Managing dyslipidaemia in the context of diabetes

RACGP QI&CPD Accredited Activity CATEGORY 2

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Learning objectives

After reading this article, the participant should be able to:

1. Outline the underlying process in the development of atherosclerosis and its contribution to major adverse cardiovascular events.
2. Define the relationship between lipid levels and cardiovascular risk in people with diabetes.
3. Describe the recommended options for lipid management in people with diabetes.

Key words

- Cardiovascular disease
- Cardiovascular risk
- Cholesterol
- Dyslipidaemia

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People with diabetes have an increased risk of cardiovascular complications, including acute coronary syndrome, stroke, heart failure and arrhythmias. The background to this risk for the development of cardiovascular complications is multifactorial and our understanding of the nature of atherosclerotic disease has progressed considerably. This article explores the latest thinking on the link between the various facets of dyslipidaemia and cardiovascular risk, and reviews current evidence for lipid management in people with diabetes.

Cardiovascular disease (CVD) is a major cause of death in Australia causing approximately 45 000 deaths in 2015. CVD kills one Australian every 12 minutes (National Heart Foundation of Australia, 2015).

People with diabetes have an increased risk of cardiovascular complications, including acute coronary syndrome, stroke, heart failure and arrhythmias. Data suggest that people with diabetes, without prior cardiovascular disease (CVD), have similar rates of myocardial infarction as people without diabetes who have had previous events (Haffner et al, 1998; Malmberg et al, 2000; Donahoe et al, 2007). Type 2 diabetes more than doubles the risk of heart failure hospitalisation and death (Davis and Davis, 2015). Women with diabetes are more likely to develop coronary heart disease (CHD; Peters et al, 2014) and are at greater relative risk of dying from CVD than their male counterparts (Juutilainen et al, 2004).

The background to this risk for the development of cardiovascular complications is multifactorial and our understanding of the nature of atherosclerotic disease has progressed considerably. The concept that atherosclerosis is a gradual process, leading to narrowing of the arteries until such a point that a thrombus forms and occludes a vessel, is naive. The concept was originally questioned by pathologists who showed that most myocardial infarctions are caused by low-grade stenosis (Falk et al, 1995). The current approach is to define atherosclerotic plaques as either stable, which can lead to high-grade obstruction, or unstable, which are vulnerable to rupture and show a high incidence of thrombosis (Davies, 1996).

The initial phase of the development of atherosclerosis is endothelial dysfunction caused by hyperglycaemia, with or without hypertension, and dyslipidaemia and the adverse effect of adipose tissue-derived inflammatory cytokines. These include tumour necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6). The effect of this is to produce adhesion molecules, inflammatory mediators and cytokines that stimulate the involvement of inflammatory cells such as monocytes, which then enter the vessel wall and further stimulate the inflammatory response by interacting with oxidised low-density lipoproteins (LDLs).

Oxidised LDLs have long been recognised as regulators of macrophage functions, including lipid accumulation and foam cell formation (Vangaveti et al, 2014). In addition, there is a reduction in the release of nitric oxide (NO), leading to vessel constriction (Xu and Zou, 2009). Subsequently, the monocytes differentiate into macrophages and foam cells, which further stimulate the release of inflammatory mediators (Hansson, 2005). What can be seen at this stage is a fatty streak. The platelet hyperactivity that is present in diabetes probably contributes to the further development of lesions at this stage (Ross, 1999). Eventually, more complicated lesions occur and the core of the plaque becomes necrotic. This necrotic core is protected by a fibrous cap, and it is those lesions that have a thin and vulnerable fibrous cap that are likely to become unstable plaques (Hansson et al, 1988).

Plaques in people with diabetes are more likely to rupture, with consequent thromboembolic events, because of the inflammatory process within (Moreno et al, 2000). Techniques using intra-vascular ultrasound with virtual histology (IVUS-VH) have advanced our knowledge of plaque morphology (Lindsey et al, 2009).

In addition to the effect on the wall, there is a subset of people with diabetes who acquire diabetic cardiomyopathy during the course of this disease. The nature of this process in not clearly defined, but there are functional and structural changes in the cardiac muscle that cause cardiac enlargement, increased stiffness and impaired diastolic function, which eventually leads to heart failure (Devereux et al, 2000). Heart failure is more common in the presence of poor glucose control, suggesting that hyperglycaemia may be an important contributor (Lind et al, 2011).

Clearly, good blood glucose control (i.e. reducing hyperglycaemia and avoiding hypoglycaemia in the process), particularly in the early stages of the disease, good blood pressure control throughout, and attention to dyslipidaemia is critically important in people with diabetes to prevent this atherosclerotic process (Colhoun et al, 2004; Holman et al, 2008).

Box 1. High-density lipoprotein cholesterol functionality: Relevance to athero- and vasculoprotection (Chapman et al, 2011).

- Regulation of glucose metabolism
- Cholesterol homeostasis and cellular cholesterol efflux
- Endothelial repair
- Anti-inflammatory activity
- Anti-oxidative activity
- Anti-apoptotic activity
- Anti-thrombotic activity
- Anti-protease activity
- Vasodilatory activity
- Anti-infectious activity

Lipid levels and cardiovascular risk

In diabetes, LDL cholesterol may not be significantly elevated compared with matched individuals without the disease, but it is a smaller, denser, more atherosclerotic particle (Mazzone et al, 2008).

The well-established treatment approach is to focus on the use of LDL cholesterol-lowering drugs such as statins. There is a clear linear relationship between the degree of LDL-cholesterol lowering achieved with statins and benefits, with a 10% and 21% reduction in all-cause mortality and major vascular events, respectively, per 1.0 mmol/L reduction in LDL cholesterol (Baigent et al, 2010).

Statin therapy reduces cardiovascular events by 22–48% (Collins et al, 2003; Colhoun et al, 2004); however, there still appears to be an excess residual cardiovascular risk among statin-treated people with diabetes compared with those without the disease (Costa et al, 2006). This residual risk may result from lipoprotein abnormalities that occur in diabetes, which are not adequately addressed by statin therapy (Mazzone et al, 2008).

Dyslipidaemia in type 2 diabetes is characterised by increased concentrations of triglyceride-rich lipoproteins, decreased concentrations of high-density lipoprotein (HDL) cholesterol and abnormalities in the composition of triglyceride-rich HDL and LDL particles (Garvey et al, 2003; Deeg et al, 2007). HDL is a very complex lipoprotein particle and changes in its composition may affect its atherosclerotic properties (Mazzone, 2007). The failure of cholesteryl ester transfer protein (CETP) inhibition with torcetrapib to protect against cardiovascular events suggests that HDL particle composition may be a more important consideration than HDL cholesterol level in the reduction of cardiovascular risk (Barter et al, 2007). However, the REVEAL trial (which will be published in late 2017) will report on the efficacy and safety of the last CETP inhibitor in ongoing trials, anacetrapib, versus placebo on major coronary events in patients taking atorvastatin (Landray et al, 2017).

Box 1 examines the relevance of HDL cholesterol functionality to athero- and vasculo-protection.

The case for non-HDL cholesterol

It is likely that combined dyslipidaemia may confer a higher magnitude of risk than elevated LDL

Page points

1. Plaques in people with diabetes are more likely to rupture, with consequent thromboembolic events, because of the inflammatory process within.
2. A subset of people with diabetes develop diabetic cardiomyopathy with cardiac muscle changes that cause cardiac enlargement, increased stiffness and impaired diastolic function, which eventually leads to heart failure.
3. In diabetes, LDL cholesterol may not be significantly elevated, but it is a smaller, more dense and atherosclerotic particle. There are increased concentrations of triglyceride (TG)-rich lipoproteins, decreased HDL cholesterol and abnormalities in composition of TG-rich HDL and LDL particles.
4. Cholesteryl ester transfer protein (CETP) inhibition aims to elevate HDL levels but, thus far, has been unsuccessful in lowering coronary events without safety signals. Anacetrapib is the last CETP inhibitor in ongoing trials; data is due for release in late 2017.

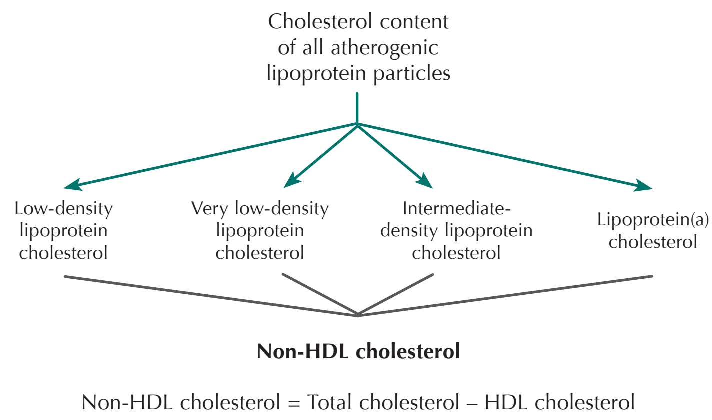

Figure 1. Components of non-high-density lipoprotein (non-HDL) cholesterol (redrawn with kind permission of the author from Virani, 2011).

cholesterol alone (Assman and Schulte, 1992). Triglycerides appear to be an independent risk factor (Austin et al, 1998), although they may be a marker of low HDL cholesterol. LDL cholesterol may underestimate CVD risk, particularly in the presence of hypertriglyceridaemia. The measurement of non-HDL cholesterol partially overcomes this problem (Anastasius et al, 2017). Non-HDL cholesterol may be defined as the difference between total and HDL cholesterol and thus represents cholesterol carried on all the potentially pro-atherogenic particles (Hsai, 2003; see *Figure 1*). By measuring total cholesterol and HDL cholesterol, and calculating non-HDL cholesterol, we can avoid the potential limitations of triglycerides as a marker of CHD risk and instead measure something that directly reflects the cholesterol content of all the particles that may be pro-atherogenic. Another advantage of non-HDL cholesterol measurement is that it does not need to be done in the fasting state. Non-HDL cholesterol may be, therefore, a readily obtainable, inexpensive and convenient measure of CHD risk that may be superior to LDL cholesterol in many respects (Hsai, 2003).

A meta-analysis of individual patient data from eight randomised trials, in which nearly 40 000 patients received statins, evaluated the relative strength of the association between conventional lipids and apolipoproteins (determined at baseline at 1 year follow-up) with cardiovascular risk. One standard deviation increases from baseline levels of LDL, apolipoprotein B (apoB) and non-HDL at 1 year were all associated with increased risks of cardiovascular events, but the differences between LDL and non-HDL were significant. Patients reaching the non-HDL target of under 3.4 mmol/L (130 mg/dL) but not the LDL target of under 2.6 mmol/L (100 mg/dL) were – assessed relative to patients achieving both targets – at lower excess risk than those reaching the LDL target but not the non-HDL target (Boekholdt et al, 2012; see *Table 1*). In other words, non-HDL cholesterol is a better predictor of risk than LDL cholesterol.

Virani (2011) reviewed non-HDL cholesterol as a metric of good quality of care. Non-HDL cholesterol has been shown to be a better marker of risk in both primary and secondary prevention studies. In an analysis of data combined from 68 studies, non-HDL cholesterol was the best predictor among all cholesterol measures both for coronary artery events

Table 1. Hazard ratios for major cardiovascular events by LDL and non-HDL cholesterol categories (Boekholdt et al, 2012).

LDL cholesterol level	Non-HDL cholesterol level	Hazard ratio	95% confidence interval
Not meeting target (2.6 mmol/L or higher)	Not meeting target (3.4 mmol/L or higher)	1.21	1.13–1.29
Not meeting target (2.6 mmol/L or higher)	**Meeting target** (under 3.4 mmol/L)	1.02	0.92–1.12
Meeting target (under 2.6 mmol/L)	Not meeting target (3.4 mmol/L or higher)	1.32	1.17–1.50
Meeting target (under 2.6 mmol/L)	**Meeting target** (under 3.4 mmol/L)	1.00*	

*Reference.
HDL=high-density lipoprotein; LDL=low-density lipoprotein.

and for strokes (Emerging Risk Factors Collaboration, 2009). In the IDEAL (Incremental Decrease in End Points through Aggressive Lipid Lowering) trial, elevated non-HDL cholesterol and apoB levels were the best predictors after acute coronary syndrome of adverse cardiovascular outcomes in patients on lipid-lowering therapy (Kastelein et al, 2008).

Elevated levels of non-HDL cholesterol, in combination with normal levels of LDL cholesterol, identify a subset of patients with elevated levels of LDL particle number, elevated apoB concentrations and LDL of small, dense morphology (Ballantyne et al, 2001). The increase in the incidence of metabolic syndrome probably reduces the accuracy of risk prediction for vascular events when LDL cholesterol is used for that purpose, whereas non-HDL cholesterol has been shown to retain predictive capability in this patient population (Sattar et al, 2004).

The use of non-HDL cholesterol to provide a better prediction of risk and treatment response than LDL cholesterol may be particularly relevant in the growing number of people with type 2 diabetes in whom an increase in atherogenic lipoproteins is not reflected by LDL cholesterol levels (JBS3 Board, 2014). Whilst non-HDL has been recommended for CVD risk assessment in National Institute for Health and Care Excellence (NICE) guidelines in the UK, it is not yet endorsed, instead of LDL cholesterol, in current Australian guidelines.

Box 2. Adults with any of the following conditions do not require absolute CVD risk assessment using the Framingham Risk Equation (The Royal Australian College of General Practitioners, 2016a).

- Diabetes and aged >60 years
- Diabetes with microalbuminuria (>20 µg/min or urine albumin-to-creatinine ratio [UACR] >2.5 mg/mmol for men and >3.5 mg/mmol for women)
- Moderate or severe chronic kidney disease (persistent proteinuria or estimated glomerular filtration rate [eGFR] <45 mL/min/1.73 m^2)
- A previous diagnosis of familial hypercholesterolaemia
- Systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg
- Serum total cholesterol >7.5 mmol/L
- Aboriginal or Torres Strait Islander peoples aged >74 years

Identifying and assessing CVD risk

There are several tools available to assess risk for the primary prevention of CVD including: Australian CVD Risk Calculator (NVDPA/National Heart Foundation; 45–75 years age range); QRISK (Joint British Societies for the Prevention of CVD [JBS3] recommendations; no specified age range); ACC (American College of Cardiology; 40–79 years) and SCORE (European Society of Cardiology; 40–65 years; Anastasius et al, 2017).

Australian diabetes guidelines (The Royal Australian College of General Practitioners [RACGP], 2016a) endorse use of the Australian CVD Risk Calculator, which been adapted from the Framingham Risk Equation and provides an estimate of CVD risk over the next 5 years, for population aged 45–75 years. Patients are categorised as low risk (<10% risk of CVD), moderate risk (10–15% risk of CVD) or high risk (>15% risk of CVD).

Box 2 lists adults already known to be clinically determined high risk of CVD who do not require assessment using the Framingham Risk Equation (RACGP, 2016a).

The need for pharmacological treatment, and therefore who may benefit from medication, is determined by the assessment and level of absolute CVD risk (Carrington and Stewart, 2011).

Remember that CVD risk will be underestimated in people taking antihypertensives or lipid-lowering drugs, those who have recently stopped smoking and those who have additional risk due to certain medical conditions or treatments (e.g. people taking medications that can cause dyslipidaemia, such as corticosteroids, antipsychotics and immunosuppressants). CVD risk is also increased by severe obesity (BMI >40 kg/m^2).

The JBS3 risk calculator is based on the QRISK2 risk assessment tool but has some additional features that are very helpful in explaining risk, such as life expectancy and life years gained by modifying risk factors. This can be accessed online at www.jbs3risk.com.

Both total and HDL cholesterol should be

Page points

1. The use of non-high density lipoprotein (HDL) cholesterol to provide a better prediction of risk and treatment response than low-density lipoprotein (LDL) cholesterol may be particularly relevant in the growing number of people with type 2 diabetes in whom an increase in atherogenic lipoproteins is not reflected by LDL cholesterol levels.
2. Australian diabetes guidelines endorse the use of the Australian Cardiovascular Disease Risk Calculator to assess risk for the primary prevention of cardiovascular disease.
3. Cardiovascular disease risk will be underestimated in people taking antihypertensives or lipid-lowering drugs, and those who have additional risk due to certain conditions or treatments. Risk is also increased by severe obesity.

Page points

1. For primary prevention, it is recommended to calculate the Absolute Cardiovascular Disease Risk (available at www.cvdcheck.org.au) and initiate therapy based on level of risk and other clinical factors.
2. For secondary prevention, statin therapy is recommended for all patients with coronary heart disease. For patients admitted to hospital, statin therapy should be started while they are in hospital. In addition, patients should be considered for low dose aspirin, ACEi/ARB, beta-blocker and management of all modifiable risk factors.
3. Patients taking statins should be offered annual medication reviews. They should also be advised to seek medical advice if they develop muscle symptoms.
4. Ezetimibe targets the NPC1L1 receptor in intestinal cells to inhibit absorption of cholesterol and plant sterols. Ezetimibe lowers LDL cholesterol by about 20%. The IMPROVE-IT study demonstrated that patients post-acute coronary syndrome receiving ezetimibe with simvastatin achieved LDL 1.4 mmol/L and relative risk reduction of 6.4% (P=0.016).

measured to give the best estimation of CVD risk. Before lipid modification therapy is offered for the primary prevention of CVD, patients should have a full lipid profile, including total cholesterol, HDL cholesterol, non-HDL cholesterol and triglycerides.

Lipid management

People at high risk of, or with, CVD should be encouraged to play a part in reducing their personal risk through lifestyle changes, including achieving and maintaining a healthy weight, eating a cardioprotective diet, taking more physical activity, stopping smoking and moderating alcohol consumption. The management of modifiable risk factors should also be optimised.

For primary prevention, it is recommended to calculate the Absolute Cardiovascular Disease Risk (available at www.cvdcheck.org.au) and initiate therapy based on level of risk and other clinical factors (National Vascular Disease Prevention Alliance, 2012).

Atorvastatin 20 mg or rosuvastatin 10 mg is the preferred option in patients with a ≥10% 10-year risk of CVD estimated using the QRISK2 assessment tool, including those with type 2 diabetes. This treatment should also be **considered for** primary prevention in all adults with type 1 diabetes and **offered to** the following people with type 1 diabetes:

- Those who are aged over 40 years.
- Those who have had the condition for more than 10 years.
- Those who have established nephropathy.
- Those who have other risk factors for CVD.

For the secondary prevention of CVD, statin therapy is recommended for all patients with existing CVD. For patients admitted to hospital, statin therapy should commence while they are in hospital. In addition, patients should be considered for low dose aspirin, ACEi/ARB, beta-blocker and management of all modifiable risk factors (National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand, 2012). A lower dose is recommended if there is a high risk of adverse effects or the potential for drug interactions, or if the patient prefers this option. The decision to start statin treatment should follow discussion with the patient regarding the risks and benefits, and consideration of additional factors, such as potential benefits from lifestyle modification, informed patient preference, comorbidities, polypharmacy, frailty and life expectancy (NICE, 2014).

Patients started on high-intensity statin treatment should have their total cholesterol, HDL cholesterol and non-HDL cholesterol checked after 3 months, with a target >40% reduction in non-HDL cholesterol. If a >40% reduction in non-HDL is not achieved, look at adherence and timing of dose and/or consider increasing the dose if the patient was started on less than 80 mg atorvastatin and is thought to be higher risk due to risk score, comorbidities or clinical judgement (NICE, 2014).

For secondary prevention of CVD, all adults with type 2 diabetes – known prior CVD (except haemorrhagic stroke) – should receive the maximum tolerated dose of a statin, irrespective of their lipid levels. Note: The maximum tolerated dose should not exceed the maximum available dose (i.e. 80 mg atorvastatin, 40 mg rosuvastatin). Patients taking statins should be offered annual medication reviews. They should also be advised to seek medical advice if they develop muscle symptoms. JBS3 provides a step-wise therapeutic approach for patients who require statin therapy but appear to be intolerant. It may be appropriate to seek specialist advice about the options for treating people at high-risk of CVD, including those with type 1 or type 2 diabetes, who are intolerant to three different statins.

Ezetimibe targets the NPC1L1 receptor in intestinal cells to inhibit absorption of cholesterol and plant sterols. Ezetimibe lowers LDL cholesterol by about 20% (Tonkin and Byrnes, 2014).

Ezetimibe monotherapy should be considered for people with primary hypercholesterolaemia in whom initial statin therapy is contraindicated or not tolerated. It is recommended as add-on therapy for people with primary hypercholesterolaemia who have started statin therapy if the total or LDL cholesterol is not appropriately controlled after appropriate dose titration of statin therapy, if appropriate dose titration is limited by intolerance or if a change from the initial statin therapy is required.

Recently, ezetimibe has received additional indication: for administration in combination with the maximum tolerated dose of a statin with proven cardiovascular benefit in patients with coronary heart disease and a history of acute coronary syndrome in need of additional lowering of LDL-C in the expectation of a modest further reduction in the risk of cardiovascular events following at least one year of therapy. This is based on the IMPROVE-IT study (Cannon et al, 2015), which demonstrated that treatment with ezetimibe when added to simvastatin provided incremental benefit in reducing the primary composite endpoint of cardiovascular death, major coronary event or non-fatal stroke compared with simvastatin alone (relative risk reduction of 6.4%, P=0.016).

Proprotein convertase subtilisin/kexin type 9 (PCSK9) enzyme regulates plasma concentrations of LDL cholesterol by interacting with LDL receptors on liver cells. After binding to an LDL receptor, PCSK9 directs it to lysosomal degradation. Thus, it inhibits recycling of the receptor to the surface of the hepatocyte and delays catabolism of LDL particles. PCSK9 inhibitors are monoclonal antibodies that reduce LDL-cholesterol concentrations by about 50% and require subcutaneous administration every 2 to 4 weeks (Tonkin and Byrnes, 2014).

In Australia, evolocumab and alirocumab are available, but require specialist consultation for prescribing (Simons, 2016). Patients with atherogenic dyslipidaemia (elevated total triglycerides, decreased HDL-C and normal or moderately elevated LDL-C) have an elevated risk of CVD events. Atherogenic dyslipidaemia may be found in type 2 diabetes (Anastasius et al, 2017).

Fenofibrate can be used with statins to address high triglyceride and low HDL levels in diabetes. It has data for reduction in foot amputations and progression of diabetic retinopathy (Keech et al, 2005).

NICE (2014) does not recommend the use of fibrates (routinely), nicotinic acid, bile-acid sequestrants (anion exchange resins), omega-3 fatty acid compounds or plant stanols or sterols in people being treated for the primary or secondary prevention of CVD, including those with type 1 or type 2 diabetes (NICE, 2014). Aspirin is **not** recommended for the primary prevention of CVD in people with diabetes (JBS3 Board, 2014). Coenzyme Q10 and vitamin D are not recommended for increasing adherence to statin therapy (NICE, 2014).

Lipid-lowering therapy for primary prevention should (while balancing risks and benefits) aim towards:

- Total cholesterol <4.0 mmol/L
- HDL-C ≥1.0 mmol/L
- Endothelial repair
- LDL-C <2.0 mmol/L*
- Non-HDL-C <2.5 mmol/L
- TG <2.0 mmol/L

Lipid levels should be interpreted in the context of an absolute CVD risk assessment after 45 years of age, or 35 years of age for Aboriginal and Torres Strait Islander peoples (The Royal Australian College of General Practitioners, 2016b).

*Note: In the secondary prevention of CVD, aim for LDL-C <1.8 mmol/L (Chew et al, 2016).

The latest evidence on lipid-lowering approaches

There have been concerns that halving the risk threshold for primary prevention will result in a large majority of men and women above the recommended age for cholesterol testing being indicated for statin therapy. However, a recently published study using mathematical modelling estimated that only a small number of patients indicated for treatment would be due to false positive tests, and these are mainly in those close to the threshold, be it 20% or 10%. The researchers believe the implications depend on the benefits of statin therapy, in those at low to medium risk, and the harms (McFadden et al, 2015).

Two of the best-known harms associated with statin therapy are muscle problems and a small or moderate increased risk of new-onset diabetes (JBS3 Board, 2014). Statin therapy was associated with a 9% increased risk for incident diabetes, but the risk is low both in absolute terms and when compared with the reduction in coronary events (Sattar et al, 2010). The Cholesterol Treatment Trialists' Collaboration concluded that statins provide a net benefit in those at low risk (Mihaylova et al, 2012). Therefore, a move to a lower threshold should extend a treatment from which almost all middle-aged men and women stand to benefit, to an increasing proportion of the population (McFadden et al, 2015).

Page points

1. Patients with atherogenic dyslipidaemia (elevated total triglycerides, decreased HDL-C and normal or moderately elevated LDL-C) have an elevated risk of cardiovascular disease events. Atherogenic dyslipidaemia may be found in type 2 diabetes mellitus. Fenofibrate with statin may be useful in this population.
2. Fenofibrate can be used with statins to address high triglyceride and low HDL levels in diabetes. It is associated with a reduction in foot amputations and progression of diabetic retinopathy.
3. Aspirin is not recommended for the primary prevention of cardiovascular disease in people with diabetes.

Box 3. Case example one.

Narrative

Mr B is a 62-year-old man who has had type 2 diabetes for 6 years. He weighs 98 kg with a BMI of 30 kg/m^2, and his HbA_{1c} level is 60 mmol/mol (7.6%). His estimated glomerular filtration rate is 58 mL/min/1.73 m^2 and his blood pressure is 146/88 mmHg. He takes metformin 0.5 g twice daily and ramipril 5 mg daily and follows a healthy lifestyle program diligently.

He had been on atorvastatin 40 mg but reported muscle pain and cramps in his legs. These disappeared when the statin was stopped but his lipid profile was unsatisfactory, with a cholesterol level of 5.4 mmol/L, high-density lipoprotein (HDL) cholesterol 0.9 mmol/L, non-HDL cholesterol 4.5 mmol/L and triglycerides 2.7 mmol/L.

Using the Australian CVD risk calculator is not necessary as he has type 2 diabetes and is aged over 60 years. Therefore he is high risk, with >15% risk of CVD over next 5 years.

Discussion

As Mr B was symptomatic and his creatine kinase level was less than four times the upper limit of normal, statin use was halted for 4 weeks. He remained unable to tolerate statin at the original dose, so a lower dose of rosuvastatin (5 mg) was prescribed. His muscle pains were no longer a problem but his targets (non-HDL cholesterol <2.5 mmol/L) remained elusive until ezetimibe 10 mg was additionally prescribed. Amlodipine 5 mg was also added to his regimen to achieve a target blood pressure of less than 130/80 mmHg, and metformin was titrated up to 2 g.

Box 4. Case example two.

Narrative

Mrs D, a teacher aged 48 years, attends a health check. She is overweight (96 kg), with central obesity and a waist measurement of 90 cm. Her blood pressure measures 150/88 mmHg. A random blood glucose test is performed in addition to tests for total cholesterol, high-density lipoprotein (HDL) cholesterol and estimated glomerular filtration rate.

Her cholesterol level was 5.8 mmol/L, with an HDL cholesterol of 0.95 mmol/L and a non-HDL cholesterol of 4.85 mmol/L. Her glucose level was 7.1 mmol/L and her renal function was normal.

Triglycerides were 2.8 mmol/L. Her HbA_{1c} level was 66 mmol/mol (8.2%). No end organ damage was identified and there was no microalbuminuria.

Discussion

Mrs D was provided with lifestyle advice and started on high-intensity statin treatment (atorvastatin 20 mg or rosuvastatin 10mg). After 3 months, a 40% reduction in HDL cholesterol had not been achieved so atorvastatin was titrated up to 40 mg (or rosuvastatin titrated up to 20mg). An angiotensin-converting enzyme inhibitor was also prescribed as her blood pressure remained high. Metformin was introduced because the HbA_{1c} level failed to fall below 48 mmol/mol (6.5%) with the diet and exercise diabetes regimen.

Because many of the statin studies have involved mainly Caucasian populations and a majority of men, there has been a lack of information regarding the efficacy of these drugs for primary prevention in people of other ethnicities and women. The HOPE 3 trial randomly assigned 12 705 participants from 21 countries who did not have CVD and were at intermediate risk to receive either rosuvastatin 10 mg/day or placebo. Only 20% of participants were Caucasian (29% Chinese and 27% Hispanic), and 46% were women (Yusuf et al, 2016).

Two possible outcomes were investigated; the first was a composite of death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke, while the second also included revascularisation, heart failure and resuscitated cardiac arrest. Patients were followed up for a median of 5.6 years (Yusuf et al, 2016).

The overall mean LDL cholesterol level was 26.5% lower in people taking rosuvastatin than those taking placebo. The first and second outcomes occurred in 3.7% and 4.4% of people taking rosuvastatin versus 4.8% and 5.7% of those taking placebo respectively. There was no evidence of heterogeneity of effect in the subgroups defined according to ethnic group or gender. There was no excess of diabetes or cancers in the participants taking rosuvastatin versus those taking placebo. While more people taking rosuvastatin had muscle pain or weakness than those taking placebo (5.8% vs 4.7%), there was no significant difference between the groups in the number of people permanently discontinuing treatment because of muscle symptoms (1.3% on rosuvastatin vs 1.2% on placebo; Yusuf et al, 2016). This study showed that for primary prevention, rosuvastatin 10 mg/day is associated with a significantly lower risk of cardiovascular events than placebo in an intermediate-risk ethnically diverse population, well represented by women (Yusuf et al, 2016).

Muscle-related side effects

Although statins are highly effective at reducing cardiovascular morbidity and mortality in high-risk patients, poor adherence can be an issue. One of the commonest causes of non-adherence to statin therapy is statin intolerance, mainly due to muscle-related symptoms (Bitzur et al, 2013). Nissen et al (2016) set out to identify patients with muscle symptoms confirmed by statin rechallenge and compare the lipid-lowering efficacy of ezetimibe and evolocumab in a 2-stage randomised clinical trial. The trial included 511 adults with uncontrolled LDL cholesterol levels and a history of intolerance to two or more statins. The trial started with a 24-week crossover procedure using atorvastatin 20 mg or placebo to identify the patients having symptoms with the statin only (phase A). Following a 2-week washout period, patients were randomised to ezetimibe (10 mg/day) or evolocumab (420 mg/month) for 24 weeks (phase B). The co-primary endpoints were the mean percentage change in LDL cholesterol from baseline to the mean of weeks 22 and 24, and from baseline to week 24 levels.

Of the 491 patients who entered phase A (mean age 60.7 years, 50.1% female, 34.6% with CHD, entry mean LDL cholesterol level 212.3 mg/dL [5.5 mmol/L]), muscle symptoms occurred in 42.6% (*n*=209) when taking atorvastatin but not when taking placebo. Of these, 199 entered phase B, together with 19 who were fast-tracked to phase B due to elevated creatine kinase (*n*=218; 73 randomised to ezetimibe, 145 to evolocumab, entry mean LDL cholesterol level 219.9 mg/dL [5.7 mmol/L]; Nissen et al, 2016).

For the mean of weeks 22 and 24, the LDL cholesterol level was 183.0 mg/dL (4.7 mmol/L) with ezetimibe (mean percentage change –16.7%, absolute change –31.0 mg/dL [0.8 mmol/L]) and 103.6 mg/dL (2.7 mmol/L) with evolocumab (mean percentage change –54.5%, absolute change –106.0 mg/dL [2.7 mmol/L]). At week 24, the LDL cholesterol level was 181.5 mg/dL (4.7 mmol/L) with ezetimibe (mean percentage change –16.7%, absolute change –31.2 mg/dL [0.8 mmol/L]) and 104.1 mg/dL (2.7 mmol/L) with evolucumab (mean percentage change –52.8%, absolute change –102.9 mg/dL (2.7 mmol/L; P<0.001). For the mean of weeks 22 and 24, the difference in LDL cholesterol between the groups was –37.8% (absolute difference 171.7 mg/dL [4.7 mmol/L]; Nissen et al, 2016).

Interestingly, in this study, muscle symptoms were reported by 28.8% of patients taking ezetimibe and 20.7% of those taking evolucumab, with the active study drug being withdrawn in 6.8% of patients taking ezetimibe and 0.7% of patients taking evolucumab. The study showed that in patients unable to tolerate statins due to muscle-related adverse effects, evolucumab resulted in a significantly greater reduction in LDL cholesterol levels at 24 weeks than ezetimibe and was also associated with fewer muscle symptoms (Nissen et al, 2016), but it would also be much more expensive.

In practice

Statins are very effective at reducing the risk of serious and life-threatening cardiovascular events and when we take a patient off statin therapy, we may be doing them harm. The European Atherosclerosis Society (EAS) released a consensus statement in 2015 to provide guidance on the diagnosis and management of statin-associated muscle symptoms (Stroes et al, 2015). In their algorithm, they recommend first stopping the drug for either 2–4 weeks (if the patient is symptomatic and has a creatine kinase level less than four times the upper limit of normal) or 6 weeks (if the patient has a creatine kinase level four times the upper limit of normal or greater with or without rhabdomyolysis). If the re-challenged patient is still unable to tolerate a statin, we should aim for a lower dose with an efficacious statin (e.g. atorvastatin or rosuvastatin), or advise the patient to take a statin every other day or twice weekly. If still unsuccessful, then recommend trying again with the highest maximally tolerated dose of statin, then adding additional lipid-lowering agents (specifically ezetimibe) to lower LDL cholesterol levels to goal. If this does not work, we should consider adding a fibrate (not gemfibrozil), bile acid sequestrants, or both, as add-ons to ezetimibe. If the patient is still not at goal, the final options are additional (future) novel therapies (e.g. PCSK9 inhibitors or CETP inhibitors; Stroes et al, 2015). Case examples relating to managing dyslipidaemia in the context of diabetes are presented in *Box 3* and *Box 4*.

Concluding remarks

The 2016 Joint European Cardiovascular Prevention Guidelines point out that reducing the population cardiovascular risk by 1% could prevent 25 000 cases of CVD and stronger laws on food, physical activity and smoking are required (European Association of Cardiology, 2016; Piepoli et al, 2016).

Rates of obesity and type 2 diabetes are continuing to rise. We know people with

Page points

1. Statins are the gold standard treatment for lowering LDL cholesterol in patients with moderate or high risk of cardiovascular disease. They are used as primary or secondary prevention.
2. In patients on maximal tolerated dose of statin unable to reach LDL cholesterol targets or intolerant of statins, the addition of ezetimibe may provide up to 20% reduction in LDL cholesterol.
3. Some patients will not achieve lipid targets using statin and ezetimibe. In this group of patients, consider using fenofibrate, older agents or PCSK9 inhibitors.

> "Statins are very effective at reducing the risk of serious and life-threatening cardiovascular events and when we take a patient off statin therapy, we may be doing them harm."

diabetes are at increased risk of cardiovascular complications, and non-HDL cholesterol now appears to be a more effective measure of risk in this population than LDL cholesterol. The management of dyslipidaemia in these patients should involve a multifactorial program to improve lifestyle and adherence to treatment. ■

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"The management of dyslipidaemia in people with diabetes should involve a multifactorial program to improve lifestyle and adherence to treatment."

Online CPD activity

Visit www.pcdsa.com.au/cpd to record your answers and gain a certificate of participation

Participants should read the preceding article before answering the multiple choice questions below. There is ONE correct answer to each question. After submitting your answers online, you will be immediately notified of your score. A pass mark of 70% is required to obtain a certificate of successful participation; however, it is possible to take the test a maximum of three times. A short explanation of the correct answer is provided. Before accessing your certificate, you will be given the opportunity to evaluate the activity and reflect on the module, stating how you will use what you have learnt in practice. The CPD centre keeps a record of your CPD activities and provides the option to add items to an action plan, which will help you to collate evidence for your annual appraisal.

1. According to Boekholdt et al (2012), which combination of LDL cholesterol and non-HDL cholesterol has the HIGHEST hazard ratio for major cardiovascular events? **Select ONE option only.**

	LDL cholesterol (mmol/L)	Non-HDL cholesterol (mmol/L)
A.	4	3
B.	2	4
C.	2	3
D.	3	2

2. When considering the primary prevention of CVD, for which ONE of the following people with diabetes is Australian CVD risk tool appropriate? **Select ONE option only.**
   - A. A 30-year-old man with type 1 diabetes
   - B. A 45-year-old woman with type 2 diabetes and familial hypercholesterolaemia
   - C. A 62-year-old man with type 2 diabetes and diabetic nephropathy
   - D. A 57-year-old woman with type 2 diabetes and hypertension
   - E. A 91-year-old man with type 2 diabetes and Parkinson's disease

3. Which ONE of the following features is found in the JBS3 risk calculator but NOT in the Australian CVD risk assessment tool? **Select ONE option only.**
   - A. Ability to include diabetes as a risk factor
   - B. Ability to include rheumatoid arthritis as a risk factor
   - C. 5-year risk
   - D. Life years gained
   - E. 10-year risk

4. A 47-year-old man with type 2 diabetes has a 5-year Australian CVD risk score of 16%. Which is the MOST appropriate INITIAL medication, if any, to reduce his cardiovascular risk? **Select ONE option only.**
   - A. Atorvastatin 20 mg
   - B. Atorvastatin 80 mg
   - C. Simvastatin 40 mg
   - D. Simvastatin 80 mg
   - E. Lifestyle changes alone recommended

5. For which ONE of the following people with type 1 diabetes is a statin as primary prevention of CVD the MOST appropriate? **Select ONE option only.**
   - A. A 17-year-old male smoker
   - B. A 26-year-old female with a total cholesterol of 6.4 mmol/L
   - C. A 35-year-old male with poor glycaemic control
   - D. A 39-year-old male diagnosed 5 years ago
   - E. A 46-year-old female with CKD stage 3

6. A 59-year-old woman with type 2 diabetes agrees to start high-intensity statin medication today for primary CVD prevention. When is the MOST appropriate time-interval (in months), if any, before re-measuring her lipid profile? **Select ONE option only.**
   - A. 1
   - B. 3
   - C. 6
   - D. 12
   - E. No repeat lipid profile required

7. What is the MINIMUM target REDUCTION in non-HDL cholesterol recommended for people with diabetes starting a high-intensity statin? **Select ONE option only.**
   - A. 10%
   - B. 20%
   - C. 30%
   - D. 40%
   - E. 50%

8. A 61-year-old man with type 2 diabetes is at high risk of CVD. He is intolerant of both atorvastatin and simvastatin due to myalgia. His creatine kinase (CK) was normal at the time of reporting symptoms. Which is the SINGLE MOST appropriate monotherapy to now recommend? **Select ONE option only.**
   - A. Fenofibrate
   - B. Ezetimibe
   - C. Nicotinic acid
   - D. Omega-3-acid ethyl esters
   - E. Rosuvastatin

9. A 49-year-old man with type 2 diabetes has a 10-year CVD risk score of 32%. Despite good lifestyle modification and concordance with maximal statin dosages, his total and LDL cholesterol remain poorly controlled. Which is the SINGLE MOST appropriate add-on therapy, if any, to recommend as primary prevention? **Select ONE option only.**
   - A. Fenofibrate
   - B. Bile acid sequestrant
   - C. Co-enzyme Q10
   - D. Ezetimibe
   - E. No add-on therapy recommended

10. A 65-year-old woman developed muscle pain after starting simvastatin 40 mg. Her CK was elevated at twice the upper limit of normal. According to European Atherosclerosis Society guidance (Stroes et al, 2015), what is the MINIMUM time-interval (in weeks) before a statin re-challenge is recommended? **Select ONE option only.**
    - A. 1
    - B. 2
    - C. 4
    - D. 8
    - E. 12