Managing lipid abnormalities in type 2 diabetes

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Many people with diabetes can benefit from treatment to reduce their cardiovascular risk, including lipid-lowering medications. Important questions include when and how to assess cardiovascular risk in people with diabetes, what diet to recommend, when to begin lipid-lowering therapy, and how to manage different types of lipid abnormality.

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KEY POINTS

- Lipid abnormalities are present in over 60% of people with diabetes.
- The decision to initiate lipid-lowering treatment should be based on absolute cardiovascular risk.
- Calculation of cardiovascular risk is appropriate in most people with diabetes.
- Statins are first-line therapy for prevention of cardiovascular disease in people with diabetes.
- Elevated triglyceride levels are common in people with diabetes and treatment may be beneficial in some patients.

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Type 2 diabetes is associated with significantly increased cardiovascular (CV) risk.[1] Multiple metabolic abnormalities associated with diabetes contribute to the increased CV risk, and conventional risk factors are also prevalent in people with diabetes. The Australian AusDiab study found that 69% of people with diabetes had hypertension and more than 60% had lipid abnormalities.[2] This review will focus on the management of lipid abnormalities and use of lipid-lowering medications in patients with type 2 diabetes, but it is essential that all CV risk factors are well managed. There is evidence that multiple risk factor intervention leads to large reductions in CV risk.[3]

The characteristic lipid abnormality that is associated with type 2 diabetes is a combination of an elevated level of triglyceride and a low level of HDL cholesterol (HDL-C), sometimes termed 'diabetic dyslipidaemia'.[4] However, elevated levels of LDL cholesterol (LDL-C) are also common, and there is overwhelming evidence that statin therapy to lower LDL-C effectively reduces CV risk in people with diabetes.[4] Statins appear to be effective even in people with diabetes who might be regarded as having 'normal' cholesterol levels.[5] For this reason, guidelines such as those of the Australian National Vascular Disease Prevention Alliance (NVDPA) now recommend that a decision to initiate treatment is based on absolute CV risk rather than any specific lipid level.[6] The exception is the management of people with elevated triglyceride levels, which is based on numerical values, as discussed below.

An approach to initiation of lipid-lowering therapy in patients with type 2 diabetes is outline in the Flowchart.

When and how should we assess cardiovascular risk in people with diabetes?

Australian guidelines recommend the assessment of absolute CV risk for most people with diabetes.[6] However, this has been controversial. A prominent study published in 1998 suggested that people with diabetes but no prior CV disease had the same absolute risk as nondiabetic patients who had experienced a myocardial infarction.[7] This led to the suggestion that all people with diabetes be treated aggressively with statin therapy. However, more recent and much larger studies dispute this, suggesting that not all people with diabetes are at high CV risk, and therefore CV risk assessment is appropriate.[8,9]

It is important to note that assessment of absolute CV risk is not appropriate for individuals whose CV risk is already known to be high. This includes people with existing CV disease and those with other conditions that place them at high risk (Box 1).[6] Although the Australian NVDPA guidelines state that all people with diabetes over the age of 60 years are at high risk, this was not the finding of a recent large study in the UK.[6,9] The author believes it is reasonable to conduct an assessment of CV risk in older people with diabetes.

A number of risk assessment tools are available and are often built into general practice software. Most of these, such as the NVDPA risk calculator, are based on the Framingham cohort and provide a reasonable assessment of risk in people with diabetes aged 45 years or older, or 35 years or older for Aboriginal or Torres Strait Islander people (available online at: www.cvdcheck.org.au).[6,10] Microvascular complications also predict increased CV risk; the presence of retinopathy, neuropathy or nephropathy each increases risk by approximately 35 to 40%, and the presence of all three effectively doubles CV risk.[9] This is not taken into account in the CV risk calculator, so a reasonable approach would be to adjust risk upwards based on the presence of microvascular complications. When using absolute risk to guide treatment, Australian guidelines define the risk of a CV event in the next five years as low (less than 10%), moderate (10 to 15%) or high (more than 15%).[6]

What is the best diet for diabetic dyslipidaemia?

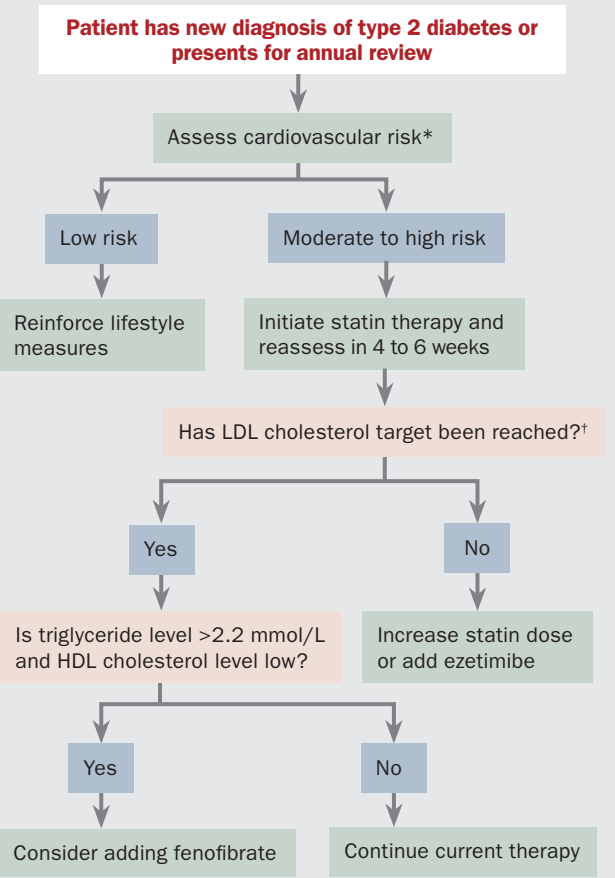
Anyone reading the lay press recently might be confused by conflicting messages regarding the correct amount of fat, carbohydrate and protein to recommend to our patients with diabetes. In the past, a low-fat diet was recommended, but many studies suggest that a diet lower in carbohydrate and higher in 'healthy' fats, particularly monounsaturated fats, produces better results.[11] Two recent meta-analyses produced a fairly consistent message: reducing carbohydrate and increasing fat caused reductions in triglyceride levels and increases in HDL-C levels.[11,12] The 'Mediterranean' diet had similar beneficial results. High-protein diets, although improving glycated haemoglobin (HbA_{1c}) level, had no effect on lipid levels. Interestingly, none of the dietary interventions significantly reduced LDL-C level.

Ideally, all patients with diabetic dyslipidaemia should be referred to a dietitian. In areas where this is not possible, GPs should evaluate the patient's diet and if it is suboptimal, advice to moderately decrease carbohydrate and increase monounsaturated fats seems appropriate.

When should we commence lipid-lowering therapy in people with diabetes?

In patients with diabetes and moderate to high CV risk, initiation of statin therapy is recommended. Because evidence suggests

AN APPROACH TO INITIATING LIPID-LOWERING THERAPY IN PATIENTS WITH TYPE 2 DIABETES



* Do not assess cardiovascular risk if the patient is already clinically at high risk (see Box 1).

† LDL-C targets vary according to the patient's cardiovascular risk:
- high risk = <1.8 mmol/L and 50% reduction
- moderate risk = <2.0 mmol/L and 30% reduction.

1. CONDITIONS REPRESENTING HIGH CARDIOVASCULAR RISK*

- Existing vascular disease: coronary, cerebral or peripheral vascular disease
- Microalbuminuria: urinary albumin/creatinine ratio more than 2.5 mg/mmol (males) or 3.5 mg/mmol (females)
- Moderate or severe chronic kidney disease: persistent proteinuria or estimated glomerular filtration rate less than 45 mL/min/1.73m^2
- Severe hypertension: systolic blood pressure at or above 180 mmHg or higher or diastolic blood pressure at or above 110 mmHg
- Very high total cholesterol level: more than 7.5 mmol/L
- A previous diagnosis of familial hypercholesterolaemia

* Risk calculation is not necessary in patients with these features.

Adapted from *Guidelines for the Management of Absolute Cardiovascular Disease Risk*, 2012.[6]

that the lower the LDL-C level achieved, the greater the reduction in CV risk, many guidelines set target LDL-C levels, with lower targets recommended for the highest-risk patients.[13] Although some guidelines simply recommend the maximum tolerated dose of statin for highest-risk patients, some patients may not need the maximum dose because they respond well to lower doses.[14] Australian guidelines recommend an LDL-C target of less than 2.0 mmol/L in moderate-risk patients and less than 1.8 mmol/L in high-risk patients.[6,13]

In addition, it is also useful to recommend that a patient achieves a certain percentage reduction in LDL-C level. International guidelines suggest an LDL-C reduction of 30% in moderate-risk patients and at least 50% in high-risk patients.[14,15] This will often require higher doses of the more potent statins, atorvastatin and rosuvastatin.[16] The author recommends that these statins should be the first choice for most people with diabetes. The expected reductions in LDL-C level with different doses of these statins are shown in the Table.[16] Two cases that illustrate the principles of prescribing for patients with type 2 diabetes and moderate to high CV risk are described in Box 2.

TABLE. EXPECTED PERCENTAGE REDUCTIONS IN LDL CHOLESTEROL WITH POTENT STATINS AVAILABLE IN AUSTRALIA*

Statin	Dose (mg)	Average LDL cholesterol reduction (%)†
Atorvastatin	10	35.5
	20	41.4
	40	46.2
	80	50.2
Rosuvastatin	10	44.1
	20	49.5
	40	54.7

* Adapted from Nicholls et al. Am J Cardiol 2010; 105: 69-76.[16]
† Note that these are expected average reductions. Individual patient responses will vary.

When should we use combination lipid-lowering therapy?

Some patients may not tolerate higher doses of statins and some, particularly those with very high LDL-C levels, may not reach the target with statin monotherapy. The cholesterol absorption inhibitor ezetimibe has been shown to reduce LDL-C levels by around 20% and is effective when used in addition to a statin.[17] Adding ezetimibe to a statin has been shown to be considerably more effective in reducing LDL-C levels than doubling the dose of the statin.[17] In a recent study of more than 18,000 people (5000 with diabetes) with acute coronary syndromes, the addition of ezetimibe to statin therapy reduced CV event rates and, interestingly, the benefit in those with diabetes was considerably greater than in those without (absolute risk reduction 14% *vs* 6%).[18]

If the LDL-C level is not at target and ezetimibe is not tolerated then the bile acid-binding resin cholestyramine can be added, although gastrointestinal side effects often limit its tolerability. Nicotinic acid also reduces LDL-C levels when added to statins, but two recent large studies showed no CV benefit and it is therefore no longer recommended.[4]

Recently, a new class of agents, inhibitors of proprotein convertase subtilisin-kexin type 9 (PCSK9) has become available. PCSK9 is a protein that binds to LDL receptors, marking them for degradation and decreasing their number, effectively reducing the clearance of LDL-C. Two monoclonal antibodies, evolocumab and alirocumab, have been approved for use in Australia and were reviewed in the October 2016 issue of *Medicine Today*.[19] These agents have been shown to reduce LDL-C levels by 60% or more and appear to be effective in people with diabetes.[20] The current cost of PCSK9 inhibitor therapy is very high (approximately $10,000 annually). At the time of writing, only evolocumab is available through the PBS, and only for patients with familial homozygous hypercholesterolaemia.

How do we manage patients who cannot tolerate statins?

The most common symptom of statin intolerance is myalgias – muscle pains without an increase in creatine kinase (CK) level. True myositis (myalgias with an elevated CK level) is rare with statin therapy, but myalgias may be reported by 15 to 20% of patients in clinical practice.[21] Risk factors include hypothyroidism, low vitamin D levels, heavy exercise and low body mass index.[22]

Because myalgia is a common and non-specific symptom, it may be mistakenly attributed to statin therapy, possibly depriving the patient of much needed treatment. This was examined in a small study where statin-intolerant patients were given either a statin or placebo, and no differences were observed in the myalgia score when patients were taking the statin compared with those taking the placebo.[21]

2. CLINICAL CASES ILLUSTRATING STATIN PRESCRIBING IN PATIENTS WITH TYPE 2 DIABETES

Case 1. A 53-year-old man with few risk factors

Mr ST, aged 53 years, was diagnosed with type 2 diabetes eight years ago. He is a nonsmoker, with no family history of cardiovascular disease. His blood pressure is 136/78 mmHg and his glycated haemoglobin (HbA_{1c}) level is 54 mmol/mol (7.1%). He has no microalbuminuria, and his estimated glomerular filtration rate (eGFR) is over 90 mL/min/1.73 m^2. His lipid levels are: total cholesterol 5.3 mmol/L; triglycerides 2.1 mmol/L; HDL cholesterol (HDL-C) 0.8 mmol/L; and LDL cholesterol (LDL-C) 3.5 mmol/L.

Discussion: Mr ST's cardiovascular risk from the NVDPA calculator is 14% (moderate risk), and therefore a statin should be commenced. As the LDL-C target is less than 2.0 mmol/L, a reduction of just over 40% is required. From the Table, a starting dose of 20 mg of atorvastatin or 10 mg of rosuvastatin would be reasonable.

Case 2. A 63-year-old woman with a high prior risk

Mrs AJ, aged 63 years, has a 14-year history of type 2 diabetes. She is a nonsmoker, with no family history of cardiovascular disease. Her blood pressure is 139/72 mmHg and HbA_{1c} is 57 mmol/mol (7.4%). She has persistent microalbuminuria with an eGFR of 46 mL/min/1.73m^2. She has undergone previous laser treatment for proliferative retinopathy. Her lipid levels are: total cholesterol 4.7 mmol/L; triglycerides 1.9 mmol/L; HDL-C 1.1 mmol/L; and LDL-C 2.7 mmol/L.

Discussion: Mrs AJ has microalbuminuria, putting her at high cardiovascular risk, which is further increased by the presence of retinopathy. Therefore formal calculation of risk is not required.

A statin should be commenced. The LDL-C target is less than 1.8 mmol/L, but a 50% reduction is also recommended. From the Table, a starting dose of at least 40 mg atorvastatin or 20 mg rosuvastatin would be reasonable, but upwards titration may be required.

For this reason, patients with myalgias but no elevation of CK level should be rechallenged to assess whether the myalgias recur when statin therapy is resumed. If symptoms do recur then strategies that may be useful include using a lower dose of the same or a different statin, possibly with the addition of ezetimibe, or use of a potent statin such as rosuvastatin 10 mg once or twice per week.[22]

Should we treat elevated triglyceride levels?

Triglyceride levels are often elevated in people with diabetes, particularly if glycaemic control is poor.[4] There is evidence that mild to moderate elevations of triglyceride level (2 to 10 mmol/L) are associated with an increased risk of CV disease even when LDL-C is controlled to target levels.[15,23] The combination of a moderately elevated triglyceride level (2.3 mmol/L or higher) and a low HDL-C level results in a 70% increase in CV risk and occurs in approximately 20% of people with type 2 diabetes.[24] These individuals tend to have LDL particles that are smaller and denser than normal and more susceptible to oxidative stress, with a tendency to be trapped in the arterial wall, leading to atherosclerosis.[4]

A frequent cause of an elevated triglyceride level is poor glycaemic control, which should be addressed. Dietary advice is important as weight loss frequently reduces triglyceride levels. Factors that can increase triglyceride levels include heavy alcohol intake, hypothyroidism and occasionally oestrogen therapy. Even in patients with dyslipidaemia, the primary treatment goal should be to reduce LDL-C levels to the recommended target level with statin therapy. Statins can reduce triglyceride levels by up to 25%, and mild elevations may be normalised without the need for additional therapy.[16]

A number of drugs are available to reduce triglyceride levels, including fibrates, omega-3 fatty acids (fish oil) and nicotinic acid. No data are available on the effect of omega-3 fatty acids on CV risk in patients with diabetes, and nicotinic acid has not been shown to reduce CV events, so neither are currently recommended. Fenofibrate has been shown to reduce CV events in two large trials of patients with diabetes, in Australia and the USA.[24,25] The effect was seen specifically in a subgroup of patients with elevated triglyceride levels (2.3 mmol/L or higher) and low HDL-C levels. In the Australian study involving more than 9000 patients with diabetes, the group with dyslipidaemia treated with fenofibrate had a 26% reduction in CV events over five years.[24] The large US trial had a similar finding when fenofibrate was added to statin therapy.[25]

Because of the strong evidence supporting the use of statins in people with diabetes who are at high CV risk, statin therapy should be first-line treatment even in patients with dyslipidaemia. However, if the LDL-C level is at target and the triglyceride level is elevated, particularly in the setting of a low HDL-C level, then adding fenofibrate should be considered.

Patients with a very high triglyceride level (over 10 mmol/L) often have an underlying genetic lipid disorder and require a different approach. Here the concern is the risk of pancreatitis, which increases as triglyceride levels rise.[15] Management can be difficult and specialist referral may be required, but initially the GP should review glycaemic control and exclude other causes of high triglyceride levels, as mentioned above. Fenofibrate should be initiated, and high doses (at least 2 g daily) of omega-3 fatty acids may be useful (six or more standard [1000 mg] fish oil capsules, each containing around 300 mg omega-3 fatty acids).[26]

Can we do anything for low HDL cholesterol levels?

Low levels of HDL-C are common in people with diabetes and well known to be associated with an increased risk of CV disease. HDL is involved in reverse cholesterol transport, accepting cholesterol from peripheral cells and returning it to the liver for degradation. In addition, HDL has strong anti-inflammatory and antioxidant properties, which also protect against atherosclerosis.[27] In people with diabetes,

HDL-C levels are not only low, but HDL is also dysfunctional with less ability to accept cholesterol from peripheral cells than HDL from people without diabetes.[28]

In a patient with diabetes with a low HDL-C level, simple measures can be quite effective. Weight loss has been shown to increase HDL-C levels but it appears that about 5% of body weight must be lost to have a significant effect.[29,30] Contrary to popular belief, exercise has a fairly weak effect on HDL-C, but exercise should be encouraged because it will assist with weight loss.[29] Statins and fibrates can increase HDL-C levels and their use has been discussed above. Nicotinic acid significantly increases HDL-C levels, but because of lack of benefit in clinical trials it is not recommended. Newer therapies to increase HDL-C level have failed to demonstrate any CV benefit. Therefore, at present the approach to patients with low HDL-C levels should be to ensure that LDL-C is at the target level and to encourage lifestyle and weight loss in those who are overweight.

Conclusion

Diabetes increases CV risk and many people with diabetes need medication to modify that risk. Risk assessment is important for many patients and standard calculators can be used. Statins are first-line treatment and should be titrated if necessary to achieve recommended target levels. Lipid abnormalities are rarely the only CV risk factor in people with diabetes, and it is important that GPs adopt a multiple risk factor intervention approach to ensure maximum benefit for their patients. MT

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A list of references is included in the website version of this article (www.medicinetoday.com.au).

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