



'Statins should be routinely prescribed in all adults with diabetes'

FOR

Russell S Drummond, MD, FRCP
Consultant Physician and Endocrinologist, Glasgow
Royal Infirmary, Glasgow, UK

Statins should indeed, in the absence of contraindications, be routinely prescribed in all adults with diabetes.

Introduction

The routine (i.e. habitual and standard) prescription of HMG-CoA reductase inhibitors (the rate limiting enzyme of the mevalonate pathway of cholesterol synthesis) is a key part of multifactorial risk factor intervention for patients with diabetes.¹ The development of coronary artery disease is clearly associated with low density lipoprotein (LDL) cholesterol with an estimated hazard ratio, comparing the upper third of values in one study to the lower third, of 2.26 (95% confidence interval 1.70–3.00).² To support the motion that statin therapy should be part of routine care, this article briefly outlines the demonstrated benefits of cholesterol lowering in patients with diabetes and the efficacy of statin therapy as pharmacological intervention in this regard; it also touches upon areas of controversy where the 'habitual prescribing' should potentially not be followed.

What do patients with diabetes benefit from by being prescribed a statin?

Both Scottish Intercollegiate Guidelines Network (SIGN) 116 and National Institute for Health and Clinical Excellence (NICE) diabetes guidelines advocate lipid lowering therapy as primary prevention ('routine use') for patients with type 2 diabetes aged over 40 (Grade A recommendation) as well as its consideration for patients aged over 40 with type 1 diabetes (Grade B recommendation).

This stems from the three large trials (CARDS, ASCOT, and HPS) which investigated the effects of statins versus placebo in patients with diabetes and no prior cardiovascular disease. The available evidence is stronger for patients with type 2 diabetes although the reduction in events in patients with type 1 diabetes did not differ, albeit statistical significance was not reached.^{3–5} Nevertheless, in these patients free from established cardiovascular disease, but with cardiovascular risk factors and with relatively low levels of cholesterol, the results were largely positive.

In general, a 1mmol/L reduction of LDL cholesterol equates to a 21% risk reduction in cardiovascular disease.⁶ NICE guidelines focus on patients over the age of 40 but differentiate initiation with or without prior cardiovascular risk assessment depending on

non-hyperglycaemic related factors. A recent meta-analysis of patients with diabetes in 14 randomised trials of statins (n=18 686) ascertained that the relative benefits were unrelated to the baseline LDL.⁷ Patients with diabetes have more cardiovascular disease for a given serum lipoprotein concentration – with high serum levels of small, dense LDL particles with enhanced LDL oxidation and elevation in serum lipoprotein(a).⁸ Additionally, when compared with the possible benefits of glucose lowering there was a greater benefit observed with lowering LDL cholesterol in a meta-analysis of five large diabetes trials.⁹ The potency of different statins varies but reductions in LDL cholesterol of 20–60% have been observed.^{10–13} A relatively recent meta-analysis of randomised controlled trials involving 70 000 patients without established cardiovascular disease confirmed the overall benefit of statins in apparently low-risk patients. The study authors could find no significant heterogeneity of the treatment effect in their clinically defined subgroups of elderly people (>65 years), women, and patients with diabetes.¹⁴

Hence, patients with diabetes are more at risk of cardiovascular disease, statins are efficacious, and they are effective in lowering cardiovascular event rates in subjects even with modest levels of cholesterol and without established cardiovascular disease. Statins should thus be part of routine and habitual prescribing.

Blanket prescribing in a high-risk primary prevention setting outwith due consideration of the presence of cardiovascular risk profiling, including diabetes as a risk equivalent, remains an area where clear benefit has not been observed. Ray and colleagues' meta-analysis of 11 randomised controlled trials, involving over 65 000 participants, sought to ascertain whether statin therapy reduced all-cause mortality in intermediate to high-risk individuals without a history of cardiovascular disease, but did not demonstrate benefit.¹⁵

Potential adverse effects of statin therapy

In terms of adverse effects, hepatic dysfunction, renal dysfunction and muscle disorders from myositis to frank rhabdomyolysis have been well described. More contentious have been the links with diabetes, examined in a recent meta-analysis of 13 statin trials with 91 140 participants.¹⁶ Although small, there was a 9% increased risk for incident diabetes (95% confidence interval 1.02–1.17).¹⁶

Hence, in summary, there is clear evidence that the routine, habitual treatment of patients with diabetes should include at least consideration of lipid lowering therapy, with statin treatment being provided for patients who meet pre-specified local guidelines. Diabetes itself would constitute significant risk and the most recent data published at the September 2010 meeting of the European Association for the Study



of Diabetes in Stockholm suggest that statin treatment is being underutilised in patients with type 2 diabetes among a large American cohort of over 100 000 subjects.¹⁷

Appreciating both the potential associated adverse effects and also that prescribing without consideration of the remainder of the patient's risk profile is incorrect, statin therapy should be routinely prescribed in adult patients with diabetes.

AGAINST

MJ Lyall¹, BSc(Hons), MBChB, MRCP

JA McKnight², MD, FRCPE

¹Core Medical Trainee, Metabolic Unit, Western General Hospital, Edinburgh, UK

²Consultant Physician, Western General Hospital; Honorary Reader, University of Edinburgh, UK

Statin therapy should only be given to those with significant risk.

Patients with type 1 or type 2 diabetes are at increased risk of developing atherosclerotic disease. As such, the assessment and modification of cardiovascular risk are an essential part of modern diabetes care. Statin (HMG-CoA reductase inhibitor) therapy remains an important tool in reducing cardiovascular risk in this patient group. However, although a good case can be made for statin therapy in many patients, the treatment of young patients with diabetes and few or no other risk factors goes against current evidence.

The decision to introduce any medical intervention should consider potential benefit versus risk, cost and patient preference. When instigating statin therapy it should be considered that the treatment is likely to be lifelong, it requires considerable patient motivation, and it is not without side effects although these are generally rare and well tolerated. One large study of 6422 patients suggests that compliance with statin therapy among patients with diabetes is generally poor in the long term and that predictors of poor compliance were young age and the absence of cardiovascular morbidity at baseline.¹ Statin therapy should therefore be considered on a case by case basis and not merely issued as a blanket prescription.

Treatment with statins has been shown to reduce cardiovascular events, stroke and mortality in a series of large studies in high-risk populations.²⁻⁷ The relative risk reduction is considerable at 25-30% over approximately five years. Two large randomised controlled trials looking specifically at the efficacy of statins in patients with diabetes found a similar risk reduction.^{8,9} This benefit was preserved even in the absence of significant pre-existing hyperlipidaemia or previously diagnosed arterial occlusive disease. This is, however, a relative risk reduction and is therefore entirely dependent on the patient's individual absolute risk. The number needed to treat (NNT) therefore is also dependent entirely on the

Conflict of interest statement

RSD has received honoraria for educational activities, advisory boards and support to attend conferences from Pfizer, Astra Zeneca, GlaxoSmithKline, Novo Nordisk, Takeda, Schering Plough and Sanofi-Aventis.

References

References are available online at www.practicaldiabetesinternational.com.

individual patient's absolute risk. For example, in a population of 100 patients with an absolute risk of 20%, a relative risk reduction of 25% would generate an NNT of 20. If the absolute risk for the same population is lower, for example 1%, the same relative risk reduction would generate an NNT of 400. The major limitation of the NNT analysis is that it is restricted to the time for which the relative risk has been calculated. A high NNT over 10 years may subsequently become a much lower NNT over 20 years, and one may not attain the same benefit if treatment is delayed.

Data are now available for the incidence of mortality from cardiovascular and cerebrovascular disease in patients with type 1 diabetes and can be used to estimate absolute risk as discussed above. Two large studies followed 23 751 patients with diabetes diagnosed before the age of 30 for between 10 and 25 years.^{10,11} The primary outcome was mortality from cerebrovascular and cardiovascular disease and, crucially, the incidence was stratified by age range. The combined data demonstrate that patients with type 1 diabetes were at an overall increased risk with standard mortality ratios for males and females of 4.5 and 8.8 for ischaemic heart disease and 3.1 and 4.4 for cerebrovascular disease, respectively. As expected, mortality increased significantly with age. The data are described in number of vascular events per 100 000 patient years and from this the 10-year estimated combined mortality risk from all vascular events can be calculated for each age range (Table 1).

Importantly, in the younger population (ages 20-29 and 30-39) although they are significantly more at risk than their chronological peers in the general population,

Table 1. Estimated combined mortality from ischaemic heart disease and cerebrovascular disease in patients with type 1 diabetes^{10,11}

| Age range (years) | Stroke/IHD mortality rate (100 000 patient years) | 10-year risk (%) | NNT for 10 years to prevent 1 death |
|-------------------|---|------------------|-------------------------------------|
| 20-29 | 24 | 0.24 | 1667 |
| 30-39 | 87 | 0.87 | 460 |
| 40-49 | 528 | 5.28 | 76 |
| 50-59 | 1013 | 10.13 | 39 |
| 60-69 | 2825 | 28.3 | 14 |

IHD: ischaemic heart disease; NNT: number needed to treat.



Table 2. Estimated combined mortality from ischaemic heart disease and cerebrovascular disease in patients with type 2 diabetes

| Age (years) | Total combined 10-year risk (%) | Number needed to treat |
|-------------|---------------------------------|------------------------|
| 30 | 1.1 | 364 |
| 40 | 2.5 | 160 |
| 50 | 5.7 | 70 |
| 60 | 12 | 33 |
| 70 | 23.5 | 17 |

the 10-year absolute risk remains low (0.24% and 0.87%, respectively). This low absolute risk therefore generates a very high NNT of 1667 and 460, respectively.

The United Kingdom Prospective Diabetes Study risk engine can be used to stratify risk by patient age for the type 2 diabetes population in the same fashion. The risk engine was developed using data from 53 000 patients. Assuming an acceptable lipid profile (total cholesterol 5.0mmol/L, HDL cholesterol 1.2mmol/L), blood pressure (140/85) and good glycaemic control (HbA_{1c} 7.0% [53mmol/mol]) and a duration of diabetes of five years, the combined mortality risk from cerebrovascular and cardiovascular events for patients with type 2 diabetes of varying ages can be estimated (Table 2). The total combined 10-year risk in the younger age groups (30 and 40 years) remains relatively low, again generating a high NNT.

In conclusion, statins remain an important therapeutic option in modern diabetes management but, as described above, are clearly not indicated in all patients. This is because, rather than the presence or absence of diabetes, the most significant predictor of cardiovascular mortality remains patient age. Therapy should instead be focused on older patients and those with other risk factors or evidence of vascular complications for which there is a more robust evidence base. The Joint British Society 2 (JBS2) guideline attempts to target treatment towards high-risk subgroups of patients with diabetes (Table 3).

There is one important caveat to this rationale. It is not yet known whether delaying therapy in younger patients reduces treatment efficacy in the long term. Therefore we should be randomising young low-risk

Table 3. The Joint British Society 2 (JBS2) guideline

The JBS2 guideline recommends lipid lowering therapy in:

- All those who are aged 40 years or more with either type 1 or 2 diabetes
- For people aged 18–39 years with either type 1 or 2 diabetes and who have at least one of the following:
 - Retinopathy (pre-proliferative, proliferative, maculopathy)
 - Nephropathy, including persistent microalbuminuria
 - Poor glycaemic control (HbA_{1c} >9% [75mmol/mol])
 - Elevated blood pressure requiring antihypertensive therapy
 - Raised total blood cholesterol (≥6.0mmol/L)
 - Features of metabolic syndrome (central obesity and fasting triglyceride >1.7mmol/L [non-fasting >2.0 mmol/L] and/or HDL cholesterol <1.0 mmol/L in men or <1.2 mmol/L in women)
 - Family history of premature cardiovascular disease in a first degree relative

patients with type 1 and type 2 diabetes now, commencing statin therapy at a range of ages and collecting data on both number and severity of vascular events and also on the incidence of other macrovascular and microvascular complications. This would help determine the point at which treatment becomes of significant benefit.

The above argument describes how the absolute risk in young patients with few or no other risk factors remains small and thus the NNT in this patient group is unacceptably high. Indeed, if we decide to treat all young patients with diabetes then we must treat others in the population at similar risk. This would include, for example, all smokers and all men above the age of 40 years. We are not ready to advocate statins as a global population intervention.

Conflict of interest statement

There are no conflicts of interest.

References

References are available online at www.practicaldiabetesinternational.com.

CONFERENCE NOTICE

Diabetes Mellitus: From the Child to the Adult

25th January 2011, Royal Society of Medicine, London

Topics include:

The psychology of diabetes in childhood, closing the loop in type 1 diabetes, staying active: sports and diabetes, multi-disciplinary teams and the transition clinic and the UK Islet transplant consortium's experience

Contact website: www.rsm.ac.uk



FOR

Russell S Drummond, MD, FRCP

Consultant Physician and Endocrinologist, Glasgow
Royal Infirmary, Glasgow, UK

References

1. Gæde P, et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003; 348: 383–93.
2. Turner RC, et al. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS: 23). *BMJ* 1998; 316: 823–8.
3. Colhoun HM, et al.; CARDS investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004; 364: 685–96.
4. Sever PS, et al.; ASCOT Investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003; 361: 1149–58.
5. Collins R, et al. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 2003; 361: 2005–16.
6. Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. *Lancet* 2005; 366: 1267–78.
7. Cholesterol Treatment Trialists' (CTT) Collaborators, Kearney PM, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet* 2008; 371: 117–25.
8. O'Brien T, et al. Hyperlipidaemia and diabetes mellitus. *Mayo Clin Proc* 1998; 73: 969–76.
9. Ray K, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. *Lancet* 2009; 373: 1765–72.
10. Larsen ML, Illingworth DR. Drug treatment of dyslipoproteinemia. *Med Clin North Am* 1994; 78: 225.
11. Levy R, et al. A quarter century of drug treatment of dyslipoproteinemia, with a focus on the new HMG-CoA reductase inhibitor fluvastatin. *Circulation* 1993; 87(Suppl 4): III45–53.
12. Illingworth DR, et al. Comparative effects of lovastatin and niacin in primary hypercholesterolemia. A prospective trial. *Arch Intern Med* 1994; 154: 1586–95.
13. Jones PH, et al.; STELLAR Study Group. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial). *Am J Cardiol* 2003; 92: 152–60.
14. Brugts JJ, et al. The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials. *BMJ* 2009; 338: b2376.
15. Ray K, et al. Statins and all-cause mortality in high-risk primary prevention: a meta-analysis of 11 randomized controlled trials involving 65 229 participants. *Arch Int Med* 2010; 170: 1024–31.
16. Sattar N, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet* 2010; 375: 735–42.
17. Radican L, et al. Underutilisation of statins in patients with type 2 diabetes treated with an antihyperglycaemic regimen. European Association for the Study of Diabetes, Stockholm, September 2010. Abstract 1302.

AGAINST

MJ Lyall¹, BSc (Hons), MBChB, MRCP

JA McKnight², MD, FRCPE

¹Core Medical Trainee, Metabolic Unit, Western General Hospital, Edinburgh, UK

²Consultant Physician, Western General Hospital; Honorary Reader, University of Edinburgh, UK

References

1. Donnelly LA, et al. Long-term adherence to statin treatment in diabetes. *Diabet Med* 2008; 25: 850–5.
2. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; 344: 1383–9.
3. Shepherd J, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995; 333: 1301–8.
4. Sever PS, et al.; ASCOT Investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003; 361: 1149–58.
5. Lewis SJ, et al. Effect of pravastatin on cardiovascular events in older patients with myocardial infarction and cholesterol levels in the average range. *Ann Intern Med* 1998; 9: 681–9.
6. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; 360: 7–22.
7. Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. *Lancet* 2005; 366: 1267–78.
8. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 2003; 361: 2005–16.
9. Colhoun HM, et al.; CARDS investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004; 364: 685–96.
10. Laing SP, et al. Mortality from heart disease in a cohort of 23 000 patients with insulin-treated diabetes. *Diabetologia* 2003; 46: 760–5.
11. Laing SP, et al. Mortality from cerebrovascular disease in a