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Cardiovascular risk: Managing dyslipidaemia in the context of diabetes

Michael Kirby

Learning objectives

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

1. Describe the key trial data supporting the lipid-modifying interventions in people with diabetes.
2. Discuss the published guidance and QOF indicators for the management of dyslipidaemia in people with diabetes.
3. Explain the recommendations and contraindications for prescribing statins in older people, children and women.

Key words

- Cardiovascular disease
- Dyslipidaemia
- Lipids
- Statins

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Cardiovascular disease remains the main cause of death in the UK (Allender et al, 2008). Although cardiovascular risk is determined by a number of factors, diabetes and dyslipidaemia are both important contributors. This article discusses the epidemiology of dyslipidaemia, reviews the evidence for pharmacological treatment, and summarises current management recommendations in the context of diabetes.

In the UK, cardiovascular (CV) disease accounts for almost 198 000 deaths each year. Around half of these are caused by coronary heart disease (CHD) and over one-quarter by stroke. CHD itself is the most common single cause of death, with around one in five men and one in seven women dying from the disease (Allender et al, 2008).

Diabetes significantly increases the risk of CHD. Men with type 2 diabetes have a two- to four-fold greater annual risk, and women with type 2 diabetes have a three- to five-fold greater annual risk, than those without the condition (Allender et al, 2008). The INTERHEART case-control study estimated that around 9% of heart attacks in Central and Eastern Europe, and 15% of heart attacks in Western Europe, are due to diagnosed diabetes (Yusef et al, 2004). Dyslipidaemia is an important CV risk factor in people with diabetes. Around 35% of heart attacks in Central and Eastern Europe, and 45% of heart attacks in Western Europe, are due to abnormal blood lipids, and people with abnormal lipids are at over three times the risk of having a heart attack than those with normal lipids (Yusef et al, 2004).

Although overall CV risk is determined by a number of factors, in the context of lipids it is principally determined by concentrations of low-density lipoprotein (LDL)-cholesterol and high-density lipoprotein (HDL)-cholesterol (inversely) and, to a lesser extent, triglyceride concentrations (British Cardiac Society [BCS] et al, 2005).

Cholesterol is an essential component of the cell's external membrane and intracellular contents. The balance of the various lipid

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fractions and membrane proteins determines the integrity of the cell membrane. LDL provides cholesterol to the tissues but is only required at low levels, for example levels of <1 mmol/L are present in infants during their period of rapid growth. HDL is the reverse cholesterol transporter. It can carry cholesterol from cholesterol-satisfied cells back to the liver or supply to other lipoproteins.

Triglycerides are essential for the structural integrity of the cell and are the essential energy source for the body tissues. They are derived either from the diet or synthesized in the liver from other available metabolites such as carbohydrates. Once absorbed from the gut they are carried on chylomicrons to the peripheral tissues where they are hydrolysed for energy supply or stored in excess. The excess storage of triglycerides in the peripheral tissues, liver and abdomen leads to insulin resistance.

People with diabetes tend to have similar LDL-cholesterol levels, but higher triglyceride and lower HDL-cholesterol levels than people without the condition (*Table 1*). However, people with diabetes also tend to have a greater concentration of small, dense LDL particles, and this combination appears to be more atherogenic than non-diabetic dyslipidaemia (Taskinen, 2002; Moon and Kashyap, 2004). The excess risk of CV disease (CVD) in people with diabetes is attributed to the combination of this type of dyslipidaemia together with hyperglycaemia and high blood pressure (National Collaborating Centre for Chronic Conditions [NCCCC], 2008). The typical lipid profile results from a sedentary lifestyle combined with excess calorie intake and weight gain leading to insulin resistance. People of south Asian origin are more vulnerable to these changes.

A low level of HDL-cholesterol confers an additional risk of CVD irrespective of total cholesterol levels. A 12-year follow-up of the Framingham Heart Study showed that individuals with high HDL-cholesterol (in the 80th percentile) were at 50% less risk of CHD than those with low HDL-cholesterol (20th percentile) (Castelli et al, 1986).

While the term "hyperlipidaemia" is used to describe raised serum levels of one or more of total cholesterol, LDL-cholesterol, triglycerides or total cholesterol and triglycerides combined (combined hyperlipidaemia), the term "dyslipidaemia" also includes low levels of HDL-cholesterol (Gross and Reese, 2005).

Between 2003 and 2009, angina was the most common complication resulting in hospital admission in people with type 2 diabetes in England, and its prevalence increased steadily over this time period (NHS Information Centre, 2010).

Modifying cholesterol levels with diet, drugs or other means, reduces the risk of CVD (BCS et al, 2005).

Evidence for lipid-modifying drugs

Statins

Trials using statins, with non-fatal and fatal clinical events as endpoints, have provided the most compelling evidence for cholesterol lowering (Shepherd et al, 1995; Pedersen et al, 1998; Downs et al, 1998; Lewis et al, 1998; LIPID [Long-term Intervention with Pravastatin in Ischaemic Disease] Study Group, 1998). Subsequent trials have extended the evidence base for this drug class in people with diabetes (Heart Protection Study Collaborative Group, 2002; Colhoun et al, 2004; Shepherd et al, 2006).

The Cholesterol Treatment Trialists conducted a meta-analysis of 14 randomised trials of statins including data from over 90 000 participants. They found that statin therapy safely reduced the 5-year risk of major coronary events, coronary revascularisation and stroke by about one-fifth per mmol/L reduction in LDL-cholesterol, irrespective of age, sex, blood pressure, pre-existing diabetes or history of previous vascular event. This meant that 48 fewer participants had major vascular events per 1000 among those with pre-existing CHD at baseline (95% confidence

Page points

1. People with diabetes tend to have similar low-density lipoprotein (LDL)-cholesterol levels, but higher triglyceride and lower high-density lipoprotein (HDL)-cholesterol levels than people without the condition.
2. While the term "hyperlipidaemia" is used to describe raised serum levels of one or more of total cholesterol, LDL-cholesterol, triglycerides or total cholesterol and triglycerides combined (combined hyperlipidaemia), the term "dyslipidaemia" also includes low levels of HDL-cholesterol.
3. Modifying cholesterol levels with diet, drugs or other means, reduces the risk of cardiovascular disease.
4. Trials using statins, with non-fatal and fatal clinical events as endpoints, have provided the most compelling evidence for cholesterol lowering.

Table 1. Typical lipid profile of a person with type 2 diabetes.

Cholesterol	Normal or elevated
High-density lipoprotein	Low
Triglycerides	Elevated
Low-density lipoprotein	Normal or elevated, tends quantitatively towards the small, dense variety

Page points

1. The URANUS (Use of Rosuvastatin Versus Atorvastatin in Type 2 Diabetes Mellitus) study compared the results of statin treatment for the reduction of low-density lipoprotein (LDL)-cholesterol in people with type 2 diabetes and LDL-cholesterol levels ≥3.3 mmol/L.
2. In ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm), atorvastatin prevented around nine people with diabetes from suffering a first major event or procedure for every 1000 treated for 1 year.
3. Statins can reduce LDL-cholesterol by between 18% and 55% and triglycerides by between 5% and 15%.

interval [CI], 39–57), compared with 25 per 1000 among those with no such history (95% CI, 19–31) (Baigent et al, 2005).

Several trials have reviewed the safety and efficacy of statins specifically in people with type 2 diabetes. The TNT (Treating to New Targets) study (Shepherd et al, 2006) involved 1501 participants with type 2 diabetes, CHD and LDL-cholesterol levels <130.0 mg/dL (<3.36 mmol/L), who were randomised to therapy with atorvastatin 10 mg or 80 mg per day. Follow-up continued for a median of 4.9 years. By study end, LDL-cholesterol levels were 98.6 mg/dL (2.55 mmol/L) with atorvastatin 10 mg versus 77.0 mg/dL (1.99 mmol/L) with atorvastatin 80 mg. Although the risk of a major CV event was significantly lower in those receiving the 80 mg dose, representing a 25% risk reduction in favour of the high-dose group (P>0.026), there were no differences between the groups in terms of treatment-related adverse events and persistent liver enzymes (Shepherd et al, 2006).

The URANUS (Use of Rosuvastatin Versus Atorvastatin in Type 2 Diabetes Mellitus; Berne et al, 2005) study compared the results of statin treatment for the reduction of LDL-cholesterol in people with type 2 diabetes and LDL-cholesterol levels ≥3.3 mmol/L. Treatment was titrated up from 10 mg/day to a maximum of rosuvastatin 40 mg/day or atorvastatin 80 mg/day over 12 weeks, to achieve an LDL-cholesterol target of <3 mmol/L. After 16 weeks of treatment, significantly more participants (94% vs 88%; P<0.05) achieved their LDL-cholesterol goal with rosuvastatin and fewer participants taking this drug required dose titration. Again, both treatments were similarly well tolerated (Berne et al, 2005).

Miller et al (2004) investigated the efficacy of simvastatin (40 and 80 mg) for raising HDL-cholesterol in participants with stable type 2 diabetes (HbA_{1c} <9% [<75 mmol/mol]). At the end of the study, both doses had significantly increased HDL-cholesterol from baseline (mean increases of 5% and 8% respectively) compared with placebo (Miller et al, 2004).

Three other studies involving people with type 2 diabetes were post hoc analyses of large trials. ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm; Sever et al, 2005) examined the effect of atorvastatin 10 mg/day on total CV outcomes in 2532 participants with hypertension and type 2 diabetes. At a median follow-up of 3.3 years, total and LDL-cholesterol levels were around 1 mmol/L lower in those randomised to atorvastatin than placebo, and 9.2% of participants had major CV events or procedures with atorvastatin versus 11.9% with placebo (P=0.036). Atorvastatin prevented around nine people with diabetes from suffering a first major event or procedure for every 1000 treated for 1 year (Sever et al, 2005).

The DALI (Diabetes Atorvastatin Lipid Intervention; van Venrooij et al, 2002) investigated the effect of 30 weeks atorvastatin therapy (10 and 80 mg) on endothelial function in 133 people with type 2 diabetes and dyslipidaemia, but no history of CVD. These people were found to have considerable endothelial dysfunction, and although aggressive lipid lowering with atorvastatin substantially lowered all atherogenic lipid parameters, it did not reverse endothelial dysfunction (van Venrooij et al, 2002).

The CARDS (Collaborative Atorvastatin Diabetes Study; Charlton-Menys et al, 2009) analysed the time between the initiation of atorvastatin 10 mg and the appearance of significant differences in the incidence of CV events when compared with placebo in 2350 people with type 2 diabetes and no prior history of CVD. By 6 months the effect of atorvastatin on CV events was already apparent and at 1 year it was similar to the 37% relative risk reduction observed at trial closure (Charlton-Menys et al, 2009).

Statins can reduce LDL-cholesterol by between 18% and 55%, and triglycerides by between 5% and 15% (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001). In addition to these benefits, statins can also increase HDL-cholesterol by between 3% and 10% (BCS et al, 2005). Although changes in lipid levels explain most of the observed benefits of statins (Simes et al, 2002), some treatment effects may be mediated through non-lipid mechanisms that modify endothelial dysfunction, inflammatory responses,

atherosclerotic plaque stability and thrombus formation (Rosenson and Tangney, 1998).

Fenofibrate

The FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study compared fenofibrate therapy with placebo in 9795 people with type 2 diabetes (2131 of which had previous CVD), who were not taking statin therapy at study entry, over 5 years (Keech et al, 2005). There were significant reductions in total cholesterol, LDL-cholesterol and triglyceride levels, and increases in HDL-cholesterol levels with fenofibrate versus placebo.

Although fenofibrate did not significantly reduce the risk of the primary outcome of coronary events, it did reduce total CV events and was also associated with less retinopathy needing laser treatment (3.6% vs 5.2% with placebo). There were slight increases in pancreatitis associated with fenofibrate treatment compared with placebo (0.8% vs 0.5%) and pulmonary embolism (1.1% vs 0.7%) respectively, but no other significant adverse effects. Gastrointestinal events were the most frequently reported adverse event (Keech et al, 2005).

Although some studies involving people with type 2 diabetes have found additional benefits on lipid profile from combining statin therapy with fenofibrate as compared with monotherapy with either (Athyros et al, 2002; Derosa et al, 2004), the more recent ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial suggests that the addition of fenofibrate to ongoing statin therapy offers only limited benefit (Toth, 2010).

Nicotinic acid

An early study of 13 participants with type 2 diabetes found that nicotinic acid 1.5 g three times daily reduced total cholesterol by 24%, plasma triglycerides by 45%, very-LDL (VLDL)-cholesterol by 58% and LDL-cholesterol by 15%, and increased HDL-cholesterol by 34% (Garg and Grundy, 1990). However, it also resulted in a deterioration of glycaemic control, as demonstrated by a 16% increase in mean plasma glucose, a 21% increase in HbA_{1c} levels, and the induction of marked glycosuria in some participants. Flushing was considered a minor complaint. Flushing can now be reduced with the combination of nicotinic acid with laropiprant.

The later ADMIT (Arterial Disease Multiple Intervention Trial) investigated efficacy and safety of nicotinic acid 3000 mg/day versus placebo, in 125 people with diabetes and a diagnosis of peripheral arterial disease, for up to 60 weeks. Nicotinic acid significantly increased HDL-cholesterol by 29% and reduced triglycerides and LDL-cholesterol by 23% and 8%, respectively. Nicotinic acid also caused small but significant increases in average glucose levels and increased uric acid levels over baseline values. Mean plasma alanine aminotransferase level was not significantly changed (Elam et al, 2000).

Omega-3 polyunsaturated fatty acids

The effect of omega-3 polyunsaturated fatty acids (omega-3 PUFA) on serum lipoproteins was investigated in a comprehensive review of the published literature. In total, 36 crossover and 29 parallel design studies using doses of around 4 g/day from fish oil were included in the analysis, a small number of which included people with diabetes. Although total cholesterol was not materially affected by long-chain omega-3 PUFA, LDL-cholesterol and HDL-cholesterol tended to increase by 5–10% and 1–3%, respectively, while serum triglyceride concentrations decreased by 25–30% (Harris, 1997).

A more recent study investigated the effects of omega-3 PUFA ethyl esters (4 g/day) in atorvastatin-treated (10, 20 and 40 mg/day) people with raised non-HDL-cholesterol and triglyceride levels. Omega-3 PUFA plus atorvastatin reduced median total cholesterol, LDL-cholesterol and triglyceride levels, and increased HDL-cholesterol levels, to a significantly greater degree than placebo plus atorvastatin (Bays et al, 2010).

However, while some trials have shown a reduction in CV risk with increased omega-3 PUFA intake (Burr et al, 1989; Siscovick et al, 1995; Gillum et al, 1996; GISSI [Gruppo Itlaiano per lo Studio della Sopravvivenza nell'Infarto miocardi] Prevenzione Trial Group, 1999; Albert et al, 2002), others have not (Morris et al, 1995; Oriencia et al, 1996; Nilsen et al, 2001; Burr et

Page points

1. In the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study, there were significant reductions in total cholesterol, low-density lipoprotein (LDL)-cholesterol, and triglyceride levels, and increases in high-density lipoprotein (HDL)-cholesterol levels with fenofibrate versus placebo.
2. An early study of 13 participants with type 2 diabetes found that nicotinic acid 1.5 g three-times daily reduced total cholesterol by 24%, plasma triglycerides by 45%, very-LDL cholesterol by 58% and LDL-cholesterol by 15%, and increased HDL-cholesterol by 34%.
3. Omega-3 polyunsaturated fatty acids (PUFA) plus atorvastatin reduced median total cholesterol, LDL-cholesterol and triglyceride levels, and increased HDL-cholesterol levels, to a significantly greater degree than placebo plus atorvastatin.
4. While some trials have shown a reduction in cardiovascular risk with increased omega-3 PUFA intake, others have not.

Page points

1. People with type 2 diabetes should be supported to try and achieve and maintain a lipid and lipoprotein profile that reduces the risk of vascular disease through combination of pharmacotherapy and dietary modification.
2. In addition to pharmacotherapy, lifestyle changes have also been shown to play an important role in managing dyslipidaemia, by reducing both total and low-density lipoprotein cholesterol levels and hence atherogenesis.

al, 2003). NICE (2007) recommends giving consideration to providing at least 1 g/day of omega-3 PUFA esters licensed for the secondary prevention of myocardial infarction (MI) for up to 4 years. It is not recommended for primary prevention by NICE, however advising people to eat two to three portions of oily fish a week seems a sensible approach.

Guidance on lipid levels in type 2 diabetes

Several guidelines have included recommendations on lipid modification for the prevention of CVD (BCS et al, 2005; SIGN, 2007; NICE, 2008a). However, the NICE guideline on type 2 diabetes (NCCCC, 2008) provides management recommendations specific to this patient group and the following sections of this module are based primarily on this guidance. In 2010, SIGN guideline 116 (SIGN, 2010) on the management of diabetes was published.

CVD risk estimation in people with type 2 diabetes

Risk equations are not generally used for people with diabetes since they are already considered to be at high risk of CVD (BCS et al, 2005; NICE, 2008a). A person with type 2 diabetes should be considered at high premature CV risk for their age, unless they (NCCCC, 2008):

- Are not overweight (according to risk associated with ethnic group).
- Are normotensive (<140/80 mmHg).
- Do not have microalbuminuria.
- Do not smoke.
- Do not have a high-risk lipid profile.
- Have no prior or family history of CVD.

If, on the basis of the above findings, a person is not considered to be at high CV risk, their risk should be estimated annually using the UK Prospective Diabetes Study risk engine (www.dtu.ox.ac.uk/riskengine). A full lipid profile, including triglyceride and HDL-cholesterol estimation, should be performed as part of this annual assessment and prior to initiating lipid-modifying therapy (NCCCC, 2008). This should be a fasting sample to allow for the accurate estimation of triglycerides and LDL-cholesterol.

People with type 2 diabetes should be supported to try and achieve and maintain a lipid and lipoprotein profile that reduces the risk of vascular disease, through combination of pharmacotherapy and dietary modification (NICE, 2008a).

Lifestyle measures for lipid lowering

In addition to pharmacotherapy, lifestyle changes have also been shown to play an important role in managing dyslipidaemia, by reducing both total and LDL-cholesterol levels and hence atherogenesis (Gross and Reese, 2005). For preventing CVD in high-risk individuals, management strategies are likely to require a combination of pharmacological and lifestyle interventions. NICE provides lifestyle recommendations based on review of the available evidence (NCCCC, 2008; NICE, 2008a; *Table 2*).

The benefits of structured exercise interventions also include reductions in HbA_{1c} and improvements in glycaemic control, independent of weight loss (Boulé et al, 2001). Although exercise alone – without dietary calorific restriction – tends to produce only modest weight loss of around 2 kg (Sigal et al, 2006), research has shown that 1 hour/day of moderate intensity exercise produced as much fat loss as the equivalent degree of caloric restriction, with greater resulting improvements in insulin sensitivity (Ross et al, 2000).

The amount of exercise required to achieve sustained major weight loss is probably much greater than that needed to achieve improved glycaemic control and CV health (Sigal et al, 2006). All people should be encouraged to exercise for 20–30 minutes twice a day and to combine this with a healthy diet, because the most successful programmes for long-term weight control have involved combinations

Table 2. Lifestyle measures for lipid modification (National Collaborating Centre for Chronic Conditions, 2008; NICE, 2008a).

- Consume a cardioprotective diet.
- Increase physical activity.
- Achieve and maintain a healthy weight.
- Moderate alcohol consumption.
- Stop smoking.

of diet, exercise and behaviour modification (Wing et al, 2002).

There are now clear dietary guidelines for intakes of omega 3 for different populations in the UK. For primary prevention of CVD in the general population, the Food Standards Agency (FSA, 2004) recommends eating two portions of fish per week, one of which should be oily. Diabetes UK (2009) recommends that all people with diabetes, who are at increased risk of CV disease, should be encouraged to oily fish at least twice per week.

The cholesterol-lowering efficacy and safety of plant sterols and stanols was investigated in a meta-analysis of 41 randomised, double-blind trials, of which 16 used plant sterols, 20 used plant stanols and five used both. The doses ranged from 0.7–3.3 g daily and were administered for an average of 7 weeks. The mean reductions in LDL-cholesterol were 9.7% for plant sterol 2.3 g/day, and 10.1% for plant stanol 2.5 g/day (Katan et al, 2003).

Furthermore, trials in people taking statins have shown that consuming plant sterol or stanol esters can reduce LDL-cholesterol by a further 7–11%, a greater effect than can be expected from doubling the statin dose (Thompson, 2005). However, to achieve this effect a sufficient quantity of the food supplement needs to be taken on a daily basis, which is expensive and adherence is poor as a result.

Statins

For people with type 2 diabetes aged ≥40 years, unless the CV risk from non-hyperglycaemia-related factors is low, statin therapy should be initiated with generic simvastatin (to 40 mg) or an alternative of similar efficacy and cost. If their risk from non-hyperglycaemia related factors is low, statin therapy should be initiated only if their CV risk exceeds 20% over 10 years (NCCCC, 2008). SIGN (2010) recommends lipid-lowering therapy with simvastatin 40 mg or atorvastatin 10 mg for primary prevention in people with type 2 diabetes aged >40 years regardless of baseline cholesterol.

For people with type 2 diabetes ≤40 years of age, statin therapy should be considered if their CV risk profile appears particularly poor, for example including multiple features of the metabolic syndrome, the presence of conventional risk factors, microalbuminuria, a strong family history of premature CVD or an at-risk ethic group (NCCCC, 2008).

Once initiated, statin dose may be increased to 80 mg daily in people with total cholesterol <4.0 mmol/L or LDL-cholesterol <2.0 mmol/L. In those with existing or newly diagnosed CVD, or an increased albumin excretion rate, therapy can be intensified with a more effective statin or ezetimibe, to achieve total cholesterol <4.0 mmol/L or LDL-cholesterol <2.0 mmol/L (NCCCC, 2008). However, a recent safety warning from the Medicines and Healthcare products Regulatory Agency (MHRA, 2010) about intensive therapy with simvastatin 80 mg, based on evidence from the SEARCH (Study of the Effectiveness of Additional Medications in Cholesterol and Homocysteine) trial, has led to alternative high-potency statins being used (SEARCH Collaborative Group et al, 2007).

Regarding arterial risk reduction in type 1 diabetes, NICE (2004) provides helpful advice. Arterial risk factors should be assessed annually. Arterial risk tables, equations or engines for calculation of arterial risk should not be used because they underestimate risk in adults with type 1 diabetes.

Ezetimibe

The combination of a statin with ezetimibe – the only cholesterol absorption inhibitor – can have a particular role to maximise LDL-cholesterol lowering and is recommended by NICE (NCCCC, 2008) when lipid targets are not met. It is useful when statins are not tolerated and can be effective when combined with low doses of statins when they cause side-effects. As yet there is no convincing outcome data to support this approach.

Fibrates

People with a history of elevated serum triglycerides should have a full fasting lipid profile, including triglyceride and HDL-cholesterol, performed as part of their annual CV risk estimation. Possible secondary causes of hypertriglyceridaemia, for example hypothyroidism, renal impairment and

Page points

1. For people with type 2 diabetes aged ≥40 years, unless the cardiovascular risk from non-hyperglycaemia-related factors is low, statin therapy should be initiated with generic simvastatin (to 40 mg) or an alternative of similar efficacy and cost.
2. The combination of a statin with ezetimibe, the only cholesterol absorption inhibitor, can have a particular role to maximise low-density lipoprotein-cholesterol lowering and is recommended by NICE when lipid targets are not met.
3. People with a history of elevated serum triglycerides should have a full fasting lipid profile, including triglyceride and high-density lipoprotein-cholesterol, performed as part of their annual cardiovascular risk estimation.

Page points

1. Although NICE does not recommend routine use of nicotinic acid in people with type 2 diabetes, it may have a role in a small number of people with more extreme disorders of blood lipid metabolism and intolerance to other therapies, but only when managed by specialists in this area.
2. Fish oil preparations are not recommended for the primary prevention of cardiovascular disease in people with type 2 diabetes, unless prescribed by a healthcare professional with expertise in blood lipid management for hypertriglyceridaemia.
3. Although statin therapy is associated with a slightly increased risk of developing diabetes, the risk is low in both absolute terms and when compared with the reduction in coronary events.

liver inflammation, should be investigated and managed if found.

Fibrate therapy, and fenofibrate first-line, is recommended if triglyceride levels remain >4.5 mmol/L. Where CV risk is high and triglyceride levels remain between 2.3–4.5 mmol/L despite statin therapy, a fibrate may be added (NCCCC, 2008), but this recommendation was made before the results of the ACCORD trial were available.

The ACCORD study published this year showed that combination therapy with fenofibrate and simvastatin failed to reduce the risk of fatal CV events, non-fatal MI or non-fatal stroke in high-risk people with diabetes. However, subgroup analysis suggested that those with higher baseline triglycerides and lower HDL-cholesterol levels benefited from the combination more than the overall cohort (ACCORD Study Group et al, 2010).

Nicotinic acid

Although NICE does not recommend routine use of nicotinic acid in people with type 2 diabetes, it may have a role in a small number of people with more extreme disorders of blood lipid metabolism and intolerance to other therapies, but only when managed by specialists in this area (NCCCC, 2008). If nicotinic acid is used in people with diabetes, their antidiabetes medication may need to be titrated up.

Omega-3 fish oils

Fish oil preparations are not recommended for the primary prevention of CVD in people with type 2 diabetes, unless prescribed by a healthcare professional with expertise in blood lipid management for hypertriglyceridaemia. A trial of a highly concentrated licensed product may be considered for people with refractory hypertriglyceridaemia if fibrate therapy and lifestyle measures have failed (NCCCC, 2008).

Follow-up

After initiating lipid-lowering therapy in a person with type 2 diabetes, assess their lipid profile, modifiable risk factors and any new diagnosis of CVD within 1–3 months after starting treatment, then annually thereafter (NCCCC, 2008). It is appropriate to check hepatic, renal, thyroid function and creatinine kinase (CK) prior to starting statins, as a baseline. Routine measurement of CK in the absence of symptoms is unlikely to be helpful and may be confusing because of day-to-day variability.

It is reasonable to check alanine transaminase (ALT) levels at 1–3 months when the first follow-up lipid level is checked. In asymptomatic patients a rise of ALT up to three times and a CK up to five times the upper limit can be acceptable but would need to be monitored more regularly.

Statins and risk of incident diabetes

JUPITER (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin; Ridker et al, 2008) reported an increased risk for diabetes in patients assigned to the rosuvastatin arm, and the PROSPER (Pravastatin in Elderly Individuals at Risk of Vascular Disease; Shepherd et al, 2002) trial reported similar findings with pravastatin.

A recent meta-analysis (Sattar et al, 2010) investigated this relationship via 13 statin trials conducted between 1999 and 2009 that involved 91 140 participants, of whom 4278 (2226 assigned statins versus 2052 assigned control treatment) developed diabetes over a mean of 4 years. Statin therapy was associated with a 9% increased risk for incident diabetes (odds ratio, 1.09; 95% CI, 1.02–1.17), with little heterogeneity between trials.

The risk of developing diabetes with statin therapy was highest in trials involving older participants. To put it into perspective, treating 255 people with statins for 4 years resulted in one extra case of diabetes. The authors concluded that although statin therapy is associated with a slightly increased risk of developing diabetes, the risk is low in both absolute terms and when compared with the reduction in coronary events (Sattar et al, 2010).

Statins in older people, children and women

Statins have been underused in older people due to limited evidence that they reduce mortality (Golomb, 2005; Afilalo et al, 2008) and concerns that their adverse effects (such as muscle and

cognitive problems) may be amplified in this group (Golomb, 2005).

The PROSPER trial found that pravastatin given for 3 years reduced the risk of coronary disease in people aged 70–82 years with or at high risk of CVD, and had no significant effect on cognitive function or disability (Shepherd et al, 2002). A more recent meta-analysis, including data from 19 569 participants with CHD aged between 65 and 85 years, estimated a relative risk reduction of 22% over 5 years. Statins reduced CHD mortality by 30%, non-fatal MI risk by 26%, need for revascularisation by 30% and risk of stroke by 25%. The number needed to treat to save one life was estimated at 28. Conclusions were that statins reduce all-cause mortality in older people with a substantially larger effect that previously estimated (Afilalo et al, 2008).

All people aged over 75 years should be assumed to be at increased risk of CVD – particularly if they have raised blood pressure or smoke – and are considered likely to benefit from statin therapy. However, the decision to initiate lipid modification therapy should be guided by informed individual preference, comorbidites, and the likely benefits and risks (NICE, 2008a). When initiating statin therapy for older people, dose adjustment is not generally necessary. Because this population has an increased risk of rhabdomyolysis, a reference CK level should be measured before starting treatment.

A number of statins are licensed for use in children aged 10 years and over for the treatment of primary hypercholesterolaemia (Electronic Medicines Compendium, 2010a; 2010b; 2010c; 2010d).

Statin therapy in pregnancy is contraindicated. Maternal treatment with a statin may reduce fetal levels of mevalonate, which is a precursor of biosynthesis. Because atherosclerosis is a chronic process, and discontinuation of lipid-lowering agents while trying to conceive and during pregnancy is likely to have little effect on long-term CV risk, the licence holders recommend that these drugs are not used in these circumstances (Electronic Medicines Compendium, 2010a; 2010b; 2010c; 2010d; 2010e).

In women with type 2 diabetes who may become pregnant, NICE does not recommend statins unless the issues have been discussed and agreed (NCCCC, 2008). NICE (2008b) guidance on the management of individuals with familial hyperlipidaemia recommends that women wishing to become pregnant should be advised to stop statins three months prior to attempting to conceive. Bile acid sequestrants can be used with caution, but may cause fat-soluble vitamin deficiency on prolonged use and may need supplementation.

Current management of dyslipidaemia in people with diabetes

The National Diabetes Audit showed that between 2008 and 2009 in England, 78% of people with type 1 diabetes and 94% of people with type 2 diabetes had their cholesterol checked. The NICE target of <5 mmol/L was achieved by 56% of people with type 1 diabetes and 73% of people with type 2 diabetes. The tighter <4 mmol/L target introduced in 2008 was achieved in only 24% of people with type 1 diabetes and 37% of people with type 2 diabetes. The <5 mmol/L target was achieved less often in those under the age of 40, possibly due to this age being a common clinical threshold for preventative treatment with statins (NHS Information Centre, 2010). *Table 3* details the current QOF indicators for lipid modification in people with diabetes.

Significant improvements have been made in lipid management in primary care. In people with type 2 diabetes, use of lipid-lowering drugs increased from 8% in 1997 to 85% in 2007, compared with 3–29% in matched individuals without diabetes (*Figure 1*). Between 2001 and 2007, people with type 2 diabetes treated with insulin experienced a mean reduction in

Page points

1. All people aged over 75 years should be assumed to be at increased risk of cardiovascular disease – particularly if they have raised blood pressure or smoke – and are considered likely to benefit from statin therapy.
2. Statin therapy in pregnancy is contraindicated.
3. Significant improvements have been made in lipid management in primary care. In people with type 2 diabetes, use of lipid-lowering drugs increased from 8% in 1997 to 85% in 2007, compared with 3–29% in matched individuals without diabetes.

Table 3. QOF indicators related to lipid modification in people with diabetes (BMA and NHS Employers, 2009).

Indicator	Points	Payment stages
DM 16: Percentage of patients with diabetes who have a record of total cholesterol within previous 15 months.	3	40–90%
DM 17: Percentage of patients with diabetes whose last total cholesterol, measured within the previous 15 months, is ≤5 mmol/L.	6	40–70%

"To improve adherence we need to ensure regular follow-up and good communication, simple drug regimens that are tailored to suit the individual, education about the condition and reasons for therapy, and the provision of dedicated cardiovascular disease and diabetes clinics to monitor progress and improve motivation."

total cholesterol of 1.4 mmol/L, from 5.6 to 4.2 mmol/L. This 25% relative improvement in total cholesterol was significantly greater than the relative improvements in HbA_{1c} level (1% in people with type 1 diabetes), and systolic and diastolic blood pressure (5%), over the same time-frame (Currie et al, 2010).

Boxes 1 and *2* contain two case studies that highlight some of the practical issues encountered in the management of people with diabetes and dyslipidaemia.

Conclusion

To prevent CVD in people with diabetes, "total" CV risk management is required to maximise risk reduction, with the modification of lipids being one essential component.

Medication adherence is the key to achieving benefits from drug therapy for the prevention of CVD, and to gain maximum benefits individuals probably need to take the drugs at the recommended doses for the rest of their lives. However, Bandolier (2007) found that the majority of people prescribed statins had either stopped taking the drug altogether or were taking less than the recommended dose within 12 months, and women showed poorer adherence than men.

To improve adherence we need to ensure regular follow-up and good communication, simple drug regimens that are tailored to suit the individual, education about the condition and reasons for therapy, and the provision of dedicated CVD and diabetes clinics to monitor progress and improve motivation. ■

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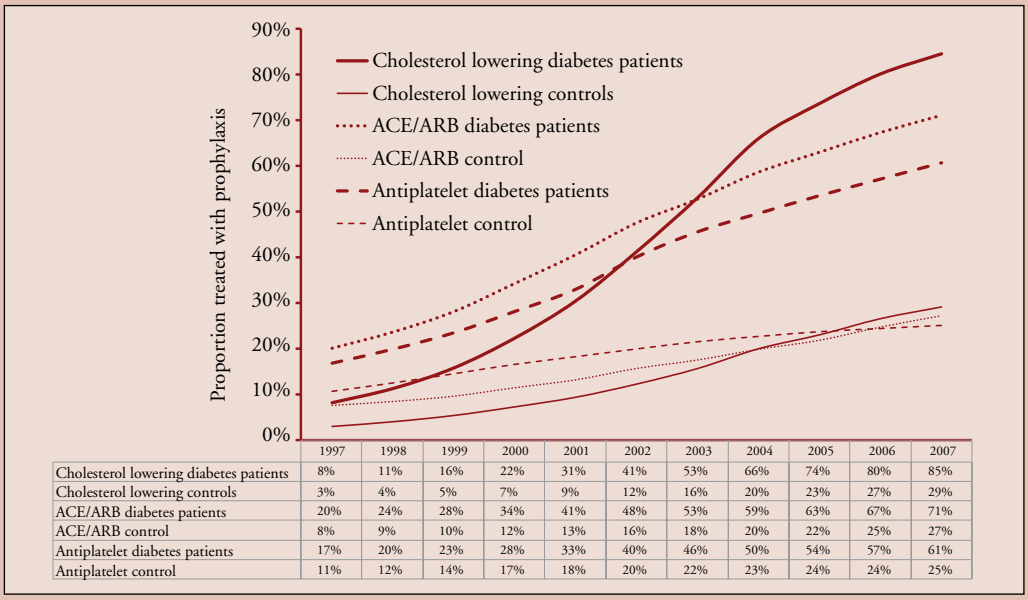

	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
Cholesterol lowering diabetes patients	8%	11%	16%	22%	31%	41%	53%	66%	74%	80%	85%
Cholesterol lowering controls	3%	4%	5%	7%	9%	12%	16%	20%	23%	27%	29%
ACE/ARB diabetes patients	20%	24%	28%	34%	41%	48%	53%	59%	63%	67%	71%
ACE/ARB control	8%	9%	10%	12%	13%	16%	18%	20%	22%	25%	27%
Antiplatelet diabetes patients	17%	20%	23%	28%	33%	40%	46%	50%	54%	57%	61%
Antiplatelet control	11%	12%	14%	17%	18%	20%	22%	23%	24%	24%	25%

Figure 1. The proportion of people with type 2 diabetes treated with cardiovascular risk-modifying drugs from 1997 to 2007. ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker. Reproduced from Currie et al (2010) with permission of Blackwell Publishing Ltd. © 2010, The Authors.

Box 1. Case study.

Narrative

Mr AG is a 62-year-old man and 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 7.6% (60 mmol/mol). His estimated glomerular filtration rate is 58 mL/min/1.73m^2, and blood pressure is 146/88 mmHg. He takes metformin 0.5 g twice daily and ramipril 5 mg daily and follows a healthy lifestyle programme diligently.

He had been on simvastatin 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 level of 0.9 mmol/L, triglyceride level of 2.7 mmol/L, and low-density lipoprotein (LDL)-cholesterol 3.27 mmol/L.

His calculated 10-year risk of coronary heart disease (CHD) was 40.6%, fatal CHD 26.4%, stroke 15.2% and fatal stroke 2.5%.

Discussion

Mr AG was subsequently started on pravastatin 40 mg. His muscle pains were no longer a problem but his targets (cholesterol level of 4 mmol/L and LDL-cholesterol level of 2 mmol/L) remained elusive until ezetimibe 10 mg was prescribed. Amlodipine 5 mg was also added to his regimen to achieve a target blood pressure of less than 130/80 mmHg, and metformin titrated up to 2 g.

Box 2. Case study.

Narrative

Mrs GH, a teacher aged 48 years, attends for an NHS 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 cholesterol, high-density lipoprotein (HDL)-cholesterol and creatinine/estimated glomerular filtration rate.

Her cholesterol level was 5.8 mmol/L with HDL-cholesterol at 0.95 mmol/L. Her glucose level was 7.1 mmol/L and her renal function was normal.

A subsequent glucose tolerance test confirmed type 2 diabetes with a fasting glucose level of 7.2 mmol/L and a 2-hour glucose level of 12 mmol/L. LDL-cholesterol level was 3.57 mmol/L and triglycerides were 2.8 mmol/L. Her HbA_{1c} level was 8.2% (66 mmol/mol). No end organ damage was identified and there was no microalbuminuria.

Discussion

Mrs GH was provided with lifestyle advice and started on simvastatin 40 mg and an angiotensin-converting enzyme inhibitor as her blood pressure remained high. Metformin will be introduced if the HbA_{1c} level fails to fall below 7.0% (53 mmol/mol) with the diet and exercise regimen.

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CPD module

Online CPD activity

Visit www.diabetesandprimarycare.co.uk/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. 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 learned in practice.

1. There is a distinction between hyperlipidaemia and dyslipidaemia. The term "dyslipidaemia" is used to describe which of the following? Select ONE option only.

A. Raised serum levels of total cholesterol, low-density lipoprotein (LDL)-cholesterol and triglycerides.
B. Raised serum levels of total cholesterol, LDL-cholesterol and high-density lipoprotein (HDL)-cholesterol.
C. Raised serum levels of total cholesterol and triglycerides combined.
D. Raised serum levels of one or more of total cholesterol, LDL-cholesterol and triglycerides plus low serum levels of HDL-cholesterol.
E. Raised serum levels of total cholesterol, LDL-cholesterol and HDL-cholesterol plus low serum levels of triglycerides.

2. A meta-analysis of 14 trials using statins showed that a 1 mmol/L reduction in LDL-cholesterol reduced the 5-year risk of major coronary events and stroke by which of the following proportions? Select ONE option only.

A. One-third.
B. One-quarter.
C. One-fifth.
D. A half.
E. Three-quarters.

3. Statins can reduce LDL-cholesterol and triglyceride levels by which of the following amounts? Select ONE option only.

A. 3–7% and 10–15%, respectively.
B. 15–30% and 3–10%, respectively.
C. 5–15% and 18–55%, respectively.
D. 18–55% and 5–15 %, respectively.
E. 25–30% and 15–20%, respectively.

4. In the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study, which compared fenofibrate with placebo, fenofibrate was associated with which of the following? Select ONE option only.

A. Insignificant reductions in total cholesterol, LDL-cholesterol and triglyceride levels.
B. Less retinopathy needing laser treatment.
C. A significant reduction in the risk of the primary outcome of coronary events.
D. A reduced incidence of pancreatitis.
E. A reduced incidence of pulmonary embolism.

5. In the two studies evaluating lipid-lowering doses of nicotinic acid, what was the common finding? Select ONE option only.

A. Nicotinic acid was associated with increased plasma glucose levels.
B. Nicotinic acid was associated with increased uric acid levels.
C. Flushing was a major complaint.
D. Mean plasma alanine aminotransferase levels were significantly changed.
E. Nicotinic acid was associated with a reduction in HDL-cholesterol levels.

6. In a comprehensive review of the published literature, omega-3 polyunsaturated fatty acids were found to most beneficially affect which of the following? Select ONE option only.

A. Total cholesterol concentrations.
B. LDL-cholesterol concentrations.
C. HDL-cholesterol concentrations.
D. Triglyceride concentrations.
E. All of the above.

7. Which of the following does NICE not include in its guidance on lipid-modification therapies for people with type 2 diabetes? Select ONE option only.

A. Statins.
B. Fibrates.
C. Bile acid sequestrants.
D. Nicotinic acid.
E. Ezetimibe.

8. A 67-year-old man with type 2 diabetes who has had stable angina and microalbuminuria for 2 years attends for review. Following NICE guidance, statin therapy or ezetimibe should be used to achieve which of the following targets in this person? Select ONE option only

A. Total cholesterol <4.0 mmol/L or LDL-cholesterol <2.0 mmol/L.
B. Total cholesterol <5 mmol/L and HDL-cholesterol >1.4 mmol/L.
C. Total cholesterol 4.0–5.0 mmol/L and LDL-cholesterol <2.0 mmol/L.
D. LDL-cholesterol <3.0 mmol/L and HDL-cholesterol >1.4 mmol/L.
E. None of the above.

9. A 59-year-old man with type 2 diabetes and known hypertension attends for review following a ST elevation myocardial infarction 3 weeks previously, during which he required two stents to be inserted. The man is on maximal statin therapy. In a person such as this, when does NICE recommend adding a fibrate to statin therapy? Select ONE option only.

A. When total cholesterol remains >4.0 and LDL-cholesterol remains >2.0 mmol/L despite statin therapy.
B. When total cholesterol remains >5.0 mmol/L and LDL-cholesterol remains >3.0 mmol/L despite statin therapy.
C. When triglyceride levels remain >1.7 mmol/L despite statin therapy.
D. When triglyceride levels remain between 2.3–4.5 mmol/L despite statin therapy.
E. When the person has secondary causes of hypertriglyceridaemia.

10. A 47-year-old Asian man with impaired glucose tolerance attends the surgery for advice about reducing cardiovascular risk. Which of the following does NICE not include in its lifestyle recommendations for lipid modification in such people? Select ONE option only.

A. Cardioprotective diet.
B. Weight management.
C. Moderate alcohol consumption.
D. Smoking cessation.
E. Stress management.