The use of statins in people with diabetes in primary care

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Article points

1. Many eligible patients are either still not receiving or are being prescribed inappropriate statins.
2. Increasingly, the decision to prescribe statins is being made by a patient's GP.
3. A number of large clinical trials have established statins as effective agents in the prevention of both primary and secondary coronary heart disease.
4. Current data suggest that statins should be prescribed for individuals with type 2 diabetes.
5. The important question for the future is whether or not people with diabetes should be considered part of the primary prevention group or a separate high-risk group.

Key words

- Type 2 diabetes
- Statins
- Primary care
- Clinical trials

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Despite overwhelming evidence of the benefits of statins for people with diabetes, many eligible patients either are still not receiving them or are being prescribed an inappropriate statin (not potent enough) or too low a dose to achieve recommended cholesterol target levels. Hence they remain at high risk of cardiovascular disease. Increasingly, the decision to prescribe statins is being made by a patient's GP. This article looks at the influences on GPs' prescribing of statins, in terms of current evidence and national guidelines.

Between 3% and 3.5% of patients in each general practice in the UK have diabetes, mostly type 2 (Harvey et al, 2002). Cardiovascular disease (CVD) accounts for the greatest proportion of mortality and morbidity in these patients. Prevention of CVD is therefore of major importance in this patient group, and the management of raised cholesterol in people with diabetes is a key issue.

Increasingly, the management of people with diabetes is provided by the primary care in-house diabetes clinic, and the decision to prescribe statins is made by a patient's GP. This article looks at the factors that are most likely to influence this decision, in terms of current evidence and national guidelines.

Particular reference will be made to data from the Heart Protection Study (HPS; Collins, 2003) and the more recently reported Collaborative Atorvastatin Diabetes Study (CARDS; Colhoun et al, 2004) and A raNdomised, Double blind, study to compare Rosuvastatin (10 mg and 20 mg) and atOrvastatin (10 Mg and 20 mg) in patiEnts with type 2 DiAbetes (ANDROMEDA; Betteridge and Gibson, 2004).

- HPS compared the use of 40 mg simvastatin vs placebo. It included the largest subsection of people with diabetes ever studied and produced highly significant data.
- CARDS specifically investigated people with diabetes and resulted in an impressive 37% reduction in primary cardiovascular endpoints.
- ANDROMEDA and CORALL (COmpare the effects of Rosuvastatin with Atorvastatin on apo B/apo A-1 ratio in patients with type 2 diabetes meLLitus and dyslipidaemia; Wolffenbuttel et al, 2005) are comparative studies of rosuvastatin and atorvastatin.

All these trials used optimum doses of powerful statins. The National Institute for Health and Clinical Excellence (NICE) statin guidelines are currently under evaluation, and their influence in terms of people with diabetes will also be considered.

Evidence for the benefits of statins in diabetes

A number of large clinical trials have established statins as effective agents in the prevention of both primary and secondary coronary heart disease (CHD; Downs et al, 1998; Shepherd et al, 2002; Collins et al, 2003; Sever et al, 2003), with a clear association between cholesterol

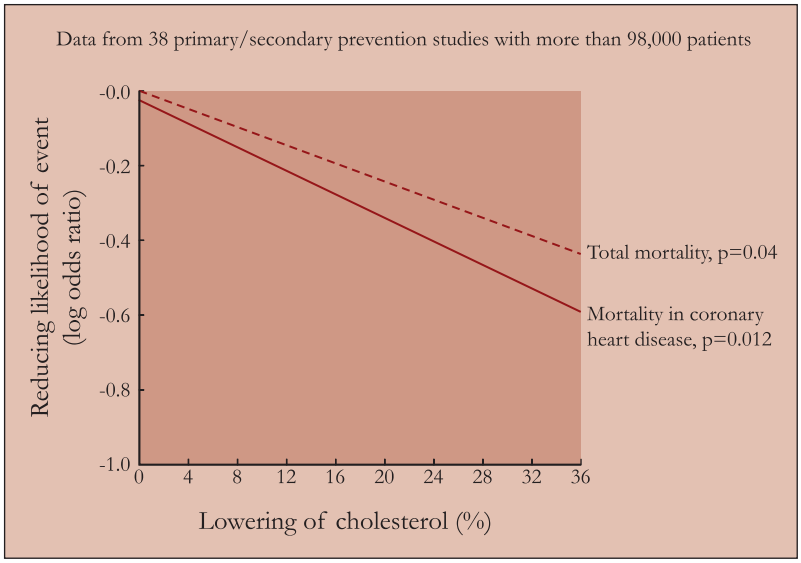

Figure 1. Relationship between cholesterol reduction and cardiovascular risk reduction in major statin trials. (Adapted from Gould et al, 1998).

reduction and outcome benefits (*Figure 1*; Gould et al, 1998). Many of these studies included significant sub-groups of people with diabetes.

The HPS demonstrated uniform risk reduction across a wide range of patients, including those with diabetes (Collins et al, 2003). Indeed, type 2 diabetes was an independent predictor of benefit from statin therapy, with a 1 mmol/l reduction in low-density lipoprotein (LDL)-cholesterol resulting in a 22 % reduction in risk of a first vascular event, independent of baseline LDL-cholesterol levels.

These data are consistent with a recent meta-analysis of diabetes sub-groups from statins trials, which demonstrated that cholesterol reduction may reduce the risk of primary and secondary cardiovascular events by 22 % and 24 % respectively (Vijan and Hayward, 2004).

Relative risk reduction is similar in primary and secondary prevention trials; however, as patients with established CHD are at greater absolute risk, statin therapy achieves substantially higher absolute reduction in secondary prevention trials than in primary prevention studies (Vijan and Hayward, 2004). Similarly, patients with type 2 diabetes are at higher absolute risk than those without diabetes, therefore statin therapy results in greater absolute benefit in patients with type 2 diabetes (Vijan and Hayward, 2004).

Data from studies such as the HPS therefore suggest that all patients with type 2 diabetes should qualify for statin therapy. CARDS further illustrated the benefits of cholesterol reduction in patients with type 2 diabetes (Colhoun et al, 2004). In this study of more than 2800 people with type 2 diabetes and at least one other CHD risk factor, an LDL-cholesterol reduction of 40 % and triglyceride reduction of 19 % were associated with a 37 % reduction in major coronary events and a 48 % reduction in stroke.

A meta-analysis of lipid-lowering trials in type 2 diabetes has concluded that the number needed to treat to prevent one CHD event was 13.8/4.9 years of secondary prevention and 34.5/4.3 years for primary prevention (Vijan and Hayward, 2004). Thus, compared with commonly adopted medical interventions, cholesterol reduction appears to be cost-effective even in the absence of overt CVD.

However, despite such strong evidence, a significant proportion of high-risk patients, including many with type 2 diabetes, are still not achieving currently accepted therapeutic cholesterol targets and thus remain at an unacceptable level of cardiovascular risk (Wright et al, 2003). Indeed, several audits of type 2 diabetes populations have revealed that many eligible patients are still not receiving lipid-modifying therapy (Brown, 2005).

Furthermore, among patients prescribed lipid-modifying therapy, sub-optimal dosing, poor adherence and inherent therapeutic limitations may limit the long-term effectiveness of cholesterol reduction. Many patients are unable to reach treatment targets at the starting dose prescribed and many will not reach treatment goals, even following dose titration (Giorda et al, 2003). Therefore, there remain substantial challenges to optimising the management of diabetic dyslipidaemia, and hence cardiovascular risk, in clinical practice. One potential approach is the use of more efficacious statin therapy.

There is currently much interest in determining which statins demonstrate the greatest LDL-cholesterol lowering efficacy. In diabetes populations, significant reductions in

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2. Thus, compared with commonly adopted medical interventions, cholesterol reduction appears to be cost-effective even in the absence of overt cardiovascular disease.

cardiovascular risk are usually associated with a statin-induced LDL-cholesterol reduction of 30–40 %; the particular statin chosen and the dosage at which it is prescribed should therefore be associated with an LDL-cholesterol reduction of at least this magnitude.

The ANDROMEDA study (Betteridge and Gibson, 2004), conducted in people with type 2 diabetes in the UK, showed that 10 mg rosuvastatin and 10 mg atorvastatin reduced LDL-cholesterol by 51.3 % and 39 %, respectively, after 8 weeks (P<0.001), resulting in 94 % and 79% of participants, respectively, reaching European treatment target goals of <2.5 mmol/l (Evans et al, 2004). A subsequent up-titration to 20 mg rosuvastatin and 20 mg atorvastatin for a further 8 weeks achieved a 57.4 % and 46 % LDL-cholesterol reduction, respectively, resulting in 96 % and 87 % of participants, respectively, reaching the European treatment target goal.

A similar profile was seen when 10 mg rosuvastatin was compared with 20 mg atorvastatin in the CORALL study, conducted in people with type 2 diabetes mellitus in the Netherlands (LDL-cholesterol reduction of 45 % and 41 % respectively, P<0.05; Wolffenbuttel et al, 2005).

What of the role of statin therapy in people with type 1 diabetes?

Approximately 20 % of people with type 1 diabetes will develop diabetic nephropathy after 20–25 years of diabetes duration (Anderson et al, 1983). Of these, more than 40 % develop CVD by the age of 40 (Tuomilehto et al, 1998). LDL-cholesterol has been shown to be closely associated with microalbuminuria, a marker for nephropathy and a strong independent risk factor for the development of CHD. Dyslipidaemia may exacerbate diabetic nephropathy through a variety of mechanisms, including perturbations of the coagulation system, changes in membrane permeability, endothelial dysfunction and enhanced atherosclerosis. There is also evidence that intensive cholesterol-lowering therapy may retard the progression of microvascular diseases, including nephropathy (Baghdsarian et al, 2004).

It is thus interesting to speculate that dyslipidaemia may be a predictor of nephropathy risk and that statin therapy may retard the development of this complication. There is, however, persisting debate regarding optimum treatment lipid levels in people with type 1 diabetes and the optimum timing of initiation of statin therapy in this group.

Cholesterol targets: The evidence base

Current data suggest that statins should be prescribed for individuals with type 2 diabetes, irrespective of baseline LDL-cholesterol levels (Armitage and Bowman, 2004).

The most recent American Diabetes Association (ADA) guidelines suggest that a target LDL-cholesterol of <2.5 mmol/l is appropriate for patients with diabetes in the absence of CVD (Haffner, 2005). For those with established CVD, the ADA advocates an even lower LDL-cholesterol target of <1.8 mmol/l (Haffner, 2005). Possible exceptions to this approach may be younger patients (under 40 years) for whom there is little current clinical trial evidence, and those with recently diagnosed type 2 diabetes who have no additional CHD risk factors or diabetes complications.

The benefits of intensive cholesterol lowering have been demonstrated in several recent outcome studies.

In the PROVE IT-TIMI 22 trial (Cannon et al, 2004), patients with recent acute coronary syndrome received either 80 mg atorvastatin or 40 mg pravastatin; target LDL-cholesterol levels achieved were 1.6 mmol/l in the atorvastatin group, compared with 2.6 mmol/l in the pravastatin group. The benefit of more

effective therapy was evident within 30 days in patients at the lower LDL-cholesterol level, with a 16% reduction in hazard ratio over 2 years. The relative risk reduction achieved by intensive cholesterol reduction was comparable in people with and without diabetes; however, since the overall rate of cardiovascular events was higher in those with diabetes, these individuals derived greater absolute benefit.

The Treating to New Targets (TNT) study (The Treating to New Targets Investigators, 2005), which included nearly 3000 people with type 2 diabetes, compared the effects of intensive lipid-lowering (10 mg atorvastatin vs 80 mg atorvastatin) with target LDL-cholesterol levels of <2.6 mmol/l and <2.0 mmol/l, respectively. Patients at the lower LDL-cholesterol level achieved a 22% relative risk reduction in the primary composite endpoint of a cardiovascular event, again with greater absolute benefit in those with type 2 diabetes, as a function of the higher overall event rate in these individuals.

Extrapolation of these data and those from the major statin outcome studies would tentatively suggest an optimum LDL-cholesterol target between 0.8 mmol/l and 1.5 mmol/l to produce maximal reduction in risk (*Figure 2*; LaRosa et al, 2005). While the relative risk reduction achieved with cholesterol reduction is similar in patients with and without type 2 diabetes, the absolute benefit is greater in those with diabetes because of their higher cardiovascular risk and baseline event rate.

Data from prospective epidemiological studies (Assmann and Schulte, 1992) and from intervention studies, such as the Helsinki Heart Study (Manninen et al, 1992), Veterans Affairs High-density lipoprotein cholesterol Intervention Trial (Robins et al, 2001) and Bezafibrate Infarct Prevention study (BIP Study Group, 2000), indicate that a significant proportion of high-risk patients may benefit not only from LDL-cholesterol reduction but also from modification of high-density lipoprotein (HDL)-cholesterol and triglyceride sub-fractions. Overweight patients and those with highest insulin resistance appear to derive the greatest benefit.

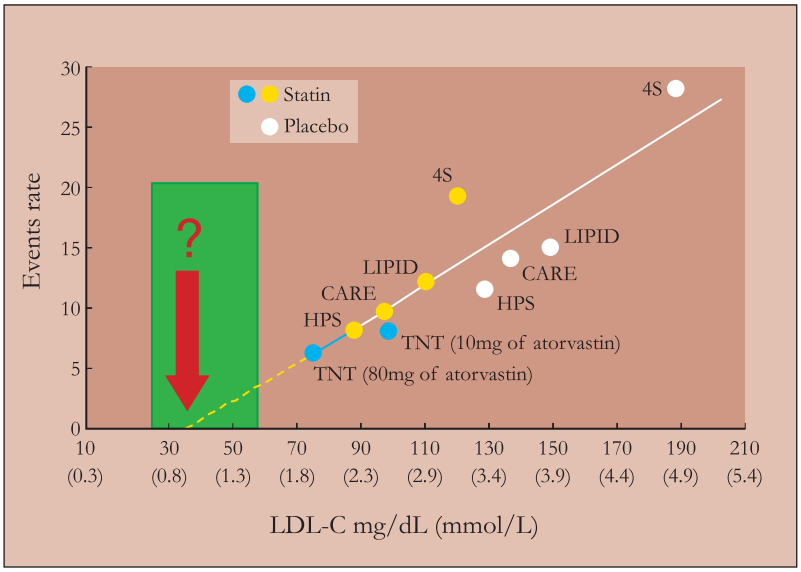

Figure 2. Results of secondary prevention studies – a potential optimum LDL-C level? (Adapted from LaRosa et al, 2005).

Based on such findings, lipid targets have been established for patients with type 2 diabetes (*Table 1*). Current National Cholesterol Education Program (NCEP; Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults, 2001), Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (De Backer et al, 2003) and ADA (2001) guidelines recommend a target LDL-cholesterol level of <2.6 mmol/l.

Furthermore, the most recent NCEP guidelines suggest that an LDL-cholesterol goal of <1.8 mmol/l may be a clinical option in those at very high risk (Liebl et al, 2002). The European Diabetes Policy Group guidelines recommend an LDL-cholesterol target of <3 mmol/l (Liebl et al, 2002), while the ADA and European Diabetes Policy Group guidelines also recommend targets for HDL-cholesterol and plasma triglyceride of >1.2 mmol/l and <2.2 mmol/l respectively (Liebl et al, 2002). Currently, however, treatment goals for both HDL-cholesterol and plasma triglyceride levels are not specified in either the NCEP or Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice guidelines.

The Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice guidelines suggest that

1. The benefits of intensive cholesterol lowering have been demonstrated in several recent outcome studies.
2. The relative risk reduction achieved by intensive cholesterol reduction was comparable in people with and without diabetes.
3. However, since the overall rate of cardiovascular events was higher in those with diabetes, these individuals derived greater absolute benefit.
4. Extrapolation of data from the major statin outcome studies would tentatively suggest an optimum LDL-cholesterol target between 0.8 and 1.5 mmol/l to produce maximal reduction in cardiovascular risk.

Table 1. Cholesterol targets – LDL-cholesterol levels are getting lower.

Guideline	Year published	LDL-cholesterol (mmol/l)	Total cholesterol target (mmol/l)
JBS	1998	<3	<5.0
EAS	1998	<3	<5.0
NSF for CHD	2000	<3 and 30% reduction	<5.0 and 25% reduction
EAS	2003	<2.5 in high risk	<4.5 in high risk
BHS IV	2004	<2 in high risk	<4.0 in high risk
EAS	2004	<3 in non-high risk, <2.5 in high risk, CVD and diabetes	<5 in non-high risk, <4.5 in high risk, CVD and diabetes
NCEP ATP III	2004	<1.8 in very high risk, <2.6 in moderately high risk and 30–40% reduction	Not specified in 2004 update

BHS IV = British Hypertension Society 2004; CVD = cardiovascular disease; EAS = European Atherosclerosis Society; JBS = Joint British Society; LDL = low-density lipoprotein; NCEP ATP III = National Cholesterol Education Program (Adult Treatment Panel III); NSF for CHD = National Service Framework for Coronary Heart Disease

HDL-cholesterol levels of <1 mmol/l in men and <1.2 mmol/l in women and triglyceride levels of >1.7 mmol/l should be considered markers of increased cardiovascular risk (Tuomilehto and Leiter, 2005). The soon-to-be-published Joint British Societies' guidelines are thought to advocate target LDL-cholesterol levels in high-risk, secondary prevention and type 2 diabetes patients of <2 mmol/l, with a minimum HDL-cholesterol level in people with type 2 diabetes of 1 mmol/l.

The forthcoming NICE statin guidelines

At the time of writing this article, only the NICE Statins Appraisal Committee's preliminary recommendations (*Table 2*) are available to give us an idea of the likely content of the revised statin guidelines (NICE, 2005). The committee were asked to consider the initiation of statins for the prevention of coronary events in patients at increased risk of developing CHD or those with established CHD.

Table 2. NICE Appraisal Committee's preliminary recommendations.

- Statins should be prescribed for
  - o All patients with CHD
  - o All patients <75 with CHD risk of >20% over 10 years
- Patients over 75 should be considered for statins on an individual basis if their CHD risk is >30%
- The statin with the lowest acquisition cost should be used, taking into account required daily dose and product price per dose.

The use of CHD risk is consistent with the *National Service Framework for Coronary Heart Disease* (Department of Health, 2000) and the original Joint British Societies' recommendations (Wood et al, 1998). However, the new Joint British Societies' recommendations will be published later this year and they are most likely to use cardiovascular (CVD) risk rather than CHD risk. We know this because the fourth British Hypertension Society guidelines (Williams et al, 2004) included the proposed new Joint British Societies' guidelines tables, which did use CVD risk and proposed intervention at CVD risk 20 %.

In these new tables, a CHD risk of 20 % over 10 years is equivalent to somewhere between 26 % and 27 % CVD risk, and a CHD risk of 30 % over 10 years is approximately equivalent to a CVD risk of 40 %. What is more, the proposed new risk tables are only for people without diabetes, as the tighter recommendation of CVD risk 20 % means that very few people with diabetes would fall outside the red zones and almost none over 50 years of age would do so.

1. The new GMS contract, which does not differentiate between people with type 1 and 2 diabetes, is another major influence.
2. Diabetes mellitus indicator 17 in the contract's Quality and Outcomes Framework requires that in 60% of people with diabetes the last measured total cholesterol, within the previous 15 months, should be ≤5mmol/l.
3. If this requirement were to become more stringent, then many GPs might simply prescribe statins to all their patients with diabetes, regardless of any guidelines.
4. The important question for the future is whether patients with diabetes should be considered part of the primary prevention group or a separate high-risk group.
5. This might well be tackled as part of the new Joint British Societies' guidelines.

The NICE guidelines may therefore be outdated very early in life, as the new Joint British Societies' guidelines (Evans et al, 2004) are likely to have a large influence on future management of cardiovascular risk, particularly in diabetes care. However, even using the old tables with the suggestion that all patients under 75 years of age at CHD risk 20 % are prescribed statins, most of our patients with diabetes will require this therapy. The advice that patients over 75 are considered as individual cases makes sense in light of the lack of evidence for initiation of therapy for primary prevention in this age group. Thus, NICE has not excluded the use of statins in people over 75, which would have been a more controversial issue.

The recommendation to use the statin with the lowest acquisition cost will mean that different statins will be appropriate for different individuals, as some people will require higher doses or the more potent statins to achieve target reductions in LDL-cholesterol.

A major influence on GP prescribing, separate from the NICE recommendations, is the new General Medical Services contract (British Medical Association, 2003), which does not differentiate between people with type 1 and 2 diabetes. Diabetes mellitus indicator 17 in the contract's Quality and Outcomes Framework (QOF) requires that in 60 % of people with diabetes the last measured total cholesterol, within the previous 15 months, should be ≤5 mmol/l.

This requirement might well change with the second round of the QOF revisions, which will be applicable from April 2006, and at this time have not been decided. If this becomes more stringent, then many GPs may simply prescribe statins to all their patients with diabetes regardless of any guidelines.

Conclusion

There is overwhelming evidence that patients with diabetes benefit from LDL-cholesterol lowering with statins, and therefore both national guidelines and government policy recommend the use of statins in the primary prevention of CHD. The evidence further supports the use of appropriately high doses of statins or the use of the more efficacious statins to provide adequate lowering of cholesterol.

The important question for the future is whether or not patients with diabetes should be considered part of the primary prevention group or a separate high-risk group. This might well be tackled as part of the new Joint British Societies' guidelines. ■

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'The important question for the future is whether or not patients with diabetes should be considered part of the primary prevention group or a separate high-risk group.'

The new Joint British Societies' Guidelines will be reported on in the next edition of *Diabetes & Primary Care*