



Update on lipid management

Commonly asked questions

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Key points

- Always repeat an abnormal lipid profile when checking for secondary causes of dyslipidaemia.
- Initiate statin therapy at a dose to achieve target LDL-C levels without dose titration. Check lipid profile, creatine kinase, liver enzymes and symptoms six to 12 weeks after statin initiation or up-titration.
- Add ezetimibe if target LDL-C is not achieved on maximum tolerated dose of statin.
- Check alcohol, refined carbohydrate and fat intakes in patients with high TG levels.
- Fibrates and high-dose fish oils are more effective than statins at lowering TG levels.
- Fenofibrate is preferred to gemfibrozil for combination with statins.
- A low HDL-C level is often secondary to a high TG level; the TG level should be controlled before treating to raise the HDL-C level.
- Any move towards target levels is of potential benefit, even though targets may not be reached.

LDL-cholesterol (LDL-C) target levels in patients with cardiovascular disease (CVD) are getting lower. New statin combinations will be more cost effective than present combinations and will help to achieve LDL-C targets. These and other drugs in development promise a new era in CVD prevention.

Lipid management is a common reason for consultation in general practice, and management is now securely grounded on evidence-based guidelines for optimisation of lipid levels and reduction in cardiovascular disease (CVD) risk. This article provides answers to common questions arising in lipid management.

WHAT ARE THE TYPES OF LIPID DISORDERS?

Lipid disorders are classified on the basis of a 12-hour fasting lipid profile into the following four types:

- hypercholesterolaemia (HC) – with predominantly elevated LDL cholesterol (LDL-C) levels
- hypertriglyceridaemia (HTG) – with high triglyceride (TG) levels and near-normal LDL-C levels

- combined or mixed hyperlipidaemia – with elevated levels of both LDL-C and TG
- isolated low HDL cholesterol – with low HDL cholesterol (HDL-C) levels and near-normal TG and LDL-C levels.

This classification replaces the older Frederickson classification of types I to V hyperlipidaemias.

Lipid phenotypes can be further subdivided according to severity as listed below.

- Hypercholesterolaemia
 - mild (total cholesterol [TC], 5.5 to 6.4 mmol/L)
 - moderate (TC, 6.5 to 7.4 mmol/L)
 - severe (TC, 7.5 mmol/L and higher).
- Hypertriglyceridaemia
 - mild (TG, 2.3 to 4.4 mmol/L)
 - moderate (TG, 4.5 to 11.0 mmol/L)
 - severe (TG, 11.0 mmol/L and higher).

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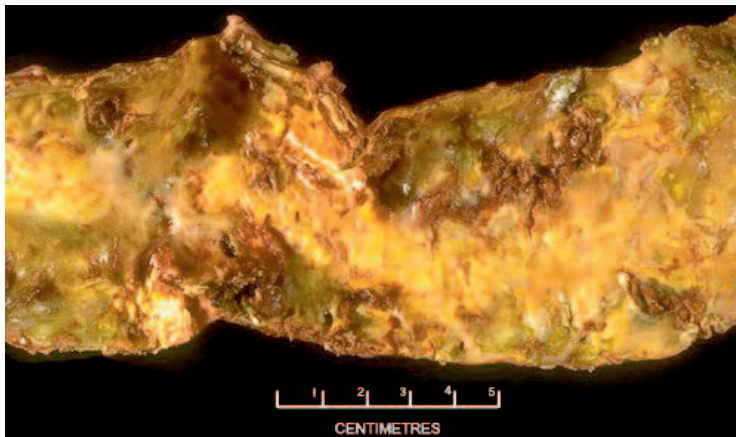


Figure 1. Atherosclerosis of abdominal aorta.

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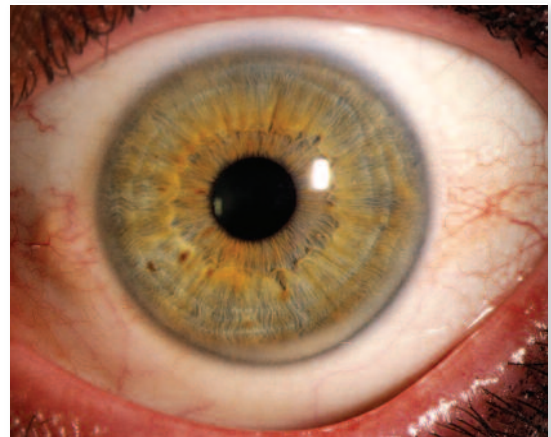


Figure 2. Early arcus senilis.

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- Low HDL-C
 - below 0.9 mmol/L in men
 - below 1.1 mmol/L in women.

The occasional patient has an anti-atherogenic lipid profile such as very low levels of LDL-C or very high levels of HDL-C, presumably on a genetic basis as the family history is often one of

longevity. In the author’s experience, the management of patients with high levels of both LDL-C and HDL-C and a normal TC:HDL-C ratio can often be resolved using imaging. Lowering the LDL-C level is indicated in those patients with positive calcium scores, carotid plaques or increased carotid intima-media thickness.

Each lipid phenotype needs to be classified according to its predominant cause, as below.

- Primary
 - familial (genetic cause identified)
 - sporadic (no cause identified).
- Secondary
 - hypothyroidism
 - diabetes
 - renal failure
 - nephrotic syndrome
 - hepatic disease (especially cholestasis)
 - pregnancy
 - anorexia nervosa
 - alcohol excess
 - drugs causing abnormal lipids – including oestrogens, anabolic steroids, glucocorticosteroids, retinoids, β -blockers, protease inhibitors and thiazides.

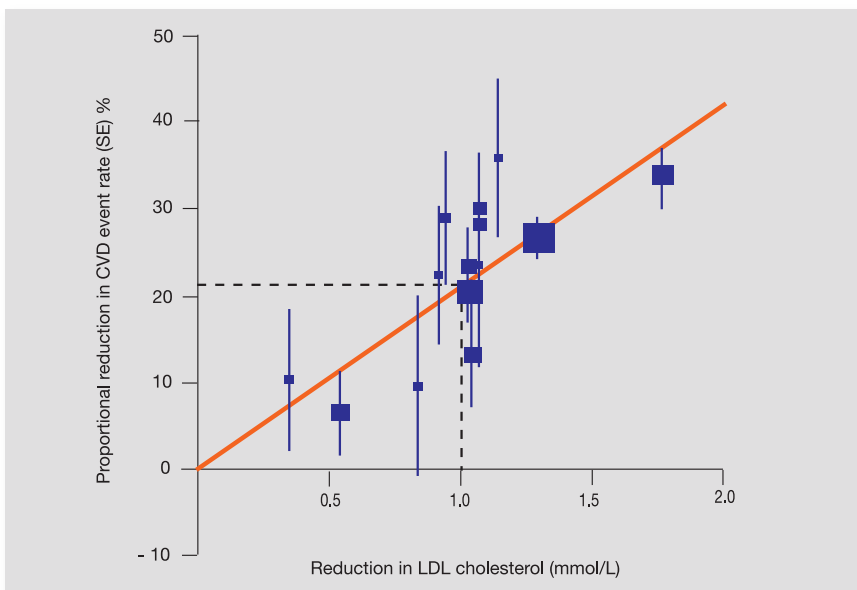


Figure 3. Percentage reduction in cardiovascular disease (CVD) events according to mean absolute LDL cholesterol reduction in 14 statin trials. For each mean 1.0 mmol/L reduction in LDL cholesterol there is a 22% reduction in CVD events.¹

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WHICH LIPID DISORDERS ARE USUALLY ENCOUNTERED IN GENERAL PRACTICE?

About 50% of the general population has cholesterol levels over 5.5 mmol/L and can be regarded as having HC, although fewer than 5% have TC levels greater than 7.5 mmol/L. The most common lipid disorder (about 25% of cases in general practice) is mild mixed hyperlipidaemia (TC, 5.5 to 6.4 mmol/L and TG,



Figures 4a and b. Tendon xanthomas. a (left). Extensor tendon xanthoma. b (right). Achilles tendon xanthoma.

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2.3 to 4.4 mmol/L) in association with obesity, the metabolic syndrome or diabetes. Levels of HDL-C are often low in patients with these conditions, and may respond to TG control. Levels of TG above 4.5 mmol/L are uncommon and occur especially in those people with uncontrolled diabetes and/or excessive alcohol intake.

WHAT IS THE CLINICAL SIGNIFICANCE OF LIPID DISORDERS?

Accelerated atherosclerosis and increased risk of ischaemic CVD are the major complications of HC, mild-to-moderate HTG and low HDL-C (Figure 1).¹ Each of the lipid components appears to be atherogenic by somewhat different mechanisms, and therefore they may act inde-

pendently and additively to increase CVD risk. Severe HTG, although not proatherogenic, may cause potentially fatal acute pancreatitis.

HOW DO LIPID DISORDERS PRESENT?

Most lipid disorders are asymptomatic, causing subclinical atherosclerosis with no overt clinical signs (the iceberg phenomenon).

Hypercholesterolaemia

Patients with moderate and severe HC may present with premature arcus senilis resulting from corneal LDL-C deposition (Figure 2). Early arcus is often difficult to visualise. Arcus is nonspecific, may occur in elderly patients who have normal cholesterol levels and does not regress with

therapy. After several decades, the usual presentation of HC is ischaemic CVD, especially coronary heart disease (CHD). The risk of CHD increases by about 1% for every 1% increase in LDL-C level, and for every 1 mmol/L reduction in LDL-C level with statins there is an about 22% reduction in CVD events (Figure 3).

Patients with severe HC may present with tendon xanthomas, cutaneous (tuberous) xanthomas, xanthelasmas (also nonspecific) and premature CHD (Figures 4 to 6). This is the typical scenario for patients with familial hypercholesterolaemia (FH).

Hypertriglyceridaemia

Patients with moderate-to-severe HTG may present with eruptive xanthomas



Figures 5a and b. Cutaneous (tuberous) xanthomas on the hands (a, above) and feet (b, right).

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Figure 6. Xanthelasma.

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Figure 7. Eruptive xanthomas.

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(Figure 7), but this condition is usually asymptomatic. Planar xanthomas of the palmar skin creases are specific for apolipoprotein (apo) E2/2 homozygosity (familial dysbetalipoproteinaemia). This condition is suspected when levels of TC and TG are elevated to a similar degree (to about 8 mmol/L). TG-rich lipoproteins in mild-to-moderate HTG are atherogenic and increase CVD risk.

Severe HTG may present with acute pancreatitis and lipaemia retinalis; in the laboratory, the plasma is noted to be lipaemic.

Isolated low HDL-C

Findings of very low levels of HDL-C (below 0.2 mmol/L) are rare; they are usually of genetic origin and may be associated with specific signs such as corneal opacity. The usual levels in patients with isolated low HDL-C (0.6 to 0.9 mmol/L) are asymptomatic and independently associated with increased CVD risk, and are frequently seen in patients with premature CVD.

WHAT LIFESTYLE MEASURES CAN BE PRESCRIBED?

Hypercholesterolaemia

HC is treated predominantly by modification of dietary fats, as listed below.

- Reduce intake of cholesterol to less than 300 mg/day;
 - reduce egg yolk intake (each yolk

contains about 250 mg cholesterol)

- avoid full-fat dairy products; use low-fat products instead
- reduce intake of red meat (red meat and dairy products are major sources of cholesterol and saturated fats in the Australian diet)
- eat vegetarian or fish meals two to three times a week
- avoid foods high in saturated fats (e.g. pastries, commercial cakes, visible animal fat)
- substitute polyunsaturated fats (safflower oil, sunflower oil) or monounsaturated fats (olive oil, canola oil) for saturated fats.
- Increase intake of plant sterols to 2 to 3 g/day – foods supplemented with plant sterols are available (e.g. certain margarines – about 1 tablespoon contains 2 to 3 g sterols).
- Increase intake of plant and vegetable foods – these contain soluble fibres which reduce cholesterol absorption.

Hypertriglyceridaemia

HTG is treated predominantly by dietary modification, specifically of the intakes of refined carbohydrates, fats and alcohol, as listed below.

- Restrict alcohol (one standard drink a day in women, two in men).
- Substitute complex carbohydrates for refined carbohydrates.

- Reduce intake of saturated fats.
- In severe HTG, reduce intake of all fats.
- Increase exercise levels.
- Lose weight – initially aim for 5% weight loss, which will improve fat metabolism due to predominantly visceral fat loss.

Isolated low HDL-C

Isolated low HDL-C is often resistant to treatment as it often has a genetic basis with low levels of apo A-1 as the primary cause. The following may be tried:

- weight loss
- reduce high refined carbohydrate intake
- increase exercise.

WHAT DRUG THERAPY CAN BE USED?

Drug therapy is restricted by the need for authorisation (ezetimibe and its combinations) and by PBS criteria for Medicare reimbursement. The PBS criteria are based on cut-off levels for starting drug therapy, rather than absolute levels of CVD risk.

On the basis of absolute risk, a case can be made to provide statins to all high-risk patients (five-year CVD risk greater than 20%) and to consider treatment for those at intermediate risk (five-year CVD risk of 10 to 20%) if they have associated conditions such as diabetes, chronic renal disease or subclinical atherosclerosis. Private prescriptions should be offered

TABLE 1. EFFICACY OF LIPID-LOWERING DRUGS IN MODIFYING LIPID PROFILE

Drug	LDL-C	TG	HDL-C
Statin (5 to 80 mg/day)	++++ * Note rule of 6% (6% added LDL-C lowering for each doubling of the statin dose) Maximum LDL-C lowering, about 55% One extended-release (fluvastatin) formulation available	++ Effect greater for higher baseline TG, more potent statins with regard to LDL-C reduction, and higher statin doses	++ Dose dependent, especially simvastatin, pravastatin and rosuvastatin
Ezetimibe (10 mg/day single dose)	++ Average 20% LDL-C reduction Well tolerated and additive to statin	Minimal	Minimal
Fibrate (62.5 to 1200 mg/day)	Variable (0/+) Use fenofibrate not gemfibrozil with statin Reduce fenofibrate dose in renal impairment	++++	+ / ++
Omega-3 fatty acids (high dose, 6 to 12 g/day)	Variable (may increase)	+++	+
Niacin (2 to 3 g/day optimal)	++ / +++ Dose dependent Poor tolerance unless extended-release formula	++ Dose dependent	++ Dose dependent
Bile acid resins (4 to 20 g/day)	+ / ++ Poor tolerance in higher doses	Minimal (increase if baseline high TG)	Minimal
Plant sterols (2 to 3 g/day)	+	Minimal	Minimal

ABBREVIATIONS: HDL-C = HDL cholesterol; LDL-C = LDL cholesterol; TG = triglycerides.

* + = extent of beneficial effect.

to these patients if they do not meet PBS criteria for reimbursement.

WHICH DRUG SHOULD BE USED FIRST?

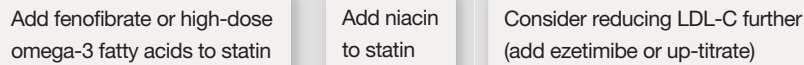
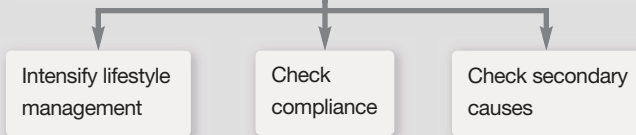
Table 1 provides an overview of the effects of various lipid-modifying drugs on lipid levels. Note that each drug has an effect on all lipid classes.

Details of when each drug should be used as first-line therapy are listed below.

- Statins are first-line therapy for all lipid disorders except moderate/severe HTG and isolated low HDL-C. High doses of more potent statins (with regard to LDL-C lowering) are usually required for controlling HTG.
- For patients not reaching target LDL-C levels on maximum-tolerated doses of statin, and for statin-intolerant patients, ezetimibe is next-line therapy.
- Fibrates are first-line therapy for moderate-to-severe HTG. Fenofibrate is usually preferred as it is likely that add-on statin therapy will be required in many cases and fenofibrate has less risk of muscle adverse effects with statins than does gemfibrozil.
- Omega-3 fatty acids (fish oils) in high dose (six to 12 capsules of 1 g daily or the equivalent liquid formula) are an alternative to fibrates for HTG, and can be added to fibrates or statins for TG control.
- Niacin (nicotinic acid) is poorly tolerated and is rarely used in the absence of the extended-release preparations (as in Australia).
- Bile acid resins raise TG levels and are relatively contraindicated in HTG, but can be useful when added to ezetimibe for controlling LDL-C levels in patients intolerant of statins
- Fibrates or niacin are first-line therapy for isolated low HDL-C. The flowcharts on page 40 provide algorithms based on current European guidelines for the management of HC in two situations:²
 - the patient on a statin with controlled LDL-C levels and elevated TG and/or low HDL-C levels¹

**MANAGEMENT OF HYPERCHOLESTEROLAEMIA:
HIGH-RISK INDIVIDUALS WITH ELEVATED TG AND/OR
LOW HDL-C AT LDL-C GOAL***

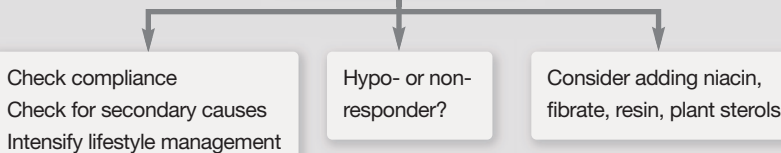
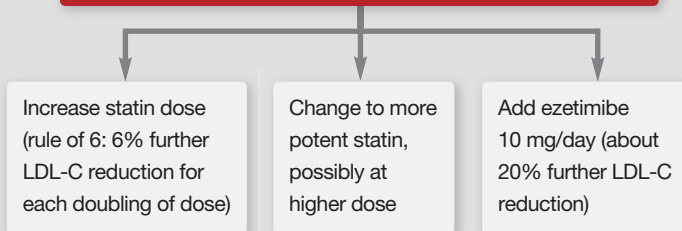
**High-risk patient at LDL-C target with
TG ≥ 1.7 mmol/L and/or HDL-C < 1.0 mmol/L†**



ABBREVIATIONS: HDL-C = HDL cholesterol; LDL-C = LDL cholesterol; TG = triglycerides.
* Adapted from Chapman MJ *et al*, 2011.²
† LDL-C goal is <2.5 mmol/L in high-risk and <2.0 mmol/L in very high risk patients.

**MANAGEMENT OF HYPERCHOLESTEROLAEMIA:
HIGH-RISK INDIVIDUALS WITH ELEVATED LDL-C,
NORMAL TG AND NORMAL HDL-C LEVELS**

**High-risk patient above LDL-C target with TG
≤ 1.7 mmol/L and/or HDL-C ≥ 1.0 mmol/L***



ABBREVIATIONS: HDL-C = HDL cholesterol; LDL-C = LDL cholesterol; TG = triglycerides.
* LDL-C goal is <2.5 mmol/L in high-risk and <2.0 mmol/L in very high risk patients.

- the patient with elevated LDL-C levels and controlled TG and HDL-C levels.

The former situation is the more common scenario as it often accompanies obesity, the metabolic syndrome and diabetes. The abnormal TG and HDL-C levels contribute to the increasingly important problem of residual risk (CVD risk occurring with statin therapy in spite of LDL-C reduction).

WHAT ARE THE TARGETS FOR TREATMENT?

Treatment targets for the various lipid disorders are listed below.

- For HC, the LDL-C target level is below 2.5 mmol/L in high-risk patients and below 2.0 mmol/L in very high-risk patients. These targets are based on epidemiological data and results of statin clinical trials.
- For severe HTG, the target TG level is below 11 mmol/L (ideally below 8 mmol/L) in order to prevent acute pancreatitis.
- For mild and moderate HTG, the target TG level is below 1.7 mmol/L on the basis of epidemiological data (no clinical trial has been conducted to validate this).
- For isolated low HDL-C, the target HDL-C level is above 1.0 mmol/L on the basis of epidemiological data (as for HTG, no clinical trial has been conducted to validate this target).

HOW IS DRUG THERAPY MONITORED, AND HOW ARE SIDE EFFECTS MANAGED?

Table 2 describes the monitoring of lipid-lowering drug therapy and the management of patients who have adverse drug reactions.

Statin-induced myalgia

Myalgia associated with statin use occurs more commonly in patients with pre-existing muscle aches and pains and after exercise. It may mask underlying

TABLE 2. LIPID-LOWERING DRUG THERAPY: MONITORING AND ADVERSE EFFECTS

Drug	Monitoring	Adverse effect and prevalence	Adverse effect management
Statins	Six to 12 weeks after initiation or dose escalation: check muscle symptoms, CK and transaminases Six to 12-monthly: check lipids and adjust dose if target levels not achieved	Myalgia (CK more than three times ULN): 1 to 17% depending on study Myositis (CK more than three times ULN): less than 1% in controlled trials Rhabdomyolysis (CK more than ten times ULN with myoglobinaemia and myoglobinuria): rare Increased transaminases (more than three times ULN): especially in early weeks of treatment; less than 1%	Myalgia and myositis: statin holiday until levels and symptoms normalise, then reintroduce lower dose or alternative statin, consider ezetimibe or other therapy; refer for chronic myalgia Rhabdomyolysis: cease statin, admit to hospital, rehydrate, monitor renal function
Niacin	As for statins Monitor glucose levels (HbA _{1c} in people with diabetes)	Increased transaminases (more than three times ULN): common in early weeks of treatment, less than 1% after 8 to 12 weeks; dose dependent Increased glucose: usually not clinically significant	Drug holiday until levels normalise then reintroduce at lower dose or consider alternative therapy (e.g. statin)
Fibrates	Monitor lipids six to 12-monthly	Generally well tolerated	–
Fish oils	As for fibrates	Platelet function inhibition rarely of clinical significance; GI disturbance <5%, dose dependent	Dose reduction
Resins	As for fibrates	Constipation; GI effects	Dose reduction
Plant sterols	As for fibrates	Well tolerated	–
Ezetimibe	As for fibrates	Well tolerated	–

ABBREVIATIONS: CK = creatine kinase; GI = gastrointestinal; ULN = upper limit of normal.

hypothyroidism (and respond to thyroid replacement) or skeletal muscle pathology (which may require biopsy to determine). Statin-induced myalgia may occur in patients with normal creatine kinase levels and therefore can be difficult to diagnose without drug withdrawal and rechallenge.

There is no validated therapy for statin-induced myalgia other than dose reduction or statin withdrawal. Anecdotal benefit has been described for several supplements and drugs (including COX-2 inhibitors, magnesium and coenzyme Q10) but convincing evidence for efficacy is lacking, as is knowledge of the mechanism(s) of statin-induced myalgia. Low levels of vitamin D may aggravate the myalgia; this aggravation may respond to the taking of vitamin D supplements and allow continuation of statin therapy.

WHICH DRUGS SHOULD BE USED IN DIABETES?

Statins are indicated for all patients with diabetes who are at high risk of CVD (those with other CVD risk factors, renal impairment or proteinuria or those aged over 60 years), with a strong evidence base for CVD benefit.

A role for fibrates has been demonstrated in trials with fenofibrate and gemfibrozil in which CVD benefit was confined to those patients with baseline low HDL-C and/or high TG levels (the so-called dyslipidaemic subgroup). The recent ACCORD and FIELD trials also showed microvascular benefits with fenofibrate (reduction in laser therapy for diabetic retinopathy, improved proteinuria, improved sensory neuropathy and reduction in leg amputations) to the extent that fenofibrate should be

considered for combination therapy with statins in all high-risk diabetes patients.

WHEN TO REFER?

Patients in whom target lipid levels are not achieved in spite of the best efforts of the general practitioner should be considered for referral, as should those with persistent side effects from therapy.

The unusual patient with premature vascular disease, a strong family history of CVD, unusual physical signs or extreme lipid levels (which usually signify genetic disorders of lipid metabolism) is another for whom referral may be appropriate. Specialised care is important for these patients, and diagnosis may require DNA analysis in specialised laboratories. Two important patient groups are those with:

- FH, who present with cholesterol levels above 7.0 mmol/L, signs of LDL-C deposition and a strong family history of premature coronary heart disease
- elevated lipoprotein(a) levels, who present with premature CVD (this condition is usually inherited).

WHEN ARE SPECIAL LIPOD TESTS REQUIRED?

The literature suggests that apoA-1 (the main protein of HDL) and apoB (the main protein of LDL) may be more predictive of CVD risk than their lipid counterparts. It suggests that a target apoB level of below 0.8 mg/dL may be more appropriate than an LDL-C target in high-risk patients.

ApoA-1 and apoB are not included in international lipid guidelines and measurement of their levels incurs additional costs. For practical purposes, measurement of the levels of LDL-C and HDL-C will suffice.

WHAT DRUGS ARE IN THE PIPELINE?

New statin combinations with ezetimibe will be available in the near future and promise to make the task of achieving LDL-C targets easier.

Extended-release niacin is unlikely to be made available in Australia in the near future. A different niacin combination available in Europe contains extended-release niacin, laropiprant (a specific prostaglandin inhibitor that reduces the skin flushing associated with niacin use) and simvastatin.

Two other novel classes of drugs are in clinical trials. The first class is the second-generation cholesterol ester transport protein (CETP) inhibitors, of which anacetrapib and dalcetrapib are the most advanced in clinical trials. These have short-term safety and efficacy in raising HDL-C levels by up to 150% or more. They are likely to be used in combination with statins.

The second class is the anti-sense RNA

compounds ('silencing RNAs'). The apoB anti-sense RNA, mipomersen, is the first of a series of drugs to target messenger RNAs, and thereby inhibit synthesis of specific proteins. Mipomersen inhibits apoB synthesis and reduces LDL-C and lipoprotein(a) levels by 20 to 80%. It is given once weekly by subcutaneous injection and is being trialled initially in patients with FH in combination with a statin.

SUMMARY

The use of statins for secondary CVD prevention is now well established and the drugs have an excellent record of safety, tolerability and clinical efficacy. We now have the ability to prevent CVD if lipid therapy is used in appropriate patients at appropriate doses, and early enough in the stage of the disease to significantly reduce atherosclerosis progression rates.

A new post-statin era of lipid therapy is on the horizon with the CETP inhibitors, drugs targeting RNA and other therapies in development. **MT**

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