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Lipid lowering therapy for adults with diabetes

The number of adults in Australia with diabetes has trebled over the past 2 decades.[1] Diabetes confers an increased risk of cardiovascular disease (CVD) and CVD is the leading cause of morbidity and mortality in patients with diabetes.[2–5] Hyperlipidaemia occurs commonly in people with diabetes and is an independent CVD risk factor.[3,5,6]

Early, intensive, long term interventions targeting multiple risk factors for CVD in people with diabetes significantly reduces the risk of macrovascular (stroke, myocardiol infarction, peripheral vascular disease) and microvascular (nephropathy, neuropathy, retinopathy) complications. This was recently demonstrated in the Steno-2 study,[7] which targeted hypertension, aspirin therapy, hyperglycaemia, smoking, microalbuminuria, hyperlipidaemia, and sedentary lifestyle in patients with diabetes and microalbuminuria. The study reported a 50% reduction in the number of micro- and macro-vascular events over a period of 7.8 years (absolute risk reduction: 20–32%, number needed to treat: 3–5).[7]

Screening and monitoring of blood lipids

Practice point: Current guidelines for the management of diabetes recommend that patients are tested for blood lipids at the time of diagnosis and then at least once every 12 months.[3,4,6] More frequent testing may be required if a patient is being actively treated for dyslipidaemia.

Targets

National and international guidelines advocate LDL cholesterol as the primary target of therapy.[3,4] Target lipid levels for patients with diabetes are:

- LDL cholesterol <2.5 mmol/L (some guidelines[5] suggest lower targets for patients with existing CVD)
- total cholesterol <4.0 mmol/L
- HDL cholesterol >1.0 mmol/L
- triglycerides <1.5 mmol/L.[4,6]

Practice point: Failure to reach targets should not be perceived as failure of therapy, as any reduction toward target is likely to be beneficial.

Diet and lifestyle

Lifestyle modification focusing on fat intake, weight loss (if indicated) and increased physical activity has been shown to improve the lipid profile in patients with diabetes.[3] Lifestyle interventions including dietary modification, should support lipid management in all people.[4] Diet should be low in total fat, cholesterol, saturated fat and transunsaturated fat.[3,6] Pharmacological treatment is indicated if there is inadequate response to diet, lifestyle modifications and improved glucose control.[3]

Practice point: In general, dietary and other lifestyle measures should be tried before pharmacotherapy. However, in high risk patients pharmacological therapy should be initiated at the same time as lifestyle interventions are commenced.

Glycaemic control

Poor glycaemic control with persistent hyperglycaemia can cause hypertriglyceridaemia. Triglyceride levels may fall to acceptable levels with adequate control of weight, diet and glycaemia. Cholesterol levels can also fall with weight reduction and metabolic control of diabetes.[3,6]

Choice of lipid lowering drug

Practice point: Mixed hyperlipidaemia (both cholesterol and triglycerides elevated) should be treated with a statin or fibrate (fenofibrate or gemfibrozil) first, depending on the dominant abnormality.[6,8]

Statins

Statins (HMG-CoA reductase inhibitors: atorvastatin, fluvastatin, pravastatin, rosuvastatin, simvastatin) are considered first

line therapy where there is elevated total cholesterol or LDL cholesterol.[3–5,8–11] They have modest triglyceride lowering and HDL raising effects.[4,8]

The average effect of statins on cholesterol levels is to reduce LDL by 30–50%, reduce triglycerides by 5–15%, and increase HDL by 5%.[8] While reduction in adverse cardiovascular events has been demonstrated with several statins, caution should be exercised in assuming a class effect.

The likelihood of adverse effects with statins, including serious muscular reactions, is dose related and increases with age and renal impairment.[8] Coexisting conditions such as diabetes, hepatic disease, untreated hypothyroidism, surgery and intercurrent illness may also increase risk, as will interactions with grapefruit juice and certain drugs, especially fibrates.[8,12]

Dosing

Practice point: Dose increases are usually made at intervals of at least 4 weeks. More than 80% of the LDL lowering effect of a statin is achieved with 50% of maximum dose.

Practice point: Test liver function and creatine kinase (CK) before commencement of therapy,[8] then at least once about 4–8 weeks after starting therapy.[10] Test after dose increases and/or when indicated clinically.[8]

Practice point: Routine monitoring of CK is not necessary, but caution and monitoring is appropriate for patients of advanced age, with impaired renal function, or those complaining of muscle weakness or pain.[4] Generally, statin therapy should be suspended for the duration of treatment with macrolide antibiotics.[4]

The incidence of statin related elevation of hepatic enzymes in clinical trials ranges from 0.0–0.8% and is dose dependent. Modest elevations of alanine aminotransferase are common and usually settle on cessation or lowering of dose.[4]

Practice point: Avoid stopping statins if symptoms of an acute coronary syndrome are present. Stopping is associated with an increased rate of cardiac events, especially in the first week after ceasing.[8]

Stop statins if:

- transaminase concentrations are persistently elevated to more than three times the upper limit of normal
- CK concentration is more than 10 times the upper limit of normal
- there is persistent unexplained muscle pain, even if CK is normal.[8]

Fibrates

Fibrates (fenofibrate, gemfibrozil) effectively reduce cardiovascular risk profile in patients with diabetes.[4] They are the first choice in marked hypertriglyceridaemia and low HDL. They reduce LDL by 5–15%, triglycerides by 25–80%, and increase HDL by 10–30%.[8,10,11]

Practice point: Choose gemfibrozil if triglyceride is >4.0 mmol/L, or for mild triglyceride elevation (2–4 mmol/L) with low HDL (<1 mmol/L).[10]

Nicotinic acid

Nicotinic acid has good LDL and triglyceride lowering effects and produces a marked increase in HDL (typically reduces LDL by 15–30%, triglycerides by 25–40% and increases HDL by 20–35%). Its use is limited by common adverse events such as flushing, nausea, vomiting, diarrhoea, and itch.[8]

Bile acid resins

Bile acid resins (cholestyramine, colestipol) are effective and safe for isolated hypercholesterolaemia. Low doses can be used with statins[8,10,11] to increase the lowering of LDL by an additional 5–10%.[11] Caution is required if triglycerides are >3 mmoL/L as resins may exacerbate hypertriglyceridaemia.[8,10]

Practice point: Bile acid resins may impair absorption of oral antihyperglycaemic agents, so the two classes of medication should be taken at least 1.5 hours apart.[6] They can also impair the absorption of other medications including statins, thyroxine and fat soluble vitamins. These problems may be avoided by taking other medicines at least 1 hour before, or 4–6 hours after, the bile acid resin.[8] Consider supplements of vitamin A, D, E and K for patients taking high doses of resins over a long period of time.[8]

Ezetimibe

Ezetimibe inhibits the absorption of cholesterol by the intestine and reduces LDL cholesterol by about 18% in short term studies.[4,8] When added to a statin, it can increase the LDL lowering effect by up to 20%,[4,8,9] but is associated with an increase in adverse effects (myalgia and increased liver enzymes).[8] There are no long term outcome studies on the efficacy and tolerability of ezetimibe.[8] If a patient requires ezetimibe to be added to a statin, a combined product is available.

Fish oil

Fish oil containing omega-3 fatty acids in doses of 2–5 g/day are effective in lowering triglycerides.[6,8] They may be a useful second line therapy for hypertriglyceridaemia or mixed hyperlipidaemia in combination with statins, with close monitoring of glycaemic control.[6,8–11] Fish oil supplements appear to have few adverse effects, although high doses may increase bleeding time. They may be useful agents if fibrates and nicotinic acid are not tolerated.

A lack of standardisation in fish oil preparations means that consumers should be advised to check labelling to ensure an adequate

dose of omega-3 fatty acids. For example, many formulations contain 300 mg omega-3 fatty acids (180 mg eicosapentaenoic acid and 120 mg docosahexaenoic acid). A patient would need to take more than 6 capsules per day of this formulation to achieve a daily dose of 2 g of omega-3 fatty acids.

Refractory mixed hyperlipidaemia

Mixed hyperlipidaemia is common in diabetes. For resistant cases, treatment with both a statin and fibrate may be required. This combination is well known to increase the risk of rhabdomyolysis and should only be undertaken with specialist guidance.[6,8,10,11] The risk of myopathy is lower – but not absent – with the combination of fenofibrate and a statin than with the combination of gemfibrozil and a statin.[3,4] Combining a statin or a fibrate with ezetimibe or a bile acid resin is an alternative.[6]

PBS subsidy

The Pharmaceutical Benefits Schedule (PBS)[13] states that patients in very high CVD risk categories may commence drug therapy with statins or fibrates immediately after a diagnosis of hyperlipidaemia (ie. simultaneously with an appropriate diet). For all other patients, dietary therapy should be trialled for at least 6 weeks before initiation of drug therapy. Patients identified as being in one of the following very high risk categories may commence drug therapy with statins or fibrates at any cholesterol level:

- coronary heart disease which has become symptomatic
- cerebrovascular disease which has become symptomatic
- peripheral vascular disease which has become symptomatic
- diabetes mellitus with microalbuminuria (defined as urinary albumin excretion rate of >20 µg/min or urinary albumin to creatinine ratio of >2.5 for males, >3.5 for females)
- diabetes mellitus in Aboriginal or Torres Strait Islander patients
- diabetes mellitus in patients aged over 60 years
- family history of coronary heart disease which has become symptomatic before the age of 55 years in two or more first degree relatives
- family history of coronary heart disease which has become symptomatic before the age of 45 years in one or more first degree relatives.

For patients with diabetes mellitus not otherwise included, the criteria for PBS subsidy of lipid lowering therapy (postdietary trial) is a total cholesterol >5.5 mmol/L.

Resources

- For further drug information including precautions, adverse effects, interactions and contraindications, please refer to the Australian Medicines Handbook 2007, and approved product information
- Further information on lipid lowering therapy may be found at the NPS website at www.nps.org.au/site.php?content=/html/ppr.php&ppr=/resources/Prescribing_Practice_Reviews/ppr17 which includes some notes on using medical software to review prescribing
- A commonly used CVD risk calculator is the New Zealand Risk Calculator, available from the Australian Heart Foundation at www.heartfoundation.com.au/downloads/hypertension_management_guide_2004.pdf.

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