Defining the role of lipid-lowering therapy in diabetes

Marc Evans

Article points

1. Diabetes increases cardiovascular risk two- to four-fold.
2. Cholesterol reduction significantly reduces cardiovascular risk in people with type 2 diabetes.
3. Dyslipidaemia and other cardiovascular risk factors need to be considered in the routine management of type 2 diabetes.
4. More judicious use of statin therapy along with an increased use of combination lipid-lowering therapies, including statin+ezetimibe, statin+fibrate and statin+niacin combinations, are recommended.

Key words

- Dyslipidaemia
- Lipid-lowering therapy
- Statins
- Vascular risk modification

Marc Evans is Consultant Diabetologist, Llandough Hospital, Cardiff.

Although strong evidence supports that cholesterol reduction significantly reduces cardiovascular risk in people with type 2 diabetes, a significant proportion of people prescribed lipid-lowering therapy are still not achieving current cholesterol targets and therefore remain at high cardiovascular risk (Heart Protection Study Collaborative Group, 2002; Colhoun et al, 2004; Baigent et al, 2005). Consequently, there remain substantial challenges to optimising the management of diabetic dyslipidaemia and, hence, cardiovascular risk in clinical practice. This article reviews current practice and advances in lipid-lowering therapy in people with type 2 diabetes, including the use of statin+ezetimibe, statin+fibrate and statin+niacin combinations, and how these may relate to optimal vascular risk modification.

Diabetes leads to a two- to four-fold increase in the risk of developing cardiovascular disease (CVD; Wei et al, 1998). Atherosclerosis in people with type 2 diabetes is often more diffuse and severe than in people without diabetes, hence morbidity and mortality rates are higher (Narayan et al, 2003). It is estimated that 75–80 % of people with type 2 diabetes die from macrovascular complications (Henry, 2001).

The dramatic decline in coronary heart disease mortality seen in the general population has not been seen in people with type 2 diabetes (Centers for Disease Control and Prevention, 2003). The Heart Protection Study (HPS; see *Appendix 1* for clinical trial acronyms) and other studies (Colhoun et al, 2004; Vijan and Hayward, 2004) have shown that cholesterol reduction significantly reduces cardiovascular risk in type 2 diabetes (Collins et al, 2003). There is therefore a clear need for dyslipidaemia and other cardiovascular risk factors to be considered in the routine management of type 2 diabetes. This article reviews current practice and advances in lipid-lowering therapy in people with type 2 diabetes and how these may relate to optimal vascular risk modification.

Diabetic dyslipidaemia: The current landscape

Target LDL-c levels are coming down in line with recent evidence (*Table 1*). The interim update to the US National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII guidelines suggest an LDL-c goal of < 1.8 mmol/l in very high risk individuals, which includes those with established CVD and diabetes (Grundy et al, 2004). The American Diabetes

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Association (ADA; 2005) and the European Diabetes Policy Group (1999) guidelines also recommend targets for HDL-c and plasma triglyceride levels – elevated plasma triglyceride and reduced HDL-c levels being characteristic of diabetic dyslipidaemia and associated with increased coronary heart disease (CHD) risk (Turner et al, 1998). The JBS 2 guidelines (British Cardiac Society et al, 2005) advocate lower and more comprehensive targets than the total cholesterol level of ≤5 mmol/l currently outlined in the nGMS contract (DoH, 2003).

The role of statins

Lifestyle modification should always form the cornerstone of type 2 diabetes management. However, pharmacotherapy is often required to meet appropriate targets. A number of large clinical trials, including significant subgroups of individuals with diabetes, have established statins as effective agents in both primary and secondary CHD prevention, which show a clear association between cholesterol reduction and outcome benefits.

- In the HPS type 2 diabetes was an independent predictor of benefit from statin therapy. In people with type 2 diabetes a 1 mmol/l reduction in LDL-c resulted in a 22 % reduction in the risk of a first vascular event, independent of baseline LDL-c levels (Collins et al, 2003).
- In the CARDS study, for people with type 2 diabetes and at least one other CHD risk factor, an LDL-c reduction of 40 % and a triglyceride reduction of 19 % were associated with a 37 % reduction in major coronary events and a 48 % reduction in stroke (Colhoun et al, 2004).

A meta-analysis of lipid-lowering trials in diabetes has concluded that cholesterol reduction in type 2 diabetes appears to be cost effective even in the absence of overt CVD (Vijan and Hayward, 2004). Despite such strong evidence, a cross-sectional study of 300 people managed in primary care showed that a significant proportion of individuals at high risk, including many with diabetes, are still not achieving the nGMS therapeutic cholesterol targets and remain at an unacceptable level of cardiovascular risk

Table 1. A selection of guideline target cholesterol levels for people with cardiovascular disease or diabetes.

	LDL-c target (mmol/l)	Total cholesterol target (mmol/l)	Triglyceride target (mmol/l)	HDL-c target (mmol/l)
European Diabetes Policy Group (1999)	<3.0 mmol/l	<4.8 mmol/l	<1.7 mmol/l	>1.2 mmol/l
NCEP ATPIII (NCEP Expert Panel, 2001; Grundy et al, 2004)	<1.8 mmol/l in very high risk <2.6 mmol/l in high risk	–	–	–
European guidelines (De Backer et al, 2003)	<3.0 mmol/l in non-high risk <2.5 mmol/l in high risk, CVD and diabetes	<5.0 mmol/l in non-high risk <4.5 mmol/l in high risk, CVD and diabetes	–	–
American Diabetes Association (2005)	<2.6 mmol/l	–	<1.7 mmol/l	>1.1 mmol/l
JBS2 (British Cardiac Society et al, 2005)	<2 mmol/l	<4 mmol/l	<1.7 mmol/l	≥1.0 mmol/l
nGMS contract (DoH, 2003)	–	≤5.0 mmol/l (in 60 % of patients with CHD, diabetes or stroke)	–	–

(Wright et al, 2003). Among those prescribed lipid-modifying therapy, suboptimal dosing, poor concordance and inherent therapeutic limitations may impair the long-term effectiveness of cholesterol reduction. Consequently, there remain substantial challenges to optimising the management of diabetic dyslipidaemia and, hence, cardiovascular risk in clinical practice.

Advances in lipid-lowering therapy

The benefits of intensive cholesterol lowering have been demonstrated in several outcome studies. In the PROVE IT trial, participants with recent acute coronary syndrome received either 80 mg atorvastatin or 40 mg pravastatin; mean LDL-c levels achieved were 1.6 mmol/l in the atorvastatin group and 2.46 mmol/l in the pravastatin group (Cannon et al, 2004). The relative risk reduction achieved by more intensive cholesterol reduction was comparable in people with diabetes and those without diabetes.

The TNT study, which included more than 1500 individuals with diabetes and compared the effects of 10 mg atorvastatin versus 80 mg atorvastatin, reported mean LDL-c levels of 2.6 mmol/l and 2.0 mmol/l for each arm respectively (LaRosa et al, 2005). Those with a lower LDL-c level achieved a 22 % relative risk reduction in the primary composite endpoint of a cardiovascular event. Extrapolation of these data and those from other major statin outcome studies would tentatively suggest an optimum LDL-c target of between 0.8 and 1.5 mmol/l to produce maximal reduction in risk (*Figure 1*).

There is currently much interest in determining which statins are most efficacious at lowering LDL-c. In populations of people with diabetes, significant reductions in cardiovascular risk are usually associated with statin-induced LDL-c reduction of 30–40 % (Insull et al, 2001). The ASSET open label, treat-to-target 54-week trial demonstrated that the diabetes subgroup treated with atorvastatin

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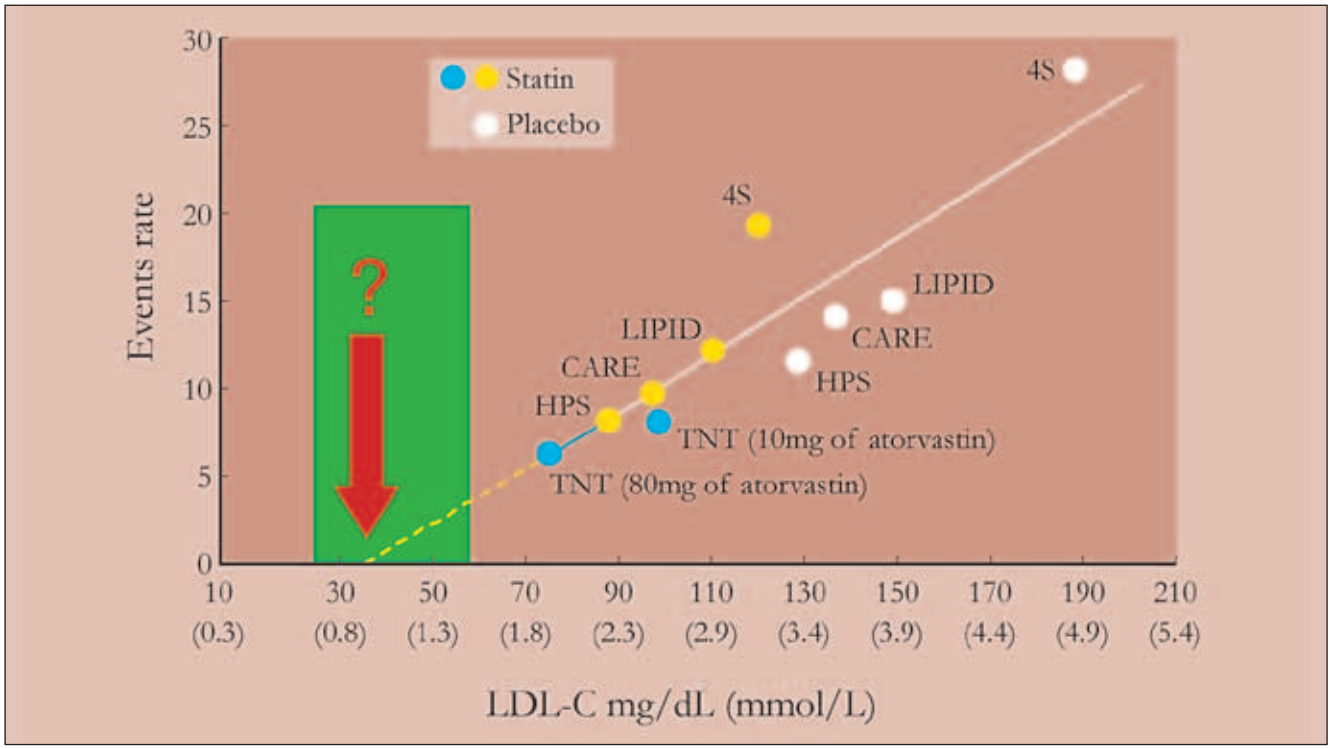

Figure 1. Results of secondary prevention studies – a potential optimum LDL-c level? (Adapted from LaRosa et al, 2005).

10 mg showed a significantly greater reduction ($P < 0.0001$) in LDL-c at 6 weeks (37.1 %) than those treated with simvastatin 10 mg (29.7 %; Insull et al, 2001). The particular statin chosen and the dose at which it is prescribed should therefore be associated with an LDL-c reduction of at least this magnitude.

In the ANDROMEDA study, rosuvastatin 10 mg and atorvastatin 10 mg reduced LDL-c by 51.3 % and 39 % ($P < 0.001$) respectively in individuals with type 2 diabetes. This resulted in 94 % and 79 % ($P < 0.001$) of participants, respectively, reaching European treatment target goals of < 2.5 mmol/l (Tuomilehto et al, 2004).

Lipid-lowering therapy beyond statins

Statin therapy remains the mainstay of lipid modification both in people with diabetes and in those without. However, in practice there can be considerable variation in clinical response to statin therapy as well as adherence issues. Concomitant drug therapy is another potential cause of variability in response with drugs that affect the same biochemical pathways as statins (Evans and Rees, 2002). Furthermore, diminishing responses over a long period may be due partly to flagging adherence.

Cholesterol absorption inhibitors

One important factor influencing statin response is variability in cholesterol absorption. Subgroup analysis of the 4S study suggested that the cholesterol reduction in response to simvastatin was significantly lower in individuals who were high cholesterol absorbers and low cholesterol synthesisers (Miettinen et al, 1998). Another study using mevalonate turnover as an index of cholesterol synthesis has also suggested that a low basal rate of cholesterol synthesis is associated with a smaller response to statins (Naoumova et al, 1996). One potential approach to improving the LDL-c response to statin therapy is to inhibit intestinal cholesterol absorption. Cholesterol absorption inhibitors include the plant stanols and sterols, which compete with cholesterol for incorporation into micelles and thus produce a modest LDL-c reduction of around 10 % (Lichtenstein and Deckelbaum, 2001).

Ezetimibe is the first synthetic cholesterol absorption inhibitor and works by selectively inhibiting cholesterol absorption at the brush border of the intestinal epithelium (Patrick et al, 2002). Bile acid sequestrants (anion exchange resins), such as colestyramine, also work by preventing reabsorption but do so by binding bile acids.

Co-administration of simvastatin and ezetimibe has been shown to produce significant reductions in LDL-c levels of up to 60 % (Murdoch and Scott, 2004). Statin+ezetimibe therapy has been shown to have superior efficacy in LDL-c reduction compared with statin monotherapy in people with type 2 diabetes, as well as in individuals with primary hypercholesterolaemia and homozygous familial hypercholesterolaemia (Murdoch and Scott, 2004). A combined ezetimibe and simvastatin tablet has recently become available in the UK and Europe (Inegy, Merck, Sharp & Dohme and Schering-Plough, Hoddesdon and Welwyn Garden City respectively). Several studies evaluating the potential outcome benefits of this therapeutic approach are underway.

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1. Combining a statin with niacin may improve the overall dyslipidaemic profile.
2. The concept of combination therapy is well established in the management of other cardiovascular risk factors in diabetes, such as hyperglycaemia and hypertension.
3. There is an urgent need for effective strategies to tackle the escalating prevalence of type 2 diabetes and its associated excess of cardiovascular mortality.

Statin+fibrate or statin+niacin combination therapy

While LDL-c is the primary lipid therapeutic target in people with type 2 diabetes, diabetic dyslipidaemia is also characterised by hypertriglyceridaemia and reduced levels of HDL-c. The typical dyslipidaemia of type 2 diabetes is characterised by moderate elevations in plasma triglycerides and low HDL-c levels (Durrington, 1999). Fibrate therapy should be considered in cases of severe hypertriglyceridaemia (>4.5 mmol/l). If the individual also has an elevated LDL-c level, a statin+fibrate combination may be used. However, it is important to remember that statin+fibrate combination therapy may increase the risk of myopathy and an assessment of the risk factors for myopathy is essential, including thyroid profile assessment, history of alcohol consumption, renal and liver function assessment and concomitant drug therapy.

Combining a statin with niacin may also improve the overall dyslipidaemic profile. In 2001 HATS showed that combined simvastatin and niacin therapy lowered LDL-c by 42% and raised HDL-c by 26% in people with coronary artery disease and low HDL-c (Brown et al, 2001).

The concept of combination therapy is well established in the management of other cardiovascular risk factors in diabetes, such as hyperglycaemia and hypertension, and the potential benefits of a combination approach to the management of dyslipidaemia in diabetes is becoming increasingly apparent. The ongoing ACCORD trial is a large-scale primary prevention study involving 10000 individuals with type 2 diabetes, that will evaluate the effects of intensive glycaemic control along with combination lipid-modifying therapy including statin alone, statin+fibrate, or antihypertensive therapy (ACCORD, 2006). The primary results are due to be published in 2010.

Peroxisome proliferator-activated receptor alpha and gamma agonists

A developing area of therapeutic interest focuses on the role of peroxisome proliferator-activated receptor (PPAR) alpha and gamma agonists in the management of type 2 diabetes. These agents have a potentially significant effect on diabetic dyslipidaemia, in particular a reduction in plasma triglyceride levels, increase in HDL-c levels and reduction in the numbers of LDL-c particles (Goldberg, 2006). Combining statins with such agents may also prove beneficial in the treatment of the multiple features of diabetic dyslipidaemia.

Conclusion

There is an urgent need for effective strategies to tackle the escalating prevalence of type 2 diabetes and its associated excess of cardiovascular mortality. The management of dyslipidaemia in such individuals represents a key therapeutic target. Despite compelling evidence for the effectiveness of lipid-modifying therapy, a number of treatment gaps remain. These may be addressed by more judicious use of statin therapy along with an increased use of combination lipid-lowering therapies, including statin+ezetimibe, statin+fibrate and statin+niacin combinations. Large-scale studies are currently under way to establish the potential of such interventions to improve outcomes in people with type 2 diabetes. ■

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Appendix 1. Clinical trial acronyms.

4S	**S**candinavian **S**imvastatin **S**urvival **S**tudy	(Miettinen et al, 1998)
ACCORD	**A**ctions to **C**ontrol **C**ardi**O**vascular **R**isk in **D**iabetes	(ACCORD, 2006)
ANDROMEDA	**A** ra**N**domised, **D**ouble blind, double dummy, multicentre phase IIIb parallel group study to compare the efficacy and safety of **R**osuvastatin (10 mg and 20 mg) and at**O**rvastatin (10 **M**g and 20 mg) in subj**E**cts with type II **D**i**A**betes mellitus	(Betteridge and Gibson, 2007)
ASSET	**A**torvastatin versus **S**imvastatin **S**afety and **E**fficacy **T**rial	(Insull et al, 2001)
CARDS	**C**ollaborative **A**to**R**vastatin **D**iabetes **S**tudy	(Colhoun et al, 2004)
CARE	**C**holesterol **A**nd **R**ecurrent **E**vents trial	(Oida, 2001)
HATS	**H**DL **A**therolsclerosis **T**reatment **S**tudy	(Brown et al, 2001)
HPS	**H**eart **P**rotection **S**tudy	(Collins et al, 2003)
LIPID	**L**ong-term **I**ntervention with **P**ravastatin in **I**schaemic **D**isease **S**tudy	(LIPID Study Group, 1998)
PROVE IT	**PR**avastatin **O**r ator**V**astatin **E**valuation and **I**nfection **T**herapy	(Cannon et al, 2004)
TNT	**T**reat to **N**ew **T**argets	(LaRosa et al, 2005)