Lipid lowering therapy in type 2 diabetes: modern evidence-based approaches

Martin Press

ARTICLE POINTS

1 Over 1 million people in the UK are diagnosed with type 2 diabetes, a prevalence that is estimated to rise to 3 million by 2010.

2 CVD is the leading cause of death in the UK and the current GMS contract recognises the dangers of CVD risk in type 2 diabetes.

3 Many data exist to show the benefits of statin therapy in type 2 diabetes patients at high CVD risk.

4 Overall, CVD risk should be the principle determinant in whether a patient receives statin therapy, rather than a threshold level of LDL cholesterol.

5 Such an approach would be expected to reduce the incidence of CVD events and hence prove cost effective.

KEY WORDS

- Lipid lowering
- Cardiovascular risk
- Cholesterol
- Risk reduction

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Introduction

Cardiovascular disease is the leading cause of mortality in the United Kingdom, and the importance of risk factor modification has been emphasised in the recent General Medical Services (GMS) contract. Diabetes is as great a cardiovascular risk factor as a combination of hypertension and smoking, but the benefit of improved diabetic control has been disappointing. However, several studies, including the recent CARDS trial, have reported major benefits of lipid lowering therapy in patients with diabetes. This article considers the implications of these studies for the management of diabetes in the UK.

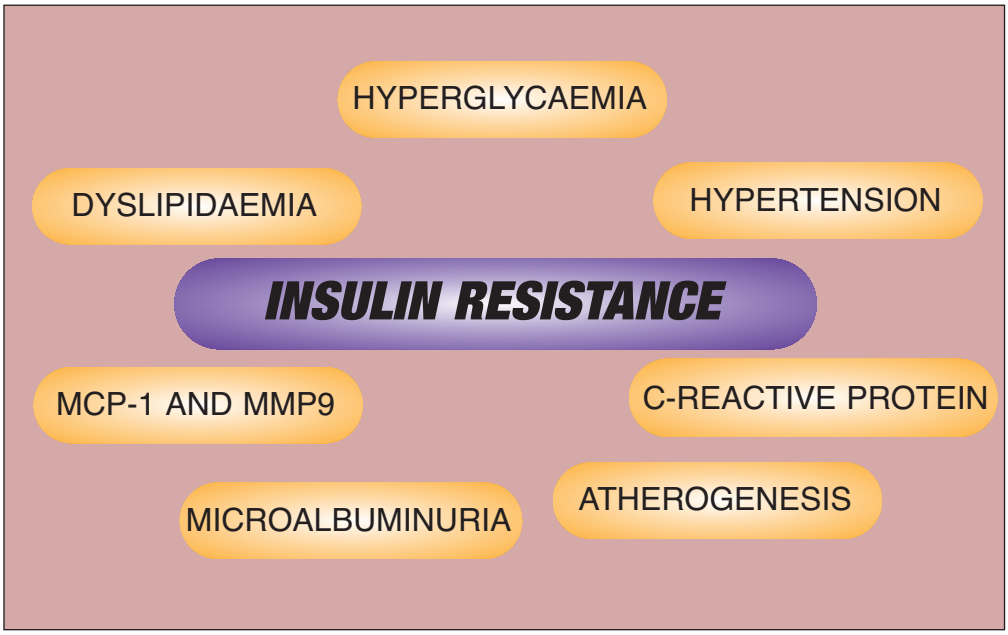
Rationale for lipid lowering in patients with diabetes

It is known that type 2 diabetes, hypertension and hyperlipidaemia are associated with each other, and with other cardiovascular risk factors, as part of the insulin resistance syndrome (*Figure 1*) (Haffner et al, 1999). The question has always been, however, which of the individual parts of the syndrome to target in order to achieve the greatest reduction in cardiovascular risk.

The United Kingdom Prospective Diabetes Study (UKPDS, 1998), showed that improved blood glucose control alone made little difference to the incidence of cardiovascular complications in patients with type 2 diabetes, although the design of the study was such that the patients were locked into monotherapy. However, patients achieving a blood pressure below 144/82 mmHg did have a significantly lower risk of not only cardiovascular (e.g. heart failure, stroke), but also microvascular, complications (e.g. retinopathy). This conclusion is particularly significant given that 35% of newly diagnosed and 70% of established type 2 diabetes patients can be classed as hypertensive (>160/95 mmHg) (UKPDS, 1990; UKPDS, 1998).

However, a much greater reduction in cardiovascular endpoints was seen in the Steno-2 study (Gaede et al, 2003), which used a stepwise approach to target all three

Figure 1. The association of insulin resistance with cardiovascular risk factors



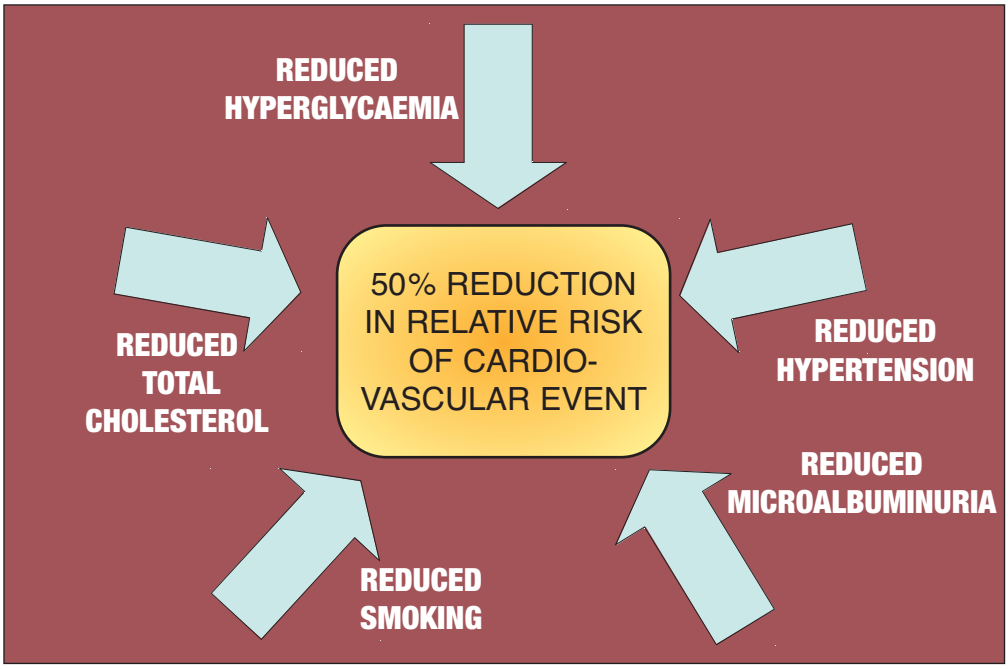


Figure 2. The benefits of a multifactorial approach to type 2 diabetes management

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1 In the HPS, a lowering of average levels of total and LDL cholesterol was observed in patients in the statin arm compared to placebo.

2 This translated into a 25% reduction in coronary and vascular event rate without significant side-effects.

3 CARDS was the first trial to specifically study the effects of statin treatment in patients with type 2 diabetes and no previous history of cardiovascular disease.

4 CARDS patients were randomised to receive either atorvastatin (10mg daily) or placebo, and the study was scheduled to run until 304 primary endpoints had accrued.

5 Following a four-year interim analysis in June 2003, CARDS was halted because, compared to placebo, patients in the atorvastatin group experienced significant CVD benefits.

major risk factors (diabetes, hypertension and hyperlipidaemia) as well as smoking cessation and aspirin therapy. Over a seven-year period, a reduction of >50% in the incidence of cardiovascular events was observed (*Figure* 2). The relative contributions of the various risk factors targeted remained uncertain, but, as outlined below, an increasing body of evidence is pointing to the importance of lipid lowering therapy in patients with type 2 diabetes.

The Heart Protection Study (HPS)

This study examined the effect of cholesterol lowering in some 6000 patients with diabetes and 14000 patients with occlusive arterial disease (Heart Protection Study Collaborative Group, 2003). Patients, who had to have a cholesterol level of >3.5 mmol/l at entry, received 40 mg simvastatin or placebo in a prospective double-blind study.

A lowering of average levels of total and LDL (low-density lipoprotein) cholesterol (by 1.1 mmol/L and 0.9 mmol/L respectively) was observed in patients in the statin arm compared to placebo.

During the five-year treatment period, this translated into a 25% reduction in coronary and vascular event rate without significant side-effects. These benefits were independent of initial lipid levels, and subgroup analysis showed that they were seen equally in the patients with diabetes and those without the condition.

The Collaborative AtoRvastatin Diabetes Study (CARDS)

CARDS (Colhoun et al, 2002) was the first trial to specifically study the effects of statin treatment in patients with type 2 diabetes and no previous history of cardiovascular disease. This multi-centre, randomised, placebo-controlled, double-blind trial recruited 2838 patients with type 2 diabetes. Patients were aged 40–75 years at recruitment and were free of known cardiovascular disease (CVD). Moreover, although they had at least one CVD risk factor (i.e. smoking, hypertension, retinopathy, or micro-/macroalbuminuria) in addition to their diabetes, they constituted a relatively low-risk group from the lipid point of view.

Inclusion criteria stipulated that LDL cholesterol and triglyceride levels had to be below 4.14 mmol/L and 6.78 mmol/L respectively, and in fact actual levels were only 3.0 mmol/L and 1.7 mmol/L respectively at baseline, not levels at which one would previously have contemplated the use of lipid lowering drugs. Patients were randomised to receive either atorvastatin (10 mg daily) or placebo, and the study was scheduled to run until 304 primary endpoints had accrued.

Following a four-year interim analysis in June 2003, CARDS was halted. This was

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1 Compared to placebo, atorvastatin evoked a 37% reduction in major CV events, 48% reduction in the incidence of stroke, and 36% reduction in acute coronary events.

2 These benefits were observed regardless of patient age, gender or baseline cholesterol levels.

3 Instead of debating whether all patients with type 2 diabetes warrant statin therapy, the argument should now focus on whether there are any patients at sufficiently low risk to justify withholding treatment.

4 The fact that more needs to be done is reflected by the prominence of type 2 diabetes in the GMS contract.

because, compared to placebo, patients in the atorvastatin group experienced significant CVD benefits. It was therefore deemed unethical to continue with the placebo arm.

CARDS showed that compared to placebo, atorvastatin evoked:

- a 37% reduction in the combined primary endpoint of major CV events (p=0.001) (*Figure 3*);
- a 48% reduction in the incidence of stroke (p=0.016);
- a 36% reduction in acute coronary events (p=0.013).

Furthermore, these benefits were observed regardless of patient age, gender, or baseline cholesterol levels. The proportion of patients remaining below LDL-cholesterol guideline levels of 2.6 mmol/L are shown in *Figure 4*. The incidence of side-effects was no different from placebo and patient compliance rates were high, with a mean value of 85.3% in the atorvastatin arm.

The authors concluded that:

- atorvastatin (10 mg daily) is highly effective at reducing the risk of first CVD events in patients with type 2 diabetes and relatively low cholesterol levels;
- the incidence of side-effects with this dose of atorvastatin was no greater than for placebo;
- there is no justification for using a threshold level of LDL cholesterol as the criterion by which to judge whether or not a patient should receive statin treatment;
- overall CVD risk should be the principle determinant for statin treatment;
- instead of debating whether all patients with type 2 diabetes warrant statin therapy, the argument should now focus on whether there are any patients at sufficiently low risk to justify withholding treatment.

Impact of the CARDS study on diabetes management in the UK

This major study has already contributed to a paradigm shift in UK diabetes management, but significantly more can be done to reduce CVD morbidity and mortality. Over 1 million people in the UK are diagnosed with type 2 diabetes, a prevalence that is projected to rise to 3 million by 2010 (Amos et al, 1997). Similarly, CVD is already the main cause of death in the UK, with one in three people dying from the condition (39%) (British Heart Foundation, 2004a).

The fact that more needs to be done to halt or reverse these trends is reflected by the prominence of type 2 diabetes in the GMS contract (18% of clinical points are related to diabetes management). In addition to measures of glycaemic control,

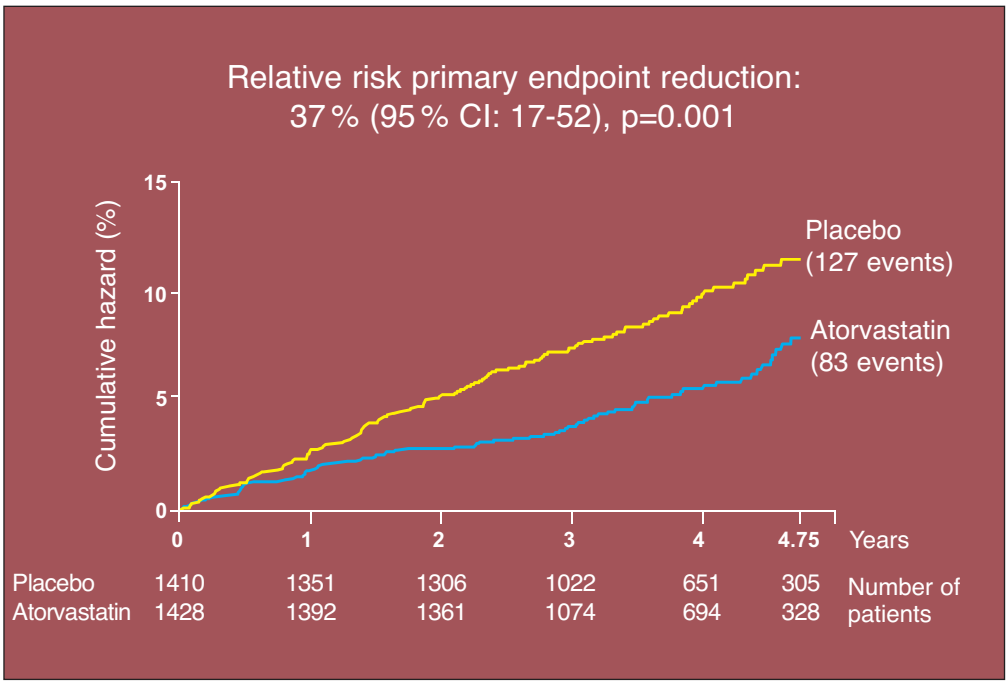

Figure 3. Cumulative risk of CARDS trial patients experiencing the primary endpoint of a major cardiovascular event.

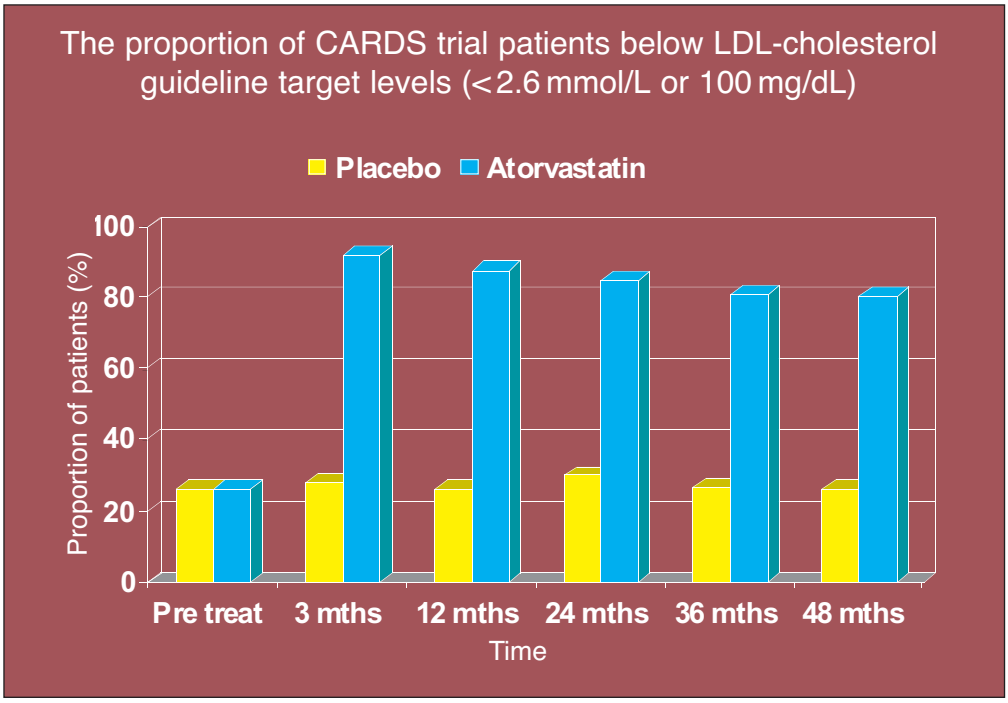

Figure 4. The proportion of CARDS patients remaining below the LDL-cholesterol guideline target levels of 2.6 mmol/L

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1 Since the risk of cardiovascular events in patients with diabetes is comparable to that in people without diabetes who have established coronary heart disease, the two groups should be managed similarly.

2 The CARDS results suggest that such an approach is justified, and that the use of statins in patients with diabetes should be based on the patients' cardiovascular risk rather than on any cholesterol threshold.

3 Epidemiological data suggest that for every 1000 patients who match the CARDS criteria, 95 will experience a major CVD event over a four-year period. The administration of atorvastatin would be expected to reduce this to 58.

the contract recognises the importance of targeting CVD risk factors such as dyslipidaemia, hypertension, and smoking, with 40 of the 99 points relating to the management of these variables.

Diabetes guidelines such as the National Service Framework for Coronary Heart Disease and Joint British Recommendations currently only advocate statin treatment for patients with elevated cholesterol or established heart disease. International guidelines, however, are more aggressive, and take the view that, since the risk of cardiovascular events in patients with diabetes is comparable to that in people without diabetes who have established coronary heart disease, the two groups should be managed similarly.

The CARDS results suggest that such an approach is justified, and that the use of statins in patients with diabetes should be based on the patients' cardiovascular risk rather than on any cholesterol threshold.

Although no direct data exist, such an approach is also likely to be cost-effective. Coronary heart disease accounts for about half of the deaths associated with CVD, and at £7.1 billion per year, is the single most burdensome NHS-managed condition (British Heart Foundation, 2004b). Epidemiological data suggest that for every 1000 patients who match the CARDS criteria, 95 will experience a major CVD event over a four-year period. The administration of atorvastatin would be expected to reduce this to 58, so that 39% of patients will avoid the costly healthcare associated with a heart attack or stroke. ■

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