The efficacy and safety of statins in type 2 diabetes

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ARTICLE POINTS

1 Coronary heart disease is the main cause of death in people with type 2 diabetes.

2 Treatment of hyperglycaemia alone is insufficient to reduce the risk of macrovascular disease since these people have many other risk factors for coronary heart disease, including dyslipidaemia.

3 Recent UK guidelines on the management of type 2 diabetes recommend aggressive treatment of dyslipidaemia in type 2 diabetes.

4 UK guidelines recommend statins as first-line treatment in type 2 diabetes.

KEY WORDS
- Coronary heart disease
- Risk factors
- Dyslipidaemia
- Statins
- Guidelines

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Introduction

There is clear evidence that risk-factor modification reduces the incidence of coronary heart disease (CHD) in people with type 2 diabetes. This is an important finding, since this group of people are at greatly increased risk of developing CHD compared with people without diabetes. While the benefits of antihypertensive and hypoglycaemic agents have been recognised for some time, there has been slower uptake of statins in these people. This article considers evidence for the efficacy and safety of statins in type 2 diabetes in light of the recent publication of NICE guidelines (2002).

Diabetes has been defined as 'a state of premature cardiovascular death which is associated with chronic hyperglycaemia and may also be associated with blindness and renal failure' (Fisher, 2003). Risk factors for type 2 diabetes and atherosclerotic vascular disease are similar, to the extent that both diseases are considered to be manifestations of the insulin resistance syndrome (Laakso and Kuusisto, 2003). All manifestations of CHD, including myocardial infarction (MI), acute coronary syndrome, sudden death and angina, are at least twice as common in people with type 2 diabetes as in individuals without diabetes, Over 50% of people with type 2 diabetes die from CHD, making it the leading cause of death in this group (Laakso and Kuusisto, 2003).

While CHD mortality is declining in individuals without diabetes, it has not fallen in those with type 2 diabetes (Laakso and Kuusisto, 2003). This has alarming implications for the NHS in terms of the future burden of the disease and the workload in primary and secondary care.

Risk factors

In the United Kingdom Prospective Diabetes Study (UKPDS), tight control of blood glucose with sulphonylureas or insulin was associated with a significant reduction in microvascular complications and a non-significant reduction in MI and other macrovascular-related endpoints (UKPDS 1998a). In contrast, metformin resulted in significant reductions in the risk of macrovascular as well as microvascular complications in overweight patients with type 2 diabetes (UKPDS, 1999b).

Metformin may have benefits beyond blood-glucose lowering, perhaps by acting on insulin resistance (a strong predictor for both the development of type 2 diabetes) and subsequent cardiovascular events (Fisher, 2003). The results of the UKPDS blood pressure lowering study (UKPDS; 1998c) showed that tight control of blood pressure produced significant reductions in macrovascular and microvascular endpoints. This evidence suggests that lowering blood glucose will not by itself reduce the risk of cardiovascular disease in people with type 2 diabetes. Indeed, like other high-risk patients, people with type 2 diabetes require a combination of lifestyle modification and pharmaceutical agents to treat known cardiovascular risk factors such as hypertension and dyslipidaemia.

Dyslipidaemia

Up to 70% of adults with type 2 diabetes are hypertensive (DoH, 2003). Based on evidence from UKPDS, together with intervention studies including large numbers of people with diabetes such as the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT, 2002), it is well recognised that tight control of blood pressure reduces cardiovascular risk in type 2 diabetes. Dyslipidaemia is also prevalent in these individuals (DoH, 2003), and significantly increases cardiovascular risk. The UKPDS found that for every 1 mmol/l increase in low-density lipoprotein

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1 The UKPDS found that people with LDL-C > 3.89 mmol/l were 2.3 times more likely to develop angina or MI than those with LDL-C levels of < 3 mmol/l.

2 Smoking cessation is one of the most effective ways of reducing the risk of developing cardiovascular disease in people with type 2 diabetes.

3 Statins act by inhibiting the enzyme HMG-coenzyme-A-reductase, resulting in reduced production of cholesterol and an increased ability to lower blood LDL-C by the liver.

4 Statins are the most effective of the available drugs in lowering LDL-C and they also reduce elevated triglyceride levels and produce a modest increase in HDL-C.

5 Few primary prevention trials of lipid lowering have explicitly included people with diabetes.

cholesterol (LDL-C), the risk of angina or MI increased by over 50%. People with LDL-C > 3.89 mmol/l were 2.3 times more likely to develop angina or MI than those with LDL-C levels of < 3 mmol/l (Turner et al, 1998).

Increased concentrations of LDL-C and total cholesterol are also risk factors for CHD in the general population. However, LDL-C may be more atherogenic in people with type 2 diabetes because of the presence of small dense LDL-C particles and oxidation of glycated LDL-C (Turner et al, 1998). In addition, people with type 2 diabetes tend to have lower high-density lipoprotein cholesterol (HDL-C) levels and raised triglycerides (TG), both of which are also risk factors for cardiovascular disease (Koskinen et al, 1992).

Risk reduction

Smoking cessation is one of the most effective ways of reducing the risk of developing cardiovascular disease in people with type 2 diabetes (as in the rest of the population) and also reduces the risk of future microvascular complications (DoH, 2003). Consensus guidelines on both primary and secondary CHD prevention give clear advice on other lifestyle measures, such as healthy eating, weight loss and increased physical activity (Wood et al, 1998). These interventions will also help to improve glycaemic profile in people with type 2 diabetes (DoH, 2003).

Recent guidelines from the National Institute for Clinical Excellence (NICE, 2002) recommend that the lipid profile should be assessed on diagnosis of type 2 diabetes on the basis of total cholesterol, LDL-C, HDL-C and TG levels, using fasting measurements if possible. No pharmacological treatment is necessary if the total cholesterol is < 5 mmol/l or LDL-C < 3 mmol/l and TG are < 2.3 mmol/l. However, people should be followed up with annual measurements of total cholesterol and HDL-C, and LDL-C and TG if fasting measurement is feasible.

NICE recommendations for the treatment of adverse lipid profiles in people with type 2 diabetes are shown in *Table 1*. There is evidence of benefit for treatment of dyslipidaemia only in people aged up to 69 years for primary prevention and up to 75 years for secondary prevention. However, NICE does not recommend age-related restrictions on the use of pharmacological therapy (NICE, 2002).

As shown in *Table 1*, statins are first-line treatment for most people with type 2 diabetes. Statins act by inhibiting the enzyme HMG-coenzyme-A-reductase, resulting in reduced production of cholesterol and an increased ability to lower blood LDL-C by the liver. Statins are the most effective of the available drugs in lowering LDL-C and they also reduce elevated TG levels and produce a modest increase in HDL-C. Fibrates are recommended as second-line treatment in selected people with type 2 diabetes. Fibrates lower TG and to a less extent increase HDL-C (NHLBI, 2003).

Evidence

The use of statins to lower cardiovascular risk in both people with and without type 2 diabetes is based on evidence from large randomised controlled studies. Few primary prevention trials of lipid lowering have explicitly included people with diabetes. Supportive evidence is derived from post hoc analyses of outcome in people with diabetes who were enrolled in trials such as AFCAPS/TexCAPS and the Helsinki Heart Study. These studies suggest that a reduction in LDL-C levels lowers the risk of cardiovascular events in people with type 2 diabetes by 20–30% (DoH, 2003).

About 55% of people with diabetes have CHD (Laakso and Kuusisto, 2003). The evidence for the benefits of secondary prevention with statins in these individuals is similarly based on sub-analyses of data from lipid-lowering studies performed in the 1990s. The greater clinical benefit of statins in people with diabetes compared with people without diabetes was demonstrated in: the Scandinavian Simvastatin Survival Study (4S); the Cholesterol Lowering and Recurrent Events (CARE) trial; and the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) study (Fisher, 2003).

In 2002, the results of the Heart Protection Study (HPS) extended the benefits of statin treatment to people with non-fasting total cholesterol concentrations of at least 3·5 mmol/l who were considered at substantial 5-year risk of death from CHD because of a history of diabetes, CHD, cerebrovascular disease, or hypertension. In

the 20 000 men and women aged 40–80 years, treatment with 40 mg simvastatin a day reduced the rates of MI, stroke, and revascularisation by about 25%, irrespective of patients' initial cholesterol concentrations. These benefits were seen throughout the population of the study including people with diabetes (HPS Collaborative Group, 2002).

Statins similarly improved cardiovascular outcomes in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study (Athyros et al, 2002). Of the 1600 participants in this study, 20% had diabetes. All participants had established CHD which was defined as a history of MI and > 70% stenosis of at least one coronary artery documented on angiogram. The objective of the study was to compare usual care with atorvastatin in treating patients with the latest, more stringent US LDL-C target of < 2.6 mmol/l (Expert Panel, 2001). Consequently, lipid criteria for entry to the study were > 2.6 mmol/l LDL-C and < 4.5 mmol/l TG (low by UK standards). Compared with usual care (lifestyle change plus lipid-lowering treatment as considered

Table 1. NICE recommendations for the management of dyslipidaemia in people with type 2 diabetes (NICE, 2002)

Blood lipid profile at start of therapy	10-year coronary event risk	Recommendations
TC ≥ 5.00 mmol/l (or LDL-C > 3.00 mmol/l) or TG ≥ 2.3 mmol/l and < 10 mmol/l	Lower: no history of CVD and 10-year coronary event risk ≤ 15%	Discuss CHD risk with patient and consider whether to initiate treatment when type 2 diabetes is diagnosed. Consider drug treatment at higher levels of TC and TG. If initiating treatment: ● Offer a statin ● Assess effect of the statin within 3 months and titrate dose if required ● Monitor effect of treatment annually If the statin is not initiated, monitor lipid profile and cardiovascular risk annually to consider need for therapy
TC ≥ 5.00 mmol/l (or LDL-C > 3.00 mmol/l) or TG ≥ 2.3 mmol/l and < 10 mmol/l	Higher: 10-year coronary event risk > 15% but no history of CVD	Primary prevention: ● Offer a statin ● Assess effect of the statin within 3 months and titrate dose if required ● Monitor effect of treatment annually
TC ≥ 5.00 mmol/l (or LDL-C > 3.00 mmol/l) or TG ≥ 2.3 mmol/l and < 10 mmol/l	Higher: manifest CVD	Secondary prevention: ● Offer a statin ● Assess effect of the statin within 3 months and titrate dose if required ● Consider adding a fibrate after 6 months if TG remains ≥ 2.3 mmol/l (but note increased risk of adverse effects with combination treatment) ● Ensure no evidence of drug interaction between the statin and the fibrate ● Monitor effect of treatment annually
TC ≥ 5.00 mmol/l (or LDL-C > 3.00 mmol/l) and TG ≥ 2.3 mmol/l and < 10 mmol/l	Higher: manifest CVD	Secondary prevention: ● Offer a statin or a fibrate ● Assess the effect of the statin therapy within 3 months and titrate the dose if required ● Monitor the effect of the therapy annually
Fasting TG ≥ 10 mmol/l	Higher or lower	Offer fibrate therapy and consider referral to a diabetes or lipid clinic

CHD = coronary heart disease; CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides

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1 Compared with usual care, the GREACE study showed that atorvastatin was particularly beneficial in people with diabetes.

2 An average follow-up of 5 years was originally planned for the ASCOT, but the study was stopped after a median of 3.3 years because of evidence of benefits of atorvastatin in reducing the primary endpoint of non-fatal MI and fatal CHD.

3 NICE has recently set out clear lipid targets which will commit many people with diabetes to statin therapy.

4 Adherence to treatment falls with increasing daily doses of medication, so it makes sense to simplify the statin regimen as far as possible, using once-daily treatments where they are available.

necessary by the patient's physicians), atorvastatin was particularly beneficial in people with diabetes. Stroke, coronary morbidity and mortality were reduced in all participants.

Atorvastatin (this time at a dose of 10 mg) was also compared to placebo in the lipid-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), which reported earlier this year (Sever et al, 2003). ASCOT randomised over 10 000 people with hypertension with non-fasting total cholesterol concentrations of ≤ 6.5 mmol/l without a history of CHD, but with at least three other cardiovascular risk factors including diabetes. Participants were also allowed treatment with an open-label statin if their doctor subsequently judged that they required additional lipid-lowering therapy.

An average follow-up of 5 years was originally planned, but the study was stopped early after a median 3.3 years because of early evidence of benefit of atorvastatin in reducing the primary endpoint of non-fatal MI and fatal CHD (36% compared with placebo). Similar reductions were achieved for total cardiovascular events, total coronary events, and stroke. The relative risk reductions on primary endpoint in people with diabetes were less than those among patients without diabetes. According to the investigators, since there were only 84 events in people who had diabetes, this may reflect inadequate capacity of the study. This is partly due to the shortened follow-up and greater assignment to statin therapy by physicians treating patients with diabetes in the placebo group.

Efficacy and safety

In the past, the decision to initiate primary or secondary prevention of cardiovascular disease has been based on a 10-year coronary event risk (*Table 2*). Most people with type 2 diabetes will be at high risk of developing CHD given their cardiovascular risk factors, but NICE has now also set out clear lipid targets (*Table 1*). This approach will commit many people with diabetes to statin therapy, together with other components of the 'diabetic cocktail' and treatment for other comorbidities, for example: arthritis; benign prostatic hyperplasia; and incontinence, which are common in a mostly elderly population of patients.

Since adherence to treatment falls with increasing daily doses of medication (Bloom, 2001), it makes sense to simplify the statin regimen as far as possible, using once-daily treatments where they are available. Multiple drug therapy also increases workload for the primary healthcare team, especially if treatments require titration to reach lipid targets in repeated visits to the surgery. There are, therefore, many potential advantages in choosing a statin that needs little titration and achieves lipid targets in the majority of patients. In GREACE, for example, 82% of the participants achieved the study's targets after one dose titration (from 10–20 mg once daily) of atorvastatin (Athyros et al, 2002). In ASCOT, treatment for 1 year with 10 mg of atorvastatin per day reduced total cholesterol and LDL-C by 24% and 35%, respectively. The dosage was not titrated, and the investigators concluded that higher doses would probably have produced even larger reductions in cholesterol and cardiovascular events (Sever et al, 2003).

Adverse effects also reduce adherence to treatment (Bloom, 2001), but statins are well tolerated by most people, and serious adverse effects are rare (National Heart, Lung and Blood Institute, 2003). In ASCOT there was no significant difference between active treatment with atorvastatin and placebo in the rate of serious adverse events or liver-enzyme abnormalities (Sever et al, 2003). Similarly in the Heart Protection Study (2002), there was no significant difference between simvastatin and placebo groups in the numbers of participants whose study treatment was stopped because of elevated liver enzymes. Neither was there any significant difference in rates of unexplained muscle weakness. It is also reassuring that there was no increased risk of cancer or hospitalisation for any other non-vascular reason in patients receiving active treatment (HPS, 2002).

Table 2. Definition of 10-year coronary event risk (NICE, 2002)

Higher risk
- Manifest cardiovascular disease (history or symptoms of coronary heart disease, stroke or peripheral vascular disease)
- 10-year coronary event risk assessed as above 15%

Lower risk
- No manifest cardiovascular disease
- 10-year coronary event risk of assessed at 15% or below

Conclusion

In the past, statins have been under-prescribed to high-risk patients eligible for primary prevention, and also to those with established CHD (Primatesta and Poulter, 2000). There are now clear guidelines that should result in substantial numbers of people with type 2 diabetes receiving one of these drugs. Together with aggressive treatment of other risk factors, this promises to reduce the high burden of illness currently associated with CVD in these patients. ■

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