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Management of dyslipidaemia

Evidence and practical recommendations

Background

Dyslipidaemia is a common condition managed in general practice.

Objective

This article reviews the evidence and gives practical advice for the management of dyslipidaemia in general practice.

Discussion

It is essential to identify people at risk of cardiovascular disease (CVD) and to instigate appropriate treatment strategies. An assessment of absolute risk is the most appropriate method of identifying those at a higher risk of CVD where CVD is not overt. People with an absolute risk of >15% of a cardiovascular event in the next 5 years should be actively treated. Drug therapy should also be considered in those estimated to be at 10–15% risk of a cardiovascular event in the next 5 years if they have additional risk factors. It is important to select an appropriate lipid lowering therapy (or combination of drugs) in order to reach lipid targets, which need to consider not just LDL-c but also HDL-c and triglycerides. Lifestyle management should underpin all lipid management strategies.

■ **The management of dyslipidaemia is a key aspect of managing cardiovascular risk. While this article focuses on lipid management, many patients have multiple risk factors that also require appropriate treatment. Dyslipidaemia should not be treated in isolation from other risk factors.**

Treating to lipid targets is a worthwhile goal that can be challenging to achieve (*Table 1*). Not all patients who require lipid lowering therapy achieve target levels in clinical practice. However, there is a well recognised continuous linear relationship between cholesterol levels and cardiovascular events.

Absolute risk

Recommendations for managing cardiovascular risk previously focused on individual risk factors. Today, however, there is an international trend to use absolute risk to best identify who should receive medical intervention and to what extent.¹ Absolute risk is the probability, expressed as a percentage, that an individual will have an adverse cardiovascular event over a specified time period, usually 5 or 10 years.

The absolute risk approach should be used to determine those individuals in the general population with the highest risk of future vascular events. Those with overt cardiovascular disease (CVD) (coronary heart disease, stroke, peripheral artery disease) do not require formal assessment as they are already at very high risk of subsequent events and require aggressive treatment.

The use of 5 year absolute risk of cardiovascular events is generally recommended (*Table 2*). There are several Framingham study data based computer and paper tools available for calculating absolute risk.^{2,3}

Some patients already have a higher absolute risk for CVD than is suggested by the use of a risk calculator. In these high risk groups, treatment can be initiated immediately; calculation of absolute risk is not required before intervention. These groups include patients with very high individual risk factors (eg. familial hypercholesterolaemia, severe hypertension) or target organ damage (eg. left ventricular hypertrophy or proteinuria).

Table 1. Recommended lipid targets in patients with CHD⁵

More emphasis on LDL-c rather than total cholesterol

- LDL-c <2.0 mmol/L
- HDL-c >1.0 mmol/L
- Triglycerides <1.5 mmol/L

Table 2. Identifying high risk individuals for medical intervention⁵

- Those with overt CVD
- Those with a calculated absolute risk of $\geq 15\%$ of a CVD event in the next 5 years
- People with a calculated absolute risk of 10–15% of a CVD event in the next 5 years when other risk factors are present such as:
 - family history of premature CHD (first degree relative who developed CHD before age 60 years)
 - metabolic syndrome
 - obesity
 - chronic kidney disease

Framingham based CVD risk assessment is also unsuitable for other high risk population groups – including Aboriginal people, Torres Strait Islanders and Pacific Islanders – because the actual risk of CVD is substantially underestimated, particularly in young adults and women.⁴ If these groups have an LDL-c >2.5 mmol/L after lifestyle intervention they should be considered for statin therapy, even without pre-existing vascular disease or diabetes.⁵ Risk estimation for those over 70 years of age is also problematic as no individuals over 70 years of age were included in the original Framingham cohort. These tools also underestimate individuals with very high isolated risk factors. For example, familial hypercholesterolaemia has specific drug therapy recommendations: statins initially for men >18 years and women >30 years of age unless pregnancy is anticipated soon.⁶ Statin therapy for severe hypercholesterolaemia has been advocated as safe even for children (>8–10 years of age).⁶

Central obesity and the metabolic syndrome

The metabolic syndrome is a cluster of risk factors that confers an increased risk of CVD. The components include hypertension, dyslipidaemia and glucose intolerance. Central (visceral) obesity is a prerequisite for diagnosis and is assessed using waist circumference.⁷

Treating to new and more aggressive targets

It is often challenging to reach lipid targets in clinical practice. The higher the baseline LDL-c, the harder it is to reach the treatment target. However, the advent of more potent therapies at well tolerated doses provides prescribers with good therapeutic

options. A large body of clinical trial data has shown that achieving lower levels of LDL-c translates to increased therapeutic benefit, particularly when lowered to <2.0 mmol/L in high risk patients.^{8–10}

National Heart Foundation treatment guidelines suggest a modest increase in the level of HDL-c is also beneficial.⁵ While raising HDL-c is desirable, it is sometimes difficult as at least 50% of the variability in HDL-c concentration is determined genetically. One major secondary intervention trial with a fibrate in subjects with metabolic syndrome type dyslipidaemia showed reductions in cardiovascular endpoints that related to improved HDL-c levels.¹¹

There is also good evidence that a high triglyceride (TG) level (>2 mmol/L) is associated with higher cardiovascular risk and should be treated, especially in the presence of low HDL-c, and when indicated in patients with combined hyperlipoproteinaemia in whom LDL-c is also raised.⁵ However, there is currently insufficient evidence to conclude that reducing TG with drugs is valuable in patients with normal LDL-c and HDL-c and no evidence of metabolic syndrome.

Management strategies based on absolute risk

Lifestyle

Management of all patients – including those at high risk – should be underpinned by lifestyle modification (*Table 3*).⁵ Lifestyle changes can also improve the efficacy of medication in treating to target. The actual management of risk factors will depend on which ones are present. Lifestyle management is likely to require ongoing support from general practitioners to be sustainable.⁵

Drug therapy

A large body of evidence supports the use of lipid modifying therapy for reducing the risk of CVD, primarily via a reduction in LDL-c (*Table 4*).⁵ The most convincing data is for statins and these agents should generally be used first line for cardiovascular protection. Specific lipid abnormalities, such as hypertriglyceridaemia, may require different lipid lowering agents.

Lipid modifying therapy is indicated for those individuals who have a >15% absolute risk of a cardiovascular event in the next 5 years.⁵ Drug therapy should also be considered in those estimated to be at 10–15% risk of a cardiovascular event in the next 5 years if they have additional risk factors. (PBS criteria for eligibility for subsidy should be taken into account, particularly for those assessed to be in the lower risk group described above.)

General practitioners are advised to select therapy that will deliver an effective reduction in LDL-c at the approved starting dose and to titrate as required. Dose titration and/or a change in medication may be required to reach target lipid levels. Additional treatment will be required if LDL-c targets are not met at the maximal tolerated dose of statin, or if HDL-c is low or TG is high, despite the LDL-c being at target. Lifestyle and adherence should also be reassessed before deciding to add additional medications.

Table 3. Lifestyle interventions

- It is most appropriate to start with smoking cessation in those who smoke. Brief advice from a GP is a cost effective strategy for assisting patients to quit smoking¹²
- Nutrition – referral to a dietician should be considered or discuss cholesterol lowering diet. Complementary options to reduce cholesterol include plant sterols, psyllium, and policosanol
- Moderate alcohol intake has been associated with raised HDL-c and may confer some degree of cardioprotection.¹⁷ However, this evidence is from observational studies and therefore is not recommended as an intervention
- Physical activity and weight loss are particularly effective in people with metabolic syndrome where low HDL-c is part of a dyslipidaemic pattern. The degree of improvement in HDL-c is proportional to the quantum of vigorous exercise.¹⁸ Referral to a dietician and/or exercise physiologist is recommended

Once at target, all patients at high, risk should have their lipid levels re-measured – ideally every 6 months, but no less than every 12 months – as part of the ongoing assessment of adherence and management of overall cardiovascular risk (*Figure 1*).

Secondary prevention

Patients who have CVD are considered at very high absolute risk and should be treated aggressively to reach target lipid levels. Diagnosis of diabetes implies high absolute risk, especially when patients have other CVD risk factors.⁵ In general practice it is particularly important to prevent patients with overt CVD from drifting away from evidence based therapies. It is also important to recognise CVD incidents. Be particularly vigilant in those with diabetes ('silent' AMIs) or those at high risk for peripheral arterial disease. The latter are likely to have generalised vascular disease and are at higher risk of CVD morbidity and mortality than those with overt coronary artery disease or cerebrovascular disease.¹²

Statins have been shown to be beneficial in all patients with vascular changes regardless of baseline LDL-c level. This applies to older and younger age groups and to those with diabetes.^{5,9}

Importance of HDL-c

Low HDL-c is a recognised coronary heart disease risk factor, and a moderate rise in HDL-c is desirable (*Table 5*). Many people with low HDL-c have metabolic syndrome, so it is important to manage all risk factors appropriately.

Raising HDL-c to >1.0 mmol/L has probable therapeutic benefits, although pivotal intervention trials have not yet demonstrated whether improvements in HDL-c translate to meaningful reductions in clinical events and improved clinical outcomes. A recent post-hoc analysis of data from four prospective randomised trials, involving 1455 subjects with angiographic coronary disease, showed that

Table 4. Lipid lowering agents

- Statins – considered the agents of choice for reducing the level of LDL-c, and have modest HDL-c-raising and triglyceride lowering effects. Recommended for all patients with clinical evidence of vascular disease (coronary heart disease, stroke, peripheral artery disease) regardless of LDL-c level; should be commenced in hospital for those admitted with incident CHD events⁵
- Fibrates – patients with type 2 diabetes or the metabolic syndrome with elevated triglycerides and/or low HDL-c may benefit from fibrate therapy alone, or in combination with a statin, especially when LDL-c is also raised. The effect of fenofibrate on HDL-c may be gradual and extend over 6 months. Gemfibrozil interacts with statins and should not be used in combination⁵
- Ezetimibe – member of a new class of drugs that inhibit the absorption of cholesterol by the intestine; has a synergistic effect when combined with statins; shown to reduce the concentration of LDL-c by 15–20% when given as monotherapy and up to 25% when added to a statin⁵
- Nicotinic acid – an effective drug in raising HDL-c and lowering triglycerides while also reducing LDL-c. However it is associated with flushing despite prophylactic aspirin, which inhibits its use in most patients. Newer forms, with reduced flushing effects, are under development^{19, 20}
- Fish oils – contain highly polyunsaturated long chain n-3 fatty acids which can lower TG concentrations. A 50% reduction in TG concentrations has been shown with a daily intake of 2–5 g of n-3 fatty acids (equivalent to 6–15 g of fish oil). Small and variable changes in LDL-c and HDL-c levels have also been demonstrated²¹

statin therapy for 18–24 months was associated with regression of coronary atherosclerosis (assessed via serial intravascular ultrasound) when LDL-c was substantially reduced and HDL-c was increased by more than 7.5%.¹³ The researchers suggest that statin benefits are derived from both reductions in atherogenic lipoprotein levels and increases in HDL-c.

While all statins have a modest effect on HDL-c, rosuvastatin appears to be the most potent of its class in terms of raising HDL-c.¹⁴ It is important to note that the magnitude of change in HDL-c may be overshadowed by laboratory variability and clinicians should consider this when assessing response to treatment.

Drug and lifestyle regimens that achieve the greatest reduction in LDL-c, coupled with a modest yet significant increase in HDL-c, will confer significant benefit to the majority of patients requiring treatment for dyslipidaemia in general practice.

Relationship between HDL-c and LDL-c

There is currently no solid evidence to suggest that high HDL-c will neutralise high levels of LDL-c. In some people, the function of HDL-c is inadequate and thus high levels may not confer

cardioprotection. This is particularly true in people with existing vascular disease where a high HDL-c level should not be assumed to be cardioprotective.¹⁵ Thus, while it is desirable to have raised HDL-c, it should not detract from treating high LDL-c levels to target. Patients with existing CVD need appropriate and aggressive treatment irrespective of HDL-c levels. Increasing physical activity and reducing weight (in overweight individuals) may increase HDL-c.¹⁶

Laboratory testing

The decision to initiate drug treatment should not be made on the basis of a single measurement. It is important to ask specifically for HDL-c to be measured, as it is not a routine part of lipid testing.

Safety

In general, current lipid modifying treatments are well tolerated with a good safety profile. Liver function tests (LFTs) should be undertaken

Figure 1. Management of dyslipidaemia: a population based approach in people with no evidence of vascular disease

Measure fasting cholesterol every 5 years in adults aged >45 years (primary prevention)

Assess other cardiovascular risk factors



If dyslipidaemia:

- remeasure, including full lipid profile
- assess absolute risk
- provide lifestyle intervention (smoking cessation, dietary changes, increased physical activity)



Re-assess 6–8 weeks

If all lipid values at target or above target and low/moderate absolute risk:

- re-assess (ideally 3–6 months)

If not at target and absolute risk is high:

- commence statin* (discuss side effects, targets, evidence for prevention of events)
- measure pre-treatment LFTs
- re-assess and reinforce lifestyle changes



- Review 4–6 weeks

- Assess presence of side effects (LFTs, CK if myalgia); re-assess and reinforce lifestyle changes

If at/near target LDL-c but TG and HDL-c remain abnormal and absolute risk is high:

- consider adding fibrate and fish oil

Targets reached:

- review 3 months then every 6 months thereafter

Targets not reached:

- review lifestyle, adherence
- titrate statin dose
- consider fibrate if TG, HDL-c remain abnormal



Review 4–6 weeks

Targets reached:

- review 6–12 months

Targets not reached:

- step titrate statin dose or switch to another statin. Consider adding a second or third agent



Review 4–6 weeks

* The starting dose of statin therapy depends on baseline cholesterol. Start with the dose most likely to achieve LDL-c reductions and treatment targets with minimal side effects. Consult relevant prescribing information for specific details and refer to PBS criteria

at the start of drug therapy and should be checked after initiation to compare blood levels with baseline. Minor abnormalities are common in patients with diabetes and the metabolic syndrome and relate to hepatic steatosis (fatty liver). They are not a contraindication to using lipid lowering therapy. It is recommended that creatine kinase (CK) be measured at commencement of statin therapy. Ongoing monitoring of CK is not recommended, although particular caution and monitoring is appropriate for patients with predisposing factors for myopathy, eg. patients taking gemfibrozil, colchicine or cimetidine, the elderly, those with kidney dysfunction and patients who report muscle symptoms.⁵

Statins are occasionally associated with myalgia. This is usually tolerable and often subsides after a few weeks of therapy, but CK should be checked to exclude myopathy. Rarely muscle pain is associated with a CK rise over 3 times the upper limit of normal and this suggests myopathy, a potentially serious condition. In these cases the statin should be stopped and the CK retested. Re-introduction of statin therapy should be undertaken with extreme caution and preferably with specialist supervision. It is important to be aware that minor elevations of CK without muscle pain are common and are usually of no significance. The risk of myopathy and its most extreme form – the life threatening rhabdomyolysis – is increased with statin/fibrate combination therapy, particularly with gemfibrozil but more rarely with fenofibrate. On this basis, fenofibrate is the fibrate of choice if combination statin/fibrate therapy is required.

The incidence of statin related elevation of hepatic enzymes in clinical trials has ranged from 0.0–0.8% and is dose dependent.⁵ Modest elevations of alanine transferase (ALT) are common and usually settle on cessation or lowering of dose. A three-fold rise in AST or ALT is a signal to stop statin treatment. Repeat LFT measurements are unnecessary if they are normal at first post-treatment measurement and the patient remains well.

Ezetimibe appears to be well tolerated, however further long term safety data is required, particularly in relation its use in combination with statin therapy.⁵ Ezetimibe is prescribed either when maximal statin therapy has not resulted in appropriate

Table 5. Cholesterol: its fractions and associated risks

- Achieving low levels of LDL-c translates to increased therapeutic benefit
- Low HDL-c should be treated with the aim of reaching at least 1 mmol/L; however, even if HDL-c is above this level the appropriate treatment of LDL-c and other risk factors should not be neglected
- The lipoprotein phenotype comprising low HDL-c and high TG confers at least a similar risk to that of a high LDL-c concentration²²
- Isolated raised TG in the presence of normal LDL-c and normal HDL-c requires lifestyle intervention. People with poorly controlled diabetes often have raised TG that responds to optimising glucose metabolism

Table 6. Strategies to improve adherence

- Emphasise that this is lifelong therapy for most (unless there are profound and sustained lifestyle changes in those without overt CVD or in those with residual high absolute risk, which may warrant a trial off medication)
- Let patients know that the longer they stay on therapy, the greater the likely benefit
- Establish and share clear goals of treatment and target levels
- Provide feedback about changes in lipid levels, blood pressure, absolute risk, waist circumference
- Emphasise diet and lifestyle modification throughout
- Provide resources
- Appreciate the cost to the patient of multiple treatments

LDL-c lowering or the patient is intolerant to statins. The currently available form of nicotinic acid is poorly tolerated and best prescribed by specialist clinics.

Patients need to understand why they need long term medication for a condition with no symptoms. Because there are no symptoms, the presence of side effects is a major reason for nonadherence. Education should equate management of 'good and bad cholesterol' for prevention of cardiovascular events. Adherence is the key to success (*Table 6*).

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