Lipid management in people with diabetes

Michael Kirby

ARTICLE POINTS

1 Most people with diabetes do not receive cholesterol-lowering therapy despite their elevated risk.

2 Recent evidence has amassed to guide lipid management in people with diabetes whether they do or do not have pre-existing coronary heart disease.

3 Analysis of the GREACE study indicated that fewer of the CHD patients with diabetes who received atorvastatin-based care when treated to a stringent target had a major cardiovascular event or died than those given usual care.

4 Treatment with statins should be considered for all people with diabetes at a high risk of cardiovascular events.

5 Regular review of patients' individual management plans will monitor concordance with treatment to ensure that lipid targets are achieved.

KEY WORDS

- **Lipid levels**
- **CHD**
- **Statins**
- **Targets**

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Introduction

People with diabetes are at a greatly increased risk of developing macrovascular disease, principally myocardial infarction and stroke, compared with people without diabetes. There is clear evidence that risk factor modification reduces this risk. The benefits of antihypertensive and hypoglycaemic agents have been extolled for some time but the uptake of lipid lowering therapy has been much slower. This review focuses on the importance of addressing this important risk factor.

Management of diabetes accounts for a growing proportion of the practice workload. Approximately 1.3 million people are currently diagnosed with diabetes in the UK and many hundreds of thousands may have type 2 diabetes without knowing it (DoH, 2001). A practice population of 10 000 is likely to include 200–300 people with diabetes and probably significantly more in parts of the country with higher proportions of people from black and ethnic minority groups.

Diabetes is a chronic and progressive disease state characterised by a raised blood glucose level. It is associated with premature death, ill health and disability. Overall, life expectancy is reduced by an average of more than 20 years in people with type 1 diabetes and by up to 10 years in people with type 2 diabetes (DoH, 2001).

Complications

The loss of control over blood glucose levels puts people with diabetes at risk of microvascular and macrovascular complications. Microvascular complications include:

- Retinopathy, which may lead to visual impairment and blindness.
- Nephropathy, which may result in progressive renal failure.
- Neuropathy, which may result in the development of foot ulcers and lower limb amputation.

Important as these complications are, it is the macrovascular complications of diabetes (principally myocardial infarction and stroke) that shorten the lives of most people who have the disease (Haffner et al, 1998). The incidence of macrovascular complications in people with type 2 diabetes in the UK is twice that of microvascular disease (Turner et al, 1996).

Cardiovascular disease arises as a result of atheromatous damage to the walls of the large blood vessels in:

- The coronary circulation, where it may result in angina, acute myocardial infarction and heart failure.
- The cerebrovascular circulation, where it may result in stroke and transient ischaemic attacks.
- The peripheral vascular system, particularly the large blood vessels supplying the lower limbs, where it may result in poor circulation and cause leg pain on walking and predisposition to the development of foot ulcers and amputation.

Up to 70% of adults with type 2 diabetes have raised blood pressure and more than 70% have abnormal cholesterol levels (DoH, 2001). Raised blood pressure and abnormal cholesterol levels increase the risk of developing cardiovascular disease as well as microvascular complications. However, epidemiological studies have shown that the greater mortality in people with type 2 diabetes compared with the general population is not explained solely by the presence of classic risk factors of hypertension, increased plasma cholesterol and smoking (Stamler et al, 1993).

We know from the UKPDS that a quintet of potentially modifiable risk factors for coronary artery disease exists in people with type 2 diabetes (Turner et al, 1998):

- Increased concentrations of low density lipoprotein (LDL) cholesterol.
- Decreased concentrations of high density lipoprotein (HDL) cholesterol.
- Raised blood pressure.
- Hyperglycaemia.
- Smoking.

Therefore, it is essential that management of people with diabetes should focus on managing these risk factors.

UK medical practice has tended to focus on blood concentrations of total and LDL-cholesterol with respect to lipid levels. Yet in both type 1 and type 2 diabetes, blood concentrations of total and LDL cholesterol are typically similar to those in the general population. Perhaps as a consequence, most people with diabetes do not receive cholesterol-lowering therapy despite their elevated risk, apart from those who have marked dyslipidaemia or pre-existing coronary heart disease (Pyorala et al, 1987). Instead, the management focus in these patients has tended to be on the control of blood glucose and blood pressure (DoH, 2001).

In type 2 diabetes, blood triglyceride concentrations tend to be elevated and HDL-cholesterol concentrations reduced even when metabolic control is good. A similar pattern tends to emerge in type 1 diabetes only when glycaemic control is poor (Pyorala et al, 1987). Furthermore, despite the normal or near-normal levels of LDL-cholesterol, the shift to a lipid profile dominated by highly atherogenic small dense LDL-cholesterol particles makes people with diabetes candidates for lipid-lowering therapy (Turner et al, 1998).

Evidence from intervention studies

In the past, many clinical trials of lipid lowering therapy excluded patients with diabetes, making it unclear whether lipid lowering had equivalent, or more or less effectiveness in this group compared with people without diabetes. Recently, however, a significant amount of evidence has amassed to guide lipid management in people with diabetes, whether they do or do not have pre-existing coronary heart disease.

The Veterans Affairs High-density Lipoprotein Cholesterol Intervention Trial

The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) study enrolled men with existing CHD and a dyslipidaemia similar to that found in people with diabetes (low HDL-cholesterol and average LDL-cholesterol levels). Participants were randomised to the fibric acid derivative gemfibrozil or placebo (Rubins et al, 1999). At 5 years follow-up, the fibrate was associated with a 22% reduction in non-fatal myocardial infarction or death from coronary causes. The benefit was similar among the participants with diabetes (25% of the total cohort), although the numbers were too small to show significance.

Sub-analyses of data from lipid lowering studies

The clinical benefit of statins in people with diabetes compared with people without diabetes was demonstrated in the Scandanavian Simvastatin Survival Study (Haffner et al, 1999), the Cholesterol Lowering and Recurrence Events study (Goldberg et al, 1998) and the Long-term Intervention with Pravastatin in Ischaemic Disease study (LIPID Study Group, 1998).

The GREACE study

The Greek Atorvastatin and Coronary-Heart Disease Evaluation (GREACE) study was conducted in 1600 patients with existing CHD. One group received 'usual care' which comprised lifestyle advice plus cholesterol lowering treatment as necessary. The other group were treated with atorvastatin. The latter group had a reduced total mortality rate of 43%. CHD mortality was reduced by 47% and stroke by 47% (Athyros et al, 2002). Patients were started on 10 mg atorvastatin and doses were titrated to reach a target LDL-cholesterol of 2.6 mmol/l, which is lower than the current UK target of 3 mmol/l. Overall, 95% of participants in the atorvastatin group achieved the LDL-cholesterol goal (the mean atorvastatin dose was 23.7 mg/day), illustrating the importance of dose titration.

Subgroup analysis of the 313 diabetes patients enrolled in this study shows that

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3 In type 2 diabetes, blood triglyceride concentrations tend to be elevated and HDL-cholesterol concentrations reduced even when metabolic control is good.

4 The shift to a lipid profile dominated by highly atherogenic small dense LDL-cholesterol particles makes people with diabetes candidates for lipid-lowering therapy.

5 The evidence for the benefits of secondary prevention with statins is now clear and has been reinforced by recent studies.

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1 Although arterial hypertension is the major predictor of stroke, statins can beneficially affect the atherosclerotic process in the carotids and prevent stroke, at least in high-risk patients.

2 In view of the significant stroke benefit in this study, it is notable that 20 mg/day of atorvastatin has previously been shown to rapidly reduce carotid intima-media thickness.

3 In the Heart Protection Study, treatment with 40 mg simvastatin reduced the rate of first major cardiovascular events by about a quarter.

4 Statin therapy should now be considered for all people with diabetes at a high risk of major cardiovascular events, irrespective of their initial cholesterol concentrations.

5 The challenge for practice diabetes teams is to extend their highly structured and systematic approachs to management to cover lipid abnormalities.

over the 3-year duration, 46 of 152 (30.3%) CHD patients with diabetes given usual care had a major vascular event or died. This was compared with 20 people out of 161 (12.5%) of those given atorvastatin-based care, which represents a relative risk reduction of 58% ($p < 0.0001$; Athyros et al, 2003). Highly significant reductions in risk were also seen in all-cause mortality (52%; $p = 0.049$), coronary mortality (62%; $p = 0.042$), coronary morbidity (59%; $p < 0.002$) and stroke (68%; $p = 0.046$).

The graph curves for all events and endpoints, such as coronary death, non-fatal myocardial infarction, and revascularisation began to show significant divergence by 6 months of treatment with atorvastatin treatment and remained significant until the end of the study. This reinforces the need for early and effective lipid lowering in people with diabetes and existing CHD.

Although arterial hypertension is the major predictor of stroke, statins can beneficially affect the atherosclerotic process in the carotids and prevent stroke, at least in high-risk patients. Meta-analyses of previous studies suggest that statin therapy lowers stroke risk by about 30% in patients with CHD (Blauw et al, 1997). In view of the significant stroke benefit in this study, it is notable that 20 mg/day of atorvastatin has previously been shown to rapidly (within 8 weeks) reduce carotid intima-media thickness, a surrogate marker for stroke risk (Youssef et al, 2002).

Overall, the GREACE study suggests that there is great benefit in adding atorvastatin to the structured care regimen of people with diabetes and coronary heart disease. Six patients would need to be treated for 3 years to avoid an event of any fatal or non-fatal event. Eight patients would need to be treated to avoid one non-fatal vascular event and 26 patients would need to be treated to avoid one death from any cause. Patients receiving atorvastatin-based structured care had significantly fewer hospitalisations for recurrent CHD events and revascularisation procedures than those receiving usual care. The study authors estimated that this was able to offset 91% of the drug cost.

Heart Protection Study

While the case for treating CHD patients with a statin is now unarguable, data are also emerging to suggest benefit in primary prevention among people with diabetes. In the Heart Protection Study (in which 20 000 patients participated) treatment with 40 mg simvastatin reduced the rate of first major cardiovascular events by about a quarter. After making allowance for non-compliance, it was estimated that 5 years of treatment would prevent about 45 people per 1000 from having at least one major cardiovascular event, and among these people, would prevent about 70 first or subsequent events during this treatment period (Collins et al, 2003).

The Collaborative Atorvastatin Diabetes Study

A further primary prevention study in people with diabetes was recently discontinued before completion due to the overwhelming benefit in the active treatment group. The Collaborative AtoRvastatin Diabetes Study (CARDS) randomised 2838 patients and was designed to compare the effectiveness of 10 mg atorvastatin with placebo in the primary prevention of cardiovascular disease in people with diabetes and additional cardiovascular risk factors. By the third year of treatment >30% reduction had been recorded in the primary endpoint of major coronary events, stroke or coronary revascularisation procedures ($p < 0.0005$). Therefore, statin therapy should now be considered for all people with diabetes at a high risk of major cardiovascular events, irrespective of their initial cholesterol concentrations.

Putting the evidence into practice

The NSF for Diabetes recommends that clinicians adopt a global approach towards management of all modifiable cardiovascular risk factors in patients with type 2 diabetes. Over the years, most practice diabetes teams have become adept at managing hyperglycaemia and hypertension in patients with diabetes. The challenge for practice diabetes teams is now to extend this highly structured and systematic approach to management to cover lipid abnormalities.

Recent NICE guidance recommends that patients with type 2 diabetes should have their blood pressure taken at least once a year and their blood lipid levels checked annually, using fasting measurements where

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1 Antihypertensive medicines should be considered, with a target blood pressure of <140/80 mmHg, where patients have a 10-year coronary event risk of >15% or a blood pressure ≥160/100 mmHg.

2 A 10-year coronary risk threshold of 15% is recommended for people with elevated blood lipid levels.

3 Prescription data shows that 30–68% of prescriptions for the three most used statins are written for the lowest dose available, suggesting considerable potential for dose-titration.

4 Audit in our practice suggests that nurse-led clinics significantly improve the assessment of patients, but with a smaller improvement in target attainment.

5 An individual management plan should be negotiated with each patient, allowing the patient to select his or her choice of long-term follow-up and to set their own goals for risk factors such as cholesterol.

feasible (NICE, 2002). Lipid measurements should be obtained of total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides.

People with a blood pressure of 140/80 mmHg or higher should initially be offered advice on lifestyle changes (such as diet and exercise) to help prevent further rises. Anti-hypertensive medicines should be considered, with a target blood pressure of < 140/80 mmHg, where patients have a 10-year coronary event risk of > 15% or a blood pressure ≥ 160/100 mmHg.

Similarly, a 10-year coronary risk threshold of 15% is recommended for people with elevated blood lipid levels. Patients should initially be offered advice on lifestyle changes, principally regarding diet and exercise. Irrespective of 10-year coronary risk, treatment with a statin should be considered for people with any of the following:

- A total cholesterol of ≥ 5.0 mmol/l.
- A LDL-cholesterol of ≥ 3.0 mmol/l.
- Triglycerides ≥ 2.3 mmol/l.

Treatment should aim to reduce total cholesterol to < 5.0 mmol/l or by 20–25% (whichever is lower), or to reduce LDL-cholesterol to below 3.0 mmol/l or by 30% (whichever is lower).

Dose titration is important to achieve lipid targets with statins. However, there is evidence that this does not happen at present. A recent study which looked at prescription data from 78 600 patients in primary care suggested that a 'rule of halves' now applies to management of cholesterol in patients with coronary heart disease (de Lusignan, 2003). Based on data from the Health Survey for England, the authors suggest that this treatment gap is likely to result in around 7150 new heart attacks nationally each year. Furthermore, prescription data shows that 30–68% of prescriptions for the three most used statins are written for the lowest dose available, suggesting considerable potential for dose-titration.

Organising diabetes care in the practice

Most practices now maintain an up-to-date register of all patients with diabetes, ensuring systematic call and recall of patients to the practice or hospital. This means that a full review is carried out at initial diagnosis and at least annually for each patient. For many practices, this care is delivered by nurses through diabetes clinics that operate according to assessment and management protocols agreed by the practice GPs.

Nurse-led clinics offer an excellent opportunity for patient education and for provision of essential advice on lifestyle issues, particularly regarding diet, exercise and alcohol consumption. Studies have now shown that nurse-led secondary prevention clinics focusing on both medical and lifestyle components significantly reduce total deaths and coronary events, with the benefit persisting for several years.

A practice audit

Audit in our practice suggests that nurse-led clinics significantly improve the assessment of patients, but with a smaller improvement in target attainment. This may be because while the nurses do an excellent job in terms of monitoring patients, alterations to treatment have to be made by the GP who may not always be available at the clinic. If we are to improve the poor state of practice regarding dose-titration of lipid lowering drugs, this is a situation that clearly needs to be addressed. In our practice, the nurse organises prescriptions to be signed by the GP. However, nurse prescribing would make life simpler and improve target attainment by dose titration.

Monitoring of lipid levels should begin at the initial visit of a patient with newly diagnosed diabetes. At this and each subsequent consultation, the nurse should provide the patient with information about the importance of monitoring their lipid levels and keeping within target levels. Advice should be given on lifestyle issues, particularly regarding diet, exercise and alcohol consumption.

An individual management plan should be negotiated with each patient, allowing the patient to select his or her choice of long-term follow-up and to set their own goals for risk factors such as cholesterol. Where possible, these goals should be consistent with those set out in the NSF for Diabetes. After 3 months stabilisation of blood glucose, a fasting blood lipid profile should be obtained. For patients with an elevated LDL-cholesterol level a statin may need to be initiated by the GP. For patients in whom

HDL-cholesterol levels are low, or triglyceride levels are elevated, a fibrate may be indicated. Where there is a mixed dyslipidaemia requiring treatment with a statin and a fibrate, advice should be sought from a diabetologist or lipid specialist who will have more advice about combination use.

Liver function tests are required following initiation of lipid lowering treatment. Prior to each patient's attendance at the annual review clinic, it may be helpful if the practice receptionist contacts the patient to ensure they are booked in for the appropriate blood tests, so that the results are available at the clinic appointment. The practice nurse should then interpret the blood results, including the lipid profile, with the patient and answer any queries that arise. Regular review of the patient's individual management plan at each appointment should help monitor concordance with treatment to ensure that lipid targets are achieved.

Conclusion

The use of statins for primary prevention in high-risk patients and also those with konwn coronary heart disease has been poor (Primatesta and Poulter, 2000). The publication of recent NICE guidelines and the NSF for Diabetes have clarified the situation and empowered clinicians to focus on the reduction of risk.

Cardiovascular risk is the major source of morbidity and mortality in people with diabetes. Recent studies support the use of statins in these patients. When statins are used in conjunction with other therapeutic agents the burden of cardiovascular disease will be reduced significantly. ■

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