluation) system.[8,9] The SCORE assessment is derived from European data and may not be applicable to South Africa.[9] There is not sufficient local data to construct a South African algorithm so an algorithm based on American data from the Framingham study is currently recommended for use in South Africa.[3,10] Treatment is recommended if the 10 year risk is more than 20%.[3]

Clinical approaches to dyslipidaemia for the pharmacist

The pharmacist can give patients advice on determining their risk of CHD (coronary heart disease). Rapid cholesterol tests can be offered in the pharmacy with the appropriate counselling and referral to the doctor if readings are high. If the patient does have hyperlipidaemia then advice on lifestyle modification which includes smoking cessation, a healthy diet with weight loss if indicated and regular aerobic exercise can be advocated. This includes patients who may already be taking lipid modifying drugs (LMDs). All patients with dyslipidaemia would benefit from lifestyle modification and drug therapy should not be seen as an alternative. The pharmacist should review the patient's medication to ascertain whether any of the medication could be contributing to increased cholesterol levels. Non-pharmacological treatment options could also be discussed with the patient with the most current evidence. Advice on the correct usage and storage of any LMDs that the patient has been prescribed would also be of benefit to the patient. Side-effects that could be indicative of myopathy such as muscle pain should be explained to the patient as well as how to cope with or avert certain side-effects e.g. insomnia where the patient could be advised to take a statin in the morning rather than the evening. Pharmacists can help manage patients who take statins to ensure early detection of drug interactions or pharmacokinetic changes that might influence serum drug levels.[11]

Adherence to LMDs could also be monitored by the pharmacist by checking the repeat prescription dates and talking with the patient when they come to have their prescription filled.

Available treatment options

1. Therapeutic lifestyle modification
2. Non-pharmacological treatment
3. Pharmacological treatment with lipid modifying drugs

Therapeutic objectives

The ultimate aim of lipid modifying therapy is to reduce cardiovascular risk for most patients i.e. to reduce the risk of first or recurrent events such as myocardial infarction (MI), angina, heart failure, ischaemic stroke, or other forms of peripheral arterial disease such as carotid stenosis or abdominal aortic aneurysm. Patients with severe hypertrigylceridaemia are primarily treated to reduce the risk of acute pancreatitis. According to the European guidelines on cardiovascular disease prevention in clinical practice 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 and patients with diabetes treatment goals should be lower: total cholesterol < 4.5 mmol/L and LDL cholesterol < 2.5 mmol/L.[8,9] The currently recommended target in South Africa is a LDL cholesterol of 2.5 mmol/L or less.[3] The American National Cholesterol Education Program has suggested a target of 1.8 mmol/l for very high-risk patients.[10] Improved lipid values are just one factor in the management of dyslipidaemia. Decisions on treatment should be based on assessment of the absolute risk of a complication of dyslipidaemia occurring. Therefore, treatment should be individualised. Two patients with the same lipid values could be treated differently according to their assessment of risk.

Therapeutic lifestyle modification

Smoking cessation

This is the single most important therapeutic action in patients with dyslipidaemia.[5] Cigarette smoking is associated with a modest drop in serum high-density lipoprotein (HDL) cholesterol.[6] It may also contribute to insulin resistance. These changes are reversible and benefits are seen within two months of cessation of smoking.[6] There is zero additional risk after two years.[5] Counselling and pharmacological therapy (nicotine replacement, bupropion) may both be necessary.[13]

Diet

Reductions in dietary total and saturated fat, cholesterol and energy intake are recommended. Total fat intake should account for no more than 30% of energy intake, and the intake of saturated fats should not be more than a third of total fat intake. (SA statement) The intake of cholesterol should be less than 300 g/day.[9] Diets high in fibre, antioxidant-containing fruits and vegetables, and cold-water fish rich in omega-3 polyunsaturated fats have been shown to reduce first and recurrent coronary events independent of drugs.[14] For diet to be effective in lowering cholesterol the change in diet should be life-long. The benefits of diet would then be additive to drug therapy with the possible reduction in drug doses. Primary prevention by diet may eliminate the need for drugs altogether.[14]

Weight loss in overweight patients

Patients who are obese should consult a dietician for tailored advice. Simply recommending a low-fat diet may result in inappropriate increases in starches and sugars and increased triglycerides and lowered HDL cholesterol. Almost all patients would benefit from consulting a dietician. Ideal weight in the general population may be defined by a BMI < 25kg/m^2. (BMI can be calculated as mass/height^2 where mass is in kilograms and height is in metres).[5] A BMI of 23kg/m^2 is desirable for patients with diabetes mellitus, hypertrigylceridaemia or low HDL cholesterol profiles.[5]

Regular aerobic exercise

An exercise prescription would validate the benefit of exercise to a patient with dyslipidaemia and give guidelines of what type and how long exercise should be sustained. Just telling the patient to exercise regularly is advice that is often ignored. The minimum effective target is thirty minutes of brisk walking, three times a week.[5] Other measures such as using stairs instead of lifts, walking rather than driving short distances, and gardening and housework would also add benefit.[5] A preferable minimum target would be greater than or equal to four hours of moderate exercise per week spread over five to six sessions.[5] An exercise prescription should be appropriate to age and clinical status.[5] If clinical CHD is present or suspected, a cardiologist's opinion should be obtained before any recommendations are made.[5] The exercise should elevate heart rate to about 75% of age-related maximum heart rate (220 beats/min minus age in years).[5]

Non-pharmacological management

Dietary supplements

Fish oil (omega-3 fatty acids)

Diets high in omega-3 polyunsaturated fatty acids (from fish oil), most commonly eicosapentaenoic acid (EPS) and docosahexaenoic acid (DHA), can lower triglyceride-rich lipoprotein production in the liver which is useful in the treatment of most forms of hypertrigyceriaemia.[1] This effect is achieved with large doses > 3 g/day. HDL cholesterol is raised but LDL cholesterol can also be raised. Eating fish two to three times per week may also be protective.

Red yeast rice

This is a fermented rice product that has been used in Chinese cuisine and medicinally to promote "blood circulation".[15] Red yeast rice contains monacolins that have HMG CoA reductase inhibitor activity.[16] Other ingredients that may also lower cholesterol include sterols, isoflavones, and monounsaturated fatty acids.[17] As with other 'natural' products, there is a lack of standardisation, so there is variability across brands in the content of the active ingredient and therefore its efficacy in lowering LDL cholesterol.[18]

Plant sterols e.g. Beta-sitosterol ester Flora Proactiv®

These 'cholesterol-like' molecules inhibit intestinal absorption of dietary and biliary cholesterol.[19] At recommended intake of about 2–2.5 g/day (about 20 g of margarine) products enriched with plant sterol/sterol esters lower plasma LDL cholesterol levels by reducing intestinal absorption by 10 to 14% without any reported side-effects.[20] They do not have an effect on HDL cholesterol.[19] These products should not be used routinely by the general population until long-term studies have been performed to ensure that there are no adverse effects.[21] Flora Proactiv® contains triglycerides so should not be used in patients with hypertriglyceridaemia.[22] Adults with hypercholesterolaemia or an atherosclerotic event who require lowering of total and LDL cholesterol are the most appropriate candidates for the use of these products.[21]

Fibre

Increased intake of soluble fibre such as oat bran, pectins and psyllium can result in additional reductions in total and LDL cholesterol (5 to 20%).[1] They have little or no effect on HDL cholesterol or triglyceride concentrations.[1] These products may also be useful in managing constipation associated with the bile acid resins.[1]

Nuts

Walnuts (which are rich in polyunsaturated fatty acids) have been shown to have a beneficial effect on serum lipids when compared to other cholesterol lowering diets. [23,24]Almonds and pistachios have also been shown to have a beneficial effect on lipids.[25,26]

Tea

A randomised trial of theaflavin-enriched green tea significantly lowered total and LDL cholesterol concentrations compared with placebo without significantly affecting HDL concentrations.[27]

Policosanol

A drug extracted from sugar cane wax (not registered as a medicine in South Africa) has been suggested by some studies to have a LDL cholesterol lowering effect.[21] Due to the variability in available preparations and the exact composition and mechanism of action being unknown, it is not recommended for the treatment of hypercholesterolaemia.[21]

Garlic, calcium and soy are not recommended to be taken with the goal of improving lipids and cardiovascular risk, although they have other health benefits.[21]

Pharmacological treatment

Lipid modifying drugs (LMDs) encompass several classes of drugs that include HMG CoA reductase inhibitors or 'statins', fibrates, nicotinic acid, ezetimibe, bile acid resins and probucol. These drugs differ in their mechanism of action and to the degree and type of lipid lowering.[28] Indications for a particular drug are influenced by the underlying lipid abnormality.[28] Refer to Table III.

In general, drugs act to lower the concentration of cholesterol within hepatocytes by producing a compensatory increase in LDL receptors on their surface, and increasing uptake of cholesterol-rich LDL from the bloodstream.[4]

Statins

The statins currently available in South Africa are simvastatin, atorvastatin, fluvastatin, lovastatin, pravastatin and rosuvastatin. A new statin, pitavastatin has been available in Japan since 2003 but is not yet marketed in South Africa.[29] Rosuvastatin is the latest addition to the statin market in South Africa. It is highly potent and when compared milligram for milligram with other potent statins, it is approximately double that of atorvastatin and four times that of simvastatin.[29] (Refer to Table V). Rosuvastatin also raises HDL cholesterol more than other statins and has less

Table III: Lipoprotein phenotype and recommended drug treatment[1]

Lipoprotein type	Lipoprotein elevation	Drug of choice	Combination therapy
I	Chylomicrons	Not indicated	Not indicated
IIa	LDL	Statins	Nicotinic acid or BARs
		Cholestyramine	Statins or nicotinic acid
		Nicotinic acid	Statins or BARs
			Ezetimibe
IIb	LDL + VLDL	Statins	BARs, fibrates or nicotinic acid
		Fibrates	Statins or nicotinic acid or BARs
		Nicotinic acid	Statins or fibrates
			Ezetimibe
III	IDL	Fibrates	Statins or nicotinic acid
		Nicotinic acid	Statins or fibrates
			Ezetimibe
IV	VLDL	Fibrates	Nicotinic acid
		Nicotinic acid	Fibrates
V	VLDL + chylomicrons	Fibrates	Nicotinic acid
		Nicotinic acid	Fish oils

LDL: low-density lipoprotein, VLDL: very-low-density lipoprotein, IDL: intermediate-density lipoprotein, HDL: high-density lipoprotein
BARs: bile acid resins; fibrates include bezafibrate, fenofibrate or gemfibrozil
BARs are not used as first-line therapy if triglycerides are elevated at baseline because hypertriglyceridaemia may worsen with BARs alone.

Table IV: Effects of drug therapy on lipids and lipoproteins[1]

Drug	Mechanism of action	Effects on Lipids	Effects on lipoproteins
Cholestyramine	↑ LDL catabolism	↓ Cholesterol	↓ LDL
	↓ Cholesterol absorption		↑ VLDL
Nicotinic acid	↓ LDL & VLDL synthesis	↓ Triglyceride	↓ VLDL
		↓ Cholesterol	↓ LDL, ↑ HDL
Bezafibrate, fenofibrate, gemfibrozil	↑ VLDL clearance	↓ Triglyceride	↓ VLDL
	↓ VLDL synthesis	↓ Cholesterol	↓ LDL, ↑ HDL
Lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, rosuvastatin	↑ LDL catabolism	↓ Cholesterol	↓ LDL
	↓ LDL synthesis		
Ezetimibe	Blocks cholesterol absorption across intestinal border	↓ Cholesterol	↓ LDL

↑ increased; ↓ decreased

potential to interact with other drugs. (Refer to Table VI). Doses should not exceed 40 mg as rare episodes of renal failure have been seen in patients treated with 80 mg per day.[30]

Statins are the most powerful drugs for lowering LDL cholesterol, with reductions in the range of 30 to 63%.[28] Statins are competitive inhibitors of HMG CoA reductase, the rate-limiting step in cholesterol biosynthesis. They occupy a portion of the binding site of HMG CoA, blocking access of this substrate to the active site on the enzyme.[28] Statins affect blood cholesterol levels by inhibiting hepatic cholesterol synthesis, which results in increased expression of the LDL receptor gene.[2] The greater number of LDL receptors on the surface of hepatocytes results in increased removal of LDL from the blood, resulting in lower LDL cholesterol levels.[2] They are indicated in the treatment of hypercholesterolaemia and mixed hyperlipidaemia.

Table V: Approximate equivalent doses of statins to obtain a 25–30% reduction in LDL cholesterol[22]

Statin	Dose (not necessarily marketed)
rosuvastatin	2.5 mg
atorvastatin	5 mg
simvastatin	10 mg
lovastatin	20 mg
pravastatin	40 mg
fluvastatin	60 mg

The choice of statin depends upon a number of factors, including the degree of hyperlipidaemia, pharmacokinetic properties, drug interactions, the presence of renal impairment, and cost.[28] Generic statins have allowed many more patients access to this important therapy especially in the state sector.[28]

Hepatic cholesterol synthesis is maximal between midnight and 2.00 am, so shorter acting statins (with half-lives of four hours or less-refer to Table VI) should be taken at night whilst longer acting statins (atorvastatin, rosuvastatin) can be taken at any time in the day.[2] Lovastatin absorption is increased by food, so ideally it should be administered with the morning and evening meals.[26] All statins show a flat dose-response curve and doubling the statin dose only lowers LDL cholesterol by a further 6%.[13]

Atorvastatin and rosuvastatin are more effective at lowering triglycerides than other statins in patients with hypercholesterolaemia and this effect is dose-dependent.[28] The more lipophilic statins (simvastatin, lovastatin, atorvastatin and fluvastatin) may be associated with more adverse effects than the more hydrophilic statins (pravastatin and rosuvastatin).[28] Adverse effects occur less frequently with statins than other LMDs.[28] Hepatic dysfunction and myopathy are serious but rare adverse effects that can occur with the statins. Myopathy is more common when high doses of statins are used or when given in combination with fibrates.[13] Myopathy may also occur if inhibitors of statin metabolism are given concurrently.[13] Examples of enzyme inhibitors include macrolide antibiotics, ciclosporin, protease inhibitors, azole antifungals, fluoxetine, cimetidine,

Table VI: Pharmacokinetics of the statins[1]

Parameter	Lovastatin	Simvastatin	Pravastatin	Fluvastatin	Atorvastatin	Rosuvastatin
CYP450 Isoenzyme	3A4	3A4	None	2C9	3A4	2C9/2C19
Lipophilic	Yes	Yes	No	Yes	Yes	No
Protein binding (%)	> 95	95– 98	~50	> 90	96	88
Active metbolites	Yes	Yes	No	No	Yes	Yes
Elimination half-life (hours)	3	2	1.8	1.2	7–14	13–20

verapamil and grapefruit juice.[13,31] Pravastation is the statin of choice when the patient is also taking cyclosporin as it is not affected by inhibitors of the CYP450 system.[28]

Statins should not be taken during pregnancy. There is a possible increase in congenital central nervous system and limb abnormalities with exposure to lipophilic statins during the first trimester.[32]

Fibrates

The fibrates available in South Africa are bezafibrate, fenofibrate and gemfibrozil. (Clofibrate and ciprofibrate are available outside South Africa). Fibrates act through a nuclear transcription factor (peroxisome proliferator activated receptor (PPAR)) regulating gene expression involved in lipid and lipoprotein metabolism.[4] The major effects of the fibrates are to lower serum triglycerides (by 35 to 50%) and raise serum HDL (by 15 to 25%).[33] Reduced hepatic secretion of VLDL and a facilitated clearance of triglyceride-enriched lipoproteins by stimulation of lipoprotein lipase activity contribute to the lower serum triglycerides.[33]

Fibrates have primarily shown reductions in cardiovascular events in subsets of patients with high triglycerides (> 2.2. mmol/L) or low HDL cholesterol (< 1.0 mmol/L) and multiple characteristics of the metabolic syndrome including a borderline elevated triglyceride level.[33]

The dose of fenofibrate should be reduced in renal disease and should be avoided in patients with severe renal impairment.[33] Fenofibrate also increases the clearance of ciclosporin which could result in episodes of acute rejection in patients with organ transplants due to a sub therapeutic ciclosporin level.[33] Fibrates also interfere with the metabolism of warfarin so the dose should be reduced by 30 per cent in patients treated with this drug.[33] Gemfibrozil significantly inhibits glucuronidation which is an important pathway for the renal excretion of lipophilic statins.[32] Fenofibrate does not have this effect so is the preferred fibrate when combination with statins is required.[33]

Fibrates have been associated with muscle toxicity which is more pronounced if the patient is also taking a statin.[32] This effect may occur due to the inhibition of CYP3A4 leading to a reduction in statin metabolism. Pravastatin and fluvastatin are not extensively metabolised by CYP3A4 so they may be safer when combined with a fibrate than the other statins.[33]

Fibrates should not be used by children or pregnant women.[2]

Nicotinic acid (Niacin)

Nicotinic acid is a B-group vitamin available only as an immediate release preparation in South Africa. Sustained release preparations are available in other countries.[19] Nicotinic acid inhibits hormone-sensitive lipase via a cyclic AMP pathway and decreases plasma fatty acid concentrations.[22] It inhibits the hepatic production of VLDL and its metabolite VDL.[34] It raises HDL levels by reducing lipid transfer of cholesterol from HDL to VLDL and by delaying HDL clearance.[34] It is the best agent available for increasing HDL-cholesterol.[2] Flushing is the most common side effect which is exacerbated if taken with alcohol or hot beverages.[19] Flushing can be reduced by taking aspirin one hour before taking nicotinic acid as the side-effect is prostaglandin mediated.[2,19] Other side-effects include pruritus, rash, dizziness, gastrointestinal disturbances (lessened if taken after food), hyperuricaemia, hyperglycaemia and impaired liver enzymes.[19] It should not be used in patients with gout or liver disease.[19] In patients with diabetes mellitus nicotinic acid should be used cautiously since it can induce insulin resistance which can cause severe hyperglycaemia.[2] Nicotinic acid should not be taken in pregnancy.[2] Combined with a statin it reduces the residual risk observed on statin treatment as it modifies most aspects of the lipid profile left untreated by statins.[29] High doses are required (1.5 g – 3 g per day) and 100 mg tablets are only available in South Africa so the pill burden is high.[17,29]

Acipimox is also an inhibitor of hormone-sensitive lipase but is not diabetogenic.[5,22] At recommended doses it appears to be less potent than nicotinic acid.[5,22]

Newer formulations of nicotinic acid combined with prostaglandin receptor blockers are being explored.[29]

Ezetimibe

Ezetimibe is a cholesterol absorption inhibitor which impairs the dietary and biliary cholesterol absorption at the brush border of the intestine without affecting the absorption of triglycerides or fat soluble vitamins.[36] It selectively inhibits the Niemann-Pick C1 like 1(NPC1L1) protein localised at the brush border of the enterocytes.[19] NPC1L1 is a transporter that moves cholesterol from the bile acid micelles into enterocytes.[19] It reduces the delivery of cholesterol to the liver, decreasing hepatic cholesterol and promoting the upregulation of LDL receptors which leads to a decrease in LDL cholesterol.[19] The precipitated compensatory increase in cholesterol synthesis caused by the reduction in cholesterol absorption can be inhibited with a statin.[2] Ezetimibe can reduce LDL cholesterol by 15 to 20% as monotherapy at a dose of 10 mg/day.[2] This reduction is equivalent to or less than, that achieved with 10 to 20 mg doses of most statins.[2] Therefore ezetimibe as monotherapy should be limited to statin-intolerant patients.[2] Therapy with both ezetimibe and statins prevents the enhanced cholesterol synthesis induced by ezetimibe and the increase in cholesterol absorption by the statins.[2] There is a further reduction of 15 to 20% in LDL cholesterol when ezetimibe is combined with any statin at any dose.[2] When doses of statins are increased from 20 mg to 80 mg there is only a 12% additional decrease in LDL cholesterol whereas adding ezetimibe 10 mg daily to 20 mg of a statin reduces LDL cholesterol by an additional 18 to 20%.[2] Ezetimibe may be helpful for avoiding high doses of statins (which may potentially increase susceptibility of myopathy) in patients who do not meet cholesterol targets on low dose statin therapy alone.[37] Ezetimibe may be taken at any time of the day with or without food. Bile acid resins inhibit the absorption of ezetimibe so they should not be given together.[2]

Bile acid resins (BARs)

Cholestyramine is the only BAR available in South Africa. Colestipol and coleservalam are available elsewhere in the world. The BARs are highly positively charged and they bind negatively charged bile acids.[2] BARs are not systemically absorbed and the bound bile acids are excreted in the faeces.[2] 95% of bile acids are normally reabsorbed so interruption of this process depletes bile acids and causes the hepatocyte to upregulate LDL receptors so as to obtain cholesterol to synthesise more bile acids.[2] The resin-induced increase in bile acid production is accompanied by an increase in hepatic triglyceride synthesis which could lead to hypertriglyceridaemia in susceptible patients.[19] They have little effect on HDL cholesterol levels.[19] The use of BARs is often limited by side-effects.[37] The major adverse effects are gastrointestinal; constipation, bloating, epigastric fullness, nausea and flatulence are most commonly reported.[1,37] BARs also bind to and impair the absorption of other drugs such as digoxin, warfarin and fat soluble vitamins.[37] It is best to advise patients taking BARs to take other drugs one hour before or four hours after the BARs.[37]

Probucol

Probucol modestly lowers LDL cholesterol, but it also reduces HDL cholesterol.[37] It also increases the resistance of LDL to oxidative modification to more atherogenic forms.[37] It facilitates resorption of cutaneous and tendon xanthomas in patients with homozygous familial hypercholesterolaemia.[37] Probucol induces cholesterol ester transfer protein activity which promotes transfer of cholesterol out of the HDL and explains the HDL cholesterol lowering property of this drug.[22] It seems to act synergistically with BARs where it can also lessen the constipation caused by these drugs.[22] This drug was used fairly commonly before statins became available but now is hardly prescribed at all.[28]

Evidence-based recommendations

The South African Heart Association has now officially adopted the European guidelines on cardiovascular disease prevention. The European guidelines update the South African Lipid Guidelines published in February 2003.[9] In the treatment and management of all dyslipidaemias any secondary causes (refer to Table II) of dyslipidaemia should be identified and rectified if possible before drug therapy is instituted. Any medical disorder that may be causing the hyperlipidaemia such as diabetes or hypothyroidism should be treated first.[4] The patient's current drug therapy should be reviewed and any drugs that may increase lipid levels identified and if possible changed for an alternative.

Therapeutic lifestyle changes such as smoking cessation, a diet low in saturated fat and cholesterol, weight loss and regular aerobic exercise should be instituted. The choice of drug therapy is dependent on the underlying lipid abnormality.

Hypercholesterolaemia

Statins are the first choice for lowering LDL cholesterol.[19] Doses should be titrated at 4 to 6 weekly intervals.[19] Doubling the dose of a statin will reduce the LDL cholesterol by a further 6%.[19] If LDL cholesterol targets are not met even with lifestyle modification or if increasing the dose is not possible (due to side-effects such as myopathy) then combination therapy will need to be considered. Combination therapy will be necessary in some patients due to severe hyperlipidaemia and or statin intolerance.[19] Combination therapy is associated with an increased risk of side-effects. Adding a plant sterol/stanol reduces LDL cholesterol by a further 10%, a BAR 15% and ezetimibe 20%.[19]

Hypertriglyceridaemia

High serum triglycerides should be treated by achieving desirable body weight (and BMI), consuming a diet low in saturated fat and cholesterol and participating in regular exercise.[1] Smoking cessation and restriction of alcohol is also required.[1] Nicotinamide should be considered as drug treatment in patients with borderline-high triglycerides with risk factors such as established CHD, family history of CHD, concomitant LDL elevation and a low HDL and genetic forms of hypertriglyceridaemia associated with CHD.[1] Fibrates, statins and fish oil can also be used.[1] Very high triglycerides are associated with acute

Table VII: Drug classes available in South Africa with dose ranges[22]

Drug class	Drug	Trade name	Generic available	Dose range (per day)
Statins	Simvastatin	Zocor®	Yes	10 to 80 mg
	Atorvastatin	Lipitor®	Yes	10 to 80 mg
	Fluvastatin	Lescol®	No	20 to 80 mg (SR)
	Lovastatin	Lovachol®	No	20 to 80 mg
	Pravastatin	Prava®	Yes	10 to 40 mg
	Rosuvastatin	Crestor®	No	10 to 40 mg
Fibrates	Bezafibrate	Bezalip®	Yes	200 to 600 mg or 400 mg SR
	Fenofibrate	Lipanthyl®	No	200 mg
	Gemfibrozil	Lopid®	No	0.9 to 1.5 g
Niacin	Nicotinic acid	Be-Tabs Nicotinic acid®	Yes	300 mg to 6 g
	Acipimox	Olbetam®	No	500 to 750 mg
Cholesterol absorption inhibitor	Ezetimibe	Ezetrol®	No	10 mg
Bile acid resin	Cholestyramine	Questran Lite®	No	4 g to 24 g

Figure 1: CV risk stratification and cholesterol targets

Category 1

Established atherosclerosis
1. Coronary heart disease
2. Cerebrovascular atherosclerotic disease
3. Peripheral vascular disease

Framingham
CHD Risk > 20%

(equivalent to > 5%
CVD mortality risk)

Diabetes Type 2
Diabetes Type 1 diabetes with microalbuminuria or proteinuria

Genetic dyslipidaemias e.g. familial hypercholesterolaemia

HIGH RISK
No RISK scoring required

Goal[a]

Total cholesterol < 4.5 mmol/l
LDL-cholesterol < 2.5 mmol/l

Category 2[b]

Use Framingham Risk Assessment Tables[c]:

RISK scoring required

(Use correct gender table)
1. Age
2. Total cholesterol[d]
3. Non-smoker/Smoker[e]
4. HDL-cholesterol
5. Systolic BP

Score:
1. _____
2. _____
3. _____
4. _____
5. _____
Point total: _____

10-year CHD event risk _____%[f]

Initial CHD risk
< 20%

Goal[a]
Total cholesterol < 5 mmol/l
LDL-cholesterol < 3 mmol/l

Initial CHD risk
> 20%
but reduced to < 20% with
lifestyle changes

Persistent CHD risk of > 20%
despite lifestyle change and
initial drug therapy

Goal[a]
Total cholesterol < 4.5 mmol/l
LDL-cholesterol < 2.5 mmol/l

[a] **Pharmacological treatment required if total-cholesterol and, more importantly, LDL-cholesterol remain above these levels despite lifestyle modification. At present statins are first line drugs for lowering LDL-cholesterol.**
[b] Secondary causes of dyslipidaemia should be excluded before progressing to risk assessment (see table on this sheet).
[c] See limitations of Framingham Risk Assessment Score on this page.
[d] Total cholesterol level is used to assign risk score, but both Total cholesterol and, more importantly, LDL-cholesterol are the targets of treatment.
[e] Cigarette smoking is defined as: Any cigarette smoking in the last month or a history of 20 cigaretters per day for 10 years (10 pack years).
[f] **For persons under the age of 60 years, risk should also be extrapolated to age 60.**

Limitations of the Framingham Risk Assessment Score charts
1. Patients who are classified in category 1 are high risk and do not require further risk score for management decisions. Other patients who fall into this category include those with severe hypertension (systolic BP > 180 mmHg and/or diastolic BP > 110 mmHg) or associated target organ damage and those with renal dysfunction.
2. Severe hypercholesterolaemia and hypertriglyceridaemia: The Framingham Risk Assessment chart is only accurate up to total cholesterol values of 7.25 mmol/l and cannot be used for patients with total cholesterol levels above this value. It also does not apply to hypertriglyceridaemia (triglyceride > 5 mmol/l).
3. Family history of early atherosclerotic disease is not taken into account. Clinicians should use their judgement in deciding whether to place a patient with an impressive family history in the high risk category, regardless of their Framingham score, or avoid calculating risk in these patients.
4. Hypertriglyceridaemia, impaired glucose tolerance and abdominal obesity are not taken into account in the risk score, despite these factors being important risk factors for CVD. Patients with features of the metabolic syndrome should be considered to be at higher risk and treated accordingly.
5. Women are assigned a lower risk than men. Physicians should exercise their clinical judgement and elevate the risk assessment if the patient has other risk factors for CVD or a strong family history of CVD.
6. Ethnicity: The Framingham Risk assessment charts are based on epidemiological data from a Caucasian North American population. Care should be advised when applying them to other patient populations and race groups. Physicians should exercise their clinical judgement in these patients.

Secondary causes of dyslipidaemia
1. Diabetes mellitus
2. Hypothyroidism
3. Liver disease
4. Renal disease
5. Alcohol excess
6. Drugs
   - Progestins
   - Steroids
   - Antiretroviral agents
   - Retinoids

Conversion from mg/dl
Cholesterol:
mmol/l = mg/dl x 0.0259
mg/dl = mmol/l x 38.7
Triclyceride:
mmol/l = mg/dl x 0.0113
mg/dl = mmol/l x 88.5

LDL-cholesterol: Low Density Lipoprotein Cholesterol; HDL-C: High Density Lipoprotein Cholesterol; TG: Triglyceride; CHD: Coronary Heart Disease; CVD: Cardiovascular Disease; BP: Blood Pressure

The Lipid Advisory Panel has been sponsored by an unrestricted educational grant from AstraZeneca (Pty) Ltd South Africa

pancreatitis.[1] Treatment includes dietary fat restriction (< 30 g of dietary triglyceride per day[19]), weight loss, alcohol restriction and treatment of comorbidites such as diabetes. Drug therapy includes the fibrates, nicotinic acid and high potency statins (atorvastatin, rosuvastatin and simvastatin).[1]

Treatment guidelines are not defined in the European guidelines for triglycerides but a fasting triglyceride of 1.7 mmol/L is considered optimal.[9]

Mixed dyslipidaemia

Treatment depends on which lipid abnormality is predominant: elevated LDL cholesterol or elevated triglyceride.[19] Treatment of the predominant abnormality takes precedence; a statin if LDL cholesterol is high or a fibrate for patients with predominant hypertriglyceridaemia.[19] If monotherapy is inadequate combination of a statin and a fibrate may be necessary.[19]

Low HDL

In the management of low HDL, the primary target for treatment remains the LDL level, but treatment emphasis focuses more on weight reduction, increased physical activity and smoking cessation.[1] If drug therapy is required fibrates and nicotinic acid are the preferred treatment options.[1] Treatment goals are not defined for HDL-cholesterol but an HDL-cholesterol of > 1 mmol/L in men and > 1.2 mmol/L in women is considered optimal.[9]

In order to implement the European guidelines the Lipid Association of Southern Africa (LASSA) and the South African Heart Association (SAHeart) have proposed a simple chart (see Figure 1 on previous page).[9]

Conclusion

Ideally all adults twenty years and older should be assessed for cardiovascular risk, and a fasting lipoprotein profile performed at least once every five years.[1] The reality in South Africa with its limited health-care resources and large population is that screening for hypercholesterolaemia should be undertaken in any person considered to be at risk for CHD, and probably at least once in the life of each adult.[5] Lifestyle modification via smoking cessation, healthy diet and regular aerobic exercise should be advocated at a general population level. LMDs should be used in high-risk patients in whom adequate response is not achieved by lifestyle modification alone. Statins are indicated as first-line therapy in addition to lifestyle modification. Combination therapy is indicated in patients whose lipoprotein concentrations are not controlled by lifestyle modification and statin monotherapy.

Pharmacists can be actively involved in the management of patients with dyslipidaemia by advocating lifestyle modification, giving medication advice and identifying any drug interactions or pharmacokinetic changes in any LMDs patients are taking.❐

References:
1. Wells B G, DiPiro C V, DiPiro J T, Schwinghammer T L. Pharmacotherapy Handbook 7th Edition (2009) by The McGraw-Hill Companies, Inc.
2. Lazo J, Brunton L, Parker K. Goodman & Gilman's The Pharmacological basis of therapeutics 11th Edition (2005) McGraw-Hill Professional Publishing.
3. Blom DJ. A clinical approach to dyslipidaemia. CME March 2009 Vol.27 No.3 108–14.
4. Bennett PN, Brown MJ. Clinical Pharmacology. 10th edition. (2009) Churchill Livingstone Elsevier.
5. South African Medical Association and Lipid and Atherosclerosis Society of South Africa Working Group. Diagnosis, Management and Prevention of the Common Dyslipidaemias in South Africa – Clinical Guideline, 2000. S Afr Med J. February 2000, Vol 90, No 2, 164–78.
6. Bayat Z. Secondary dyslipidaemia. CME March 2009 Vol.27 No.3 115–17.
7. Le Richie M. Rational use of lipid investigations. CME March 2009 Vol. 27 No. 3 129–30.
8. De Backer G, Ambrosioni E, Borch-Johnson K, et al. European guidelines on cardiovascular disease prevention in clinical practice. European Heart J 2003;24: 1601–10.
9. Raal F, Marais AD, Schamroth C. Adoption of the European guidelines on cardiovascular disease prevention in clinical practice – guide to lipid management. SA Heart Winter;3(3):1–20.
10. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third report of the national Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment panel III): Final Report. Circulation 2002; 106:3143–21.
11. Husband A. Managing statin-induced myopathy. Clinical Pharmacist. Vol 1 July/August 2009 319–20.
12. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004; 110(2):227–39.
13. Blom DJ. Dyslipidaemia. MIMS Disease Review 2009/2010. 2009 MIMS (A division of Avusa Media Limited) p26–35.
14. Wecker L, Dunaway G, Faingold C, Watts S. Brody's Human pharmacology Molecular to Clinical. 5th Edition (2010) by Mosby Inc; an affiliate of Elsevier Inc.
15. Li CL, Zhu Y, Wang Y, et al. Monascus purpureus-fermented rice (red yeast rice): a natural food product that lowers blood cholesterol in animal models of hypercholesterolaemia. Nutr Res 1998;18: 71.
16. Patrick L, Uzick M. Cardiovascular disease: C-reactive protein and the inflammatory disease paradigm: HMG-CoA reductase inhibitors, alpha tocopherol, red yeast rice, and olive oil polyphenols. A review of the literature. Altern Med Rev 2001;6: 248.
17. Heber D, Yip I, Ashley JM, et al. Cholesterol-lowering effects of a proprietary Chinese red-yeast-rice dietary supplement. Am J Clin Nutr 1999; 69: 231.
18. Red yeast rice. Med Lett Drugs Ther 2009; 51:71.
19. Rajput MC. Lipid-modifying therapy. CME March 2009 Vol.27 No.3 123–126.
20. Plat J, Mensink RP. Plant Stanol and Sterol Esters in the Control of Blood Cholesterol Levels: Mechanism and Safety Aspects. The American Journal of Cardiology Vol 96 (1A) July 4 2005.
21. Tangney CC, Rosenson RS. Lipid lowering with diet or dietary supplements. Uptodate September 2009. Available at http://www.uptodateonline.com.innopac.up.ac.za/online/content/topic.do?topickey= lipiddis/6977&selectedTitle=3%7E150&source=search_result Accessed November 27 2009.
22. South African Medicines Formulary (SAMF). 8th Edition. Edited by CJ Gibbon. Claremont: Health and Medical Publishing Group of the South African Medical Association.
23. Zambon D, Sabate J, Munoz S, et al. Substituting walnuts for monounsaturated fat improves the serum lipid profile of hypercholesterolaemic men and women. A randomized crossover trial. Am Intern Med 2000; 132:538.
24. Sabate J, Fraser GE, Burke K, et al. Effects of walnuts on serum lipid levels and blood pressure in normal men. N Engl J Med 1993;328: 603.
25. Lichtenstein Ah, Deckelbaum RJ. Stanol/Sterol Ester-Containing Foods and Blood Cholesterol Levels: A Statement for Healthcare Professionals from the Nutrition Committee of the Council on Nutrition, Physical Activity, and Metabolism of the American heart Association. Circulation 2001; 103: 1177.
26. Gebauer SK, West SG, Kay CD, et al. Effects of pistachios on cardiovascular disease risk factors and potential mechanisms of action: a dose-response study. Am J Clin Nutr 2008; 88: 651.
27. Maron DJ, Lu GP, Cai NS, et al. Cholesterol-lowering effect of a theaflavin-enriched green tea extract: a randomized controlled trial. Arch Intern Med 2003; 163: 1448.
28. Rosenson RS. Lipid lowering with statins. Uptodate September 2009. Available at http://www.uptodateonline.com.innopac.up.ac.za/online/content/topic.do?topickey=lipiddis/7436&selectedTitle=1%7E150&source=search_result# Accessed November 27 2009.
29. Blom DJ, Marais AD. New therapeutic developments in lipidology. CME. March 2009, Vol 27, No 3, 104-106.
30. Jones PH, Davidson MH, Stein EA, et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial) An J Cardiol 2003; 92: 152.
31. Knopp RH. Drug Treatment of Lipid Disorders. N Engl J Med 1999; 341: 498–511.
32. Edison RJ, Muenke M. Central nervous system and limb anomalies in case reports of the first-trimester statin exposure. N Engl J Med 2004; 350 1579.
33. Rosenson RS. Lipid lowering with fibric acid derivatives. Uptodate September 2009. Available at http://www.uptodateonline.com.innopac.up.ac.za/online/content/topic.do?topickey=lipidis/7385&selectedTitle=1%7E150&source=search_result Accessed November 27 2009.
34. Grundy SM, Mok HY, Zech L, Berman M. Influence of nicotinic acid on metabolism of cholesterol and triglycerides in man. J Lipid Res 1981;22:24.
35. Illingworth DR, Stein EA, Mitchel YB, et al. Comparative effects of lovastatin and niacin in primary hypercholesterolemia. A prospective trial. Arch Intern Med 1994; 154: 1586.
36. Sudhop T, Lutjohann D, Kodal A, et al. inhibition of intestinal cholesterol absorption by ezetimibe in humans. Circulation 2002;106:1943.
37. Rosenson RS. Lipid lowering with drugs other than statins and fibrates. Uptodate September 2009. Available at http://www.uptodateonline.com.innopac.up.ac.za/online/content/topic.do?topickey=lipidis/6977&selectedTitle=3%7E150&source=search_result Accessed November 27 2009.