# Managing CV risk in type 2 diabetes: Towards best practice

## Part 1: Lipid-modulating agents


## Roger Gadsby



**Type 2 diabetes is a complex disease with multiple complications requiring multiple interventions. The absolute risk of developing cardiovascular disease is two-fold greater in people with type 2 diabetes compared with the general population (Fox et al, 2004). Approximately 80 % of people with type 2 diabetes will die prematurely from cardiovascular (CV) complications (Barnett and O'Gara, 2003). Optimising the management of CV risk in people with type 2 diabetes is therefore essential in order to improve CV morbidity and mortality. This is part 1 of a series of three articles aiming to provide an overview of the multifactorial interventions that, according to evidence-based medicine, can improve cardiovascular morbidity and mortality in type 2 diabetes. In part 1, Roger Gadsby looks at lipid-modulating agents.**


There are a number of recognised factors known to contribute to the increased risk of cardiovascular (CV) death associated with type 2 diabetes (Castelli, 1988; Turner et al, 1998): raised low-density lipoprotein (LDL)-cholesterol levels; diabetic dyslipidaemia (reduced high-density lipoprotein [HDL]-cholesterol levels, high triglyceride levels, and the presence of small, dense atherogenic LDL particles); hypertension; insulin resistance; and hyperglycaemia.

The importance of primary care in the management of type 2 diabetes and the associated CV risk factors is reflected in the National Service Framework for diabetes (Department of Health, 2001) and the Quality and Outcomes Framework (QOF) of the new General Medical Services (nGMS) contract, revisions to which took effect from 1 April 2006 (British Medical Association [BMA], 2006; Kenny, 2006). The revised QOF outlines 16 indicators in diabetes and a maximum of 93 points will be awarded according to the percentage of patients that meet these targets (Kenny, 2006). The nGMS contract is centred on three main therapeutic interventions relating to diabetes. It encourages GPs to achieve good glycaemic control ($HbA_{1c}$ ≤7.5 %), decrease total cholesterol (to ≤5 mmol/l) and decrease blood pressure (to ≤145/85 mmHg) in people with diabetes.

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**Article points**

1. The challenge facing primary care practitioners is to implement the best possible standard of care for people with type 2 diabetes.
2. To achieve this, there needs to be an awareness of the best pharmacological tools currently available, the evidence for which comes from large clinical studies.
3. In terms of lipid modulation, the focus of future treatment strategies, the author believes, should be on agents or combinations of agents that offer a tailored approach to addressing the particular requirements of the diabetic dyslipidaemic profile.


**Key words**

- Lipid modulation
- Cardiovascular disease
- Statins
- Fibrates



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to improve outcomes. To achieve this goal, there needs to be an awareness of the best pharmacological tools currently available, the evidence for which comes from large clinical studies. Evidence-based medicine has highlighted the need for multifactorial interventions in people with type 2 diabetes (Gaede et al, 2003; Donnelly, 2005) and shown that more than one intervention is often required in the management of each risk factor.

## Current guidelines for management of lipids in type 2 diabetes

### JBS 2

The Joint British Societies' guidelines on prevention of cardiovascular disease (CVD) in clinical practice (known as JBS 2) have provided guidance on lipid-lowering therapy in diabetes (British Cardiac Society et al, 2005). JBS 2 recommends statin use in all people with diabetes (type 1 or type 2) aged ≥40 years. Statin use is also recommended in younger people with diabetes (18–39 years) with at least one other risk factor, including retinopathy, nephropathy, hypertension and features of the metabolic syndrome. The target lipid levels recommended by JBS 2 are <2 mmol/l for LDL-cholesterol and <4 mmol/l for total cholesterol.

### NICE

Guidance from the National Institute for Health and Clinical Excellence (NICE; formerly the National Institute for Clinical Excellence) recommends statin therapy for adults with clinical evidence of CVD and for adults who have a 20% or greater 10-year risk of developing CVD (NICE, 2006). The guidance also highlights the lack of validated risk calculators for people with diabetes, and recommends that risk in each case should be assessed clinically. The lipid targets outlined by NICE are <3 mmol/l for LDL-cholesterol and <5 mmol/l for total cholesterol (NICE, 2002), which are higher than the targets set by JBS 2.

## Evidence base for the use of lipid-modulating agents

As mentioned earlier, the triad of lipid abnormalities characteristic of diabetic dyslipidaemia are reduced HDL-cholesterol levels, high triglyceride levels, and the presence of small, dense LDL particles. People with type 2 diabetes do not tend to have particularly high LDL-cholesterol levels, per se, but there are differences in the qualitative nature of the LDL particle (Syvanne and Taskinen, 1997). Managing these complex lipid disorders is a crucial component of diabetes treatment that can reduce the risk of CV morbidity and mortality (Laakso et al, 1993).

In early prospective studies, increased triglyceride levels and decreased HDL-cholesterol were deemed as more powerful predictors of CVD than LDL-cholesterol in type 2 diabetes (Lehto et al, 1997). On this basis, early guidance (American Diabetes Association, 1993) for the treatment of diabetic dyslipidaemia focused on targeting triglycerides and HDL-cholesterol using fibrates, such as gemfibrozil.

Only in recent years – following the weight of evidence provided by large, randomised clinical trials – has the emphasis been put on LDL-cholesterol-lowering agents (statins) to improve CV outcomes, most recently in type 2 diabetes. Those studies that have to date provided evidence to change treatment practice with regard to lipid modulation in type 2 diabetes are described below and summarised in *Tables 1* and *2*.

### Statins

Statins act by lowering LDL-cholesterol levels. Their effectiveness in lowering LDL-cholesterol with the consequent improvement in CV outcome has been well studied and documented, as described below.

Robust evidence for the use of statins comes from the Heart Protection Study (HPS), which included 5963 people with diabetes (Collins et al, 2003). Importantly, the HPS also revealed that cholesterol-lowering therapy produces similar risk reductions for major vascular events regardless of the presence or absence of CVD and regardless of baseline LDL-cholesterol concentrations. The Collaborative AtoRvastatin Diabetes Study (CARDS) exclusively studied people with type 2 diabetes with no documented history of CVD (Colhoun et al, 2004). Consistent with the findings of the HPS, evidence from CARDS suggests that all individuals with type 2

**Page points**

1. The Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice have provided guidance on lipid-lowering therapy in diabetes.
2. Guidance from the National Institute for Health and Clinical Excellence also addresses lipid management.
3. Only in recent years has an emphasis been put on low-density lipoprotein (LDL)-cholesterol-lowering agents in improving cardiovascular outcomes.
4. Statins act by lowering LDL-cholesterol levels.

**Table 1. Statins and fibrates.**

**Statins (reduce low-density lipoprotein [LDL]-cholesterol)**

- Heart Protection Study (HPS): Simvastatin (40 mg) associated with a significant 22% reduction in major vascular events (Collins et al, 2003).
- Collaborative AtoRvastatin Diabetes Study (CARDS): Atorvastatin (10 mg) associated with a significant 37% reduction in major cardiovascular events (Colhoun et al, 2004).

*All patients with type 2 diabetes should be considered for statin therapy irrespective of their baseline LDL-cholesterol concentration.*

**Fibrates (increase high-density lipoprotein-cholesterol and reduce triglycerides)**

- Department of Veterans Affairs High-density lipoprotein Intervention Trial (VA-HIT): Gemfibrozil (1200 mg) associated with a significant 32% reduction in major cardiovascular events (Rubins et al, 2002).
- Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study: Fenofibrate (20 mg) associated with a non-significant 11% reduction in the combined incidence of coronary heart disease death and non-fatal myocardial infarction (Keech et al, 2005).

*The role of fibrates in targeting diabetic dyslipidaemia remains unclear.*

diabetes should be considered for statin therapy irrespective of their baseline LDL-cholesterol concentration.

## Fibrates

Fibrates, or peroxisome proliferator-activated receptor (PPAR)-α agonists, target diabetic dyslipidaemia by raising HDL-cholesterol levels and decreasing triglyceride levels. Two studies, the Department of Veterans Affairs High-density lipoprotein Intervention Trial (VA-HIT; Rubins et al, 2002) and the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD; Keech et al, 2005) study, have provided some information on the role of these agents in reducing CV mortality in type 2 diabetes.

It remained unclear from the results of the VA-HIT study whether increases in HDL-cholesterol levels, decreases in triglyceride levels or both were responsible for the beneficial effect on CV outcomes. To address this question in people with type 2 diabetes, the FIELD study was designed (Keech et al, 2005).

The FIELD study results are somewhat disappointing, the author feels, because they do not give a clear answer as to the role of fibrates in tackling diabetic dyslipidaemia. The findings may have been confounded by the fact that significantly more people in the placebo group were allocated a statin during the study than in the fenofibrate group (17% versus 8%). It could be that a greater increase in HDL-cholesterol levels is more important in terms of CV outcomes than a decrease in triglyceride levels. Nonetheless, current clinical trial evidence does not warrant an increase in the use of fenofibrate in people with type 2 diabetes (Colhoun, 2005).

## Other agents

Niacin, also referred to as 'nicotinic acid', is an old therapeutic agent that is very effective at raising HDL-cholesterol levels (Ashen and Blumenthal, 2005). The actions of niacin are associated with unpleasant side effects, most commonly flushing and skin rash as well as more serious hepatotoxicity and dysglycaemia. A prolonged-release formulation of niacin has been shown to minimise some of these side effects (McCormack and Keating, 2005).

Prolonged-release niacin alone was shown in four randomised controlled trials to decrease LDL-cholesterol levels (–13%), decrease triglycerides levels (–26%) and increase HDL-cholesterol levels (+18%; figures in parentheses represent pooled data; Birjmohun et al, 2004). In four comparative cohort studies of prolonged-release niacin in combination with a statin, the combination showed an additional 22% reduction in LDL-cholesterol and 8% reduction in triglycerides compared with prolonged-release niacin monotherapy (figures in parentheses represent pooled data; Birjmohun et al, 2004). Statin therapy had a small (1%) additional effect on a total 25% increase in HDL-cholesterol during prolonged-release niacin treatment.

Ezetimibe is a novel selective inhibitor of intestinal cholesterol absorption and acts by blocking cholesterol transport across the intestinal wall. Ezetimibe is an effective LDL-cholesterol-lowering agent and its pharmacological effect is complementary to that of the statins (Bays, 2002; Mikhailidis et al, 2005). Trials are ongoing to investigate the effects of ezetimibe in combination with low-dose statin.

Lipid-modulating agents like those described above are designed to target particular aspects of the lipid profile. Therefore, it is noteworthy that some oral hypoglycaemic agents, whose principal

**Page points**

1. Fibrates target diabetic dyslipidaemia by raising high-density lipoprotein (HDL)-cholesterol levels and decreasing triglyceride levels.
2. Niacin, also referred to as 'nicotinic acid', is an old therapeutic agent that is very effective at raising HDL-cholesterol levels.
3. Ezetimibe is an effective low-density lipoprotein-cholesterol-lowering agent and its pharmacological effect is complementary to that of the statins.

**Page points**

1. It is noteworthy that some oral hypoglycaemic agents, whose principal role is to lower blood glucose levels, have also been shown to have beneficial effects on lipid parameters in type 2 diabetes.
2. In the author's opinion, it is now best practice to consider statin therapy for all people with type 2 diabetes, unless there is a good reason not to.
3. If a person does not reach a total cholesterol level ≤5 mmol/l on the maximum-tolerated dose of statin, then fenofibrate, ezetimibe or prolonged-release niacin could be added.

role is to lower blood glucose levels, have also been shown to have beneficial effects on lipid parameters in type 2 diabetes. However, not all hypoglycaemic agents have been shown to confer the same beneficial effects.

The thiazolidinediones, or glitazones (pioglitazone and rosiglitazone), are PPAR-γ agonists that act as insulin-sensitising oral hypoglycaemic agents and have been shown to improve key lipid parameters in type 2 diabetes, beyond their glucose-lowering capability (Reynolds and Goldberg, 2006). Significant differences between the glitazones were highlighted in the first head-to-head, randomised controlled study of rosiglitazone and pioglitazone in people with type 2 diabetes and dyslipidaemia (these individuals were not taking any lipid-lowering agents; Goldberg et al, 2005). Pioglitazone was associated with significant decreases in triglycerides, increases in HDL-cholesterol and increases in LDL particle size (from small, dense atherogenic particles to larger, more buoyant and less atherogenic particles) compared with rosiglitazone.

When used as an oral hypoglycaemic agent in conjunction with best available care, including lipid-modulating therapies, pioglitazone may further improve CV outcomes in type 2 diabetes (Dormandy et al, 2005). It is as yet unknown whether these findings are related to an improvement in lipid profile.

By contrast, metformin has no clinically significant effects on total cholesterol, HDL-cholesterol, LDL-cholesterol or triglycerides compared with placebo (Saenz et al, 2006). Furthermore, only sparse data are available on the CV and lipid-related effects of the insulin secretagogues (Buse et al, 2004; Granberry and Fonseca, 2005). An overview comparing the effects of metformin, gliclazide, pioglitazone and rosiglitazone on lipid parameters in type 2 diabetes is shown in *Table 3*.

## Towards best practice

In the author's opinion, it is now best practice to consider statin therapy for primary prevention in all people with type 2 diabetes and to prescribe one of the two statins that have an evidence base for primary prevention, simvastatin 40 mg daily (HPS) or atorvastatin 10 mg daily (CARDS), unless there is a good reason not to. The evidence base for the use of statins extends to around the age of 80 years. However, trials usually exclude people with significant co-morbidities, and these may be seen in around two-thirds of people over the age of 75 years (Sinclair, 2000). The author feels that the use of statin therapy in people over the age of 80 years therefore needs to be considered on an individual basis.

Statins are generally well tolerated with a well-characterised safety profile. Occasionally abdominal pain and myalgia occur with the currently available agents, rarely raised liver enzymes and myopathy, and extremely rarely rhabdomyolysis (BMA and Royal Pharmaceutical Society of Great Britain, 2006).

If a person does not reach the QOF total cholesterol target (≤5 mmol/l) on the maximum-tolerated dose of statin, then fenofibrate, ezetimibe or prolonged-release niacin could be added. These three agents will lower cholesterol but there are, as yet, no studies with hard outcome data that show that lowering cholesterol with a statin in addition to any one of these

**Table 2. Summary of large-scale clinical outcome studies using lipid-lowering therapies in populations (or sub-groups) with type 2 diabetes.**

| Study | People randomised | People with diabetes | Drug (dose) | Comparator |
|---|---|---|---|---|
| HPS | 20 536 | 5 963 | Simvastatin (40 mg) | Placebo |
| CARDS | 2 838 | 2 838 | Atorvastatin (10 mg) | Placebo |
| VA-HIT | 2 531 | 627 | Gemfibrozil (1200 mg) | Placebo |
| FIELD | 9 795 | 9 795 | Fenofibrate (20 mg) | Placebo |

CARDS, Collaborative AtoRvastatin Diabetes Study; FIELD, Fenofibrate Intervention and Event Lowering in Diabetes; HPS, Heart Protection Study; VA-HIT, Department of Veterans Affairs High-density lipoprotein Intervention Trial

**Table 3. An overview of the effects of metformin, gliclazide, pioglitazone and rosiglitazone on lipid parameters in type 2 diabetes.**

| Lipid parameter | Metformin | Gliclazide | Pioglitazone | Rosiglitazone |
|---|---|---|---|---|
| TG (mmol/l) | ↔ (–0.1)[1] | ↑↓ | ↓ (–0.6)[3] | ↔ (+0.1)[3] |
| HDL-c (mmol/l) | ↔ (+0.0)[1] | ↑↓ | ↑ (+0.1)[3] | ↑ (+0.1)[3] |
| LDL-c (mmol/l) | ↔ (–0.2)[1] | ↑↓ | ↑↓ | ↑ (+0.5)[3] |
| LDL-c particle size (nm) | ↔ (+0.1)[2] | Not available | ↑ (+0.5)[3] | ↑ (+0.3)[3] |
| Total-c (mmol/l) | ↔ (–0.3)[1] | ↑↓ | ↔ (+0.2)[3] | ↑ (+0.7)[3] |

↑ = increase; ↓ = decrease; ↔ = no significant difference; ↑↓ = inconsistent effects
HDL-c, high-density lipoprotein-cholesterol; LDL-c, low-density lipoprotein-cholesterol; TG, triglycerides; Total-c, total cholesterol
[1] Wulffele et al, 2004; [2] Chu et al, 2002; [3] Goldberg et al, 2005

agents is better than a statin in addition to any other. Therefore the decision on which agent to add to the maximum-tolerated dose of statin has to be made on consideration of other issues, including price and tolerability.

Current nGMS indicators (BMA, 2006) and NICE guidelines (NICE, 2002) do not reflect the need to tackle the individual components of diabetic dyslipidaemia by providing targets for HDL-cholesterol and triglyceride levels. However, there are currently no outcome data to support interventions that increase HDL-cholesterol or decrease triglyceride levels. Nevertheless, these should not be ignored, the author believes, once statins have been initiated for LDL-cholesterol control.

## Future strategies

Evidence from CARDS and the HPS suggests that we treat all individuals with diabetes with statins regardless of their baseline LDL-cholesterol and history of CVD. We need to review current targets for LDL-cholesterol and total cholesterol since evidence encourages treatment of people who are already below these targets. The difficulty is in finding the right targets and the question remains 'how low do you go?'.

The Atorvastatin in Factorial with Omega-3 fatty acids Risk Reduction in Diabetes (AFORRD) study is a randomised controlled trial assessing the degree to which LDL-cholesterol lowering (with atorvastatin), triglyceride lowering (with omega-3 fatty acids) or both reduces the estimated risk of coronary heart disease in people with type 2 diabetes (Oxford Centre for Diabetes, Endocrinology & Metabolism, 2006). The results of AFORRD, expected in late 2006, will provide insights into the role of triglycerides in the development of coronary heart disease and could potentially provide evidence for triglyceride lowering with omega-3 fatty acids in type 2 diabetes.

There is a need to re-visit agents with HDL-cholesterol-raising or triglyceride-lowering properties. The focus of future treatment strategies, the author believes, should be on agents or combinations of agents that offer a tailored approach to addressing the particular requirements of the diabetic dyslipidaemic profile by treating to target. Such a tailored approach may further improve CV outcomes in this high-risk group of people and this need should also be reflected in future guidelines for the management of diabetic dyslipidaemia. ■

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1. There is a need to review current targets for low-density lipoprotein-cholesterol and total cholesterol since evidence encourages treatment of people who are already below these targets.
2. The results of AFORRD, expected in late 2006, could potentially provide evidence for triglyceride lowering with omega-3 fatty acids in type 2 diabetes.

American Diabetes Association (1993) Detection and management of lipid disorders in diabetes. *Diabetes Care* **16**(5): 828–34
Ashen MD, Blumenthal RS (2005) Clinical practice. Low HDL cholesterol levels. *New England Journal of Medicine* **353**(12): 1252–60
Barnett AH, O'Gara G (2003) *Diabetes and the heart.* Churchill Livingstone, London
Bays H (2002) Ezetimibe. *Expert Opinion on Investigational Drugs* **11**(11): 1587–1604
Birjmohun RS, Hutten BA, Kastelein JJ, Stroes ES (2004) Increasing HDL cholesterol with extended-release nicotinic acid: from promise to practice. *Netherlands Journal of Medicine* **62**(7): 229–34
British Cardiac Society, British Hypertension Society, Diabetes UK et al (2005) JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart* **91**(Suppl 5): v1–52

British Medical Association (BMA; 2006) *Revisions to the GMS contract, 2006/07.* BMA, London. Available at http://www.bma.org.uk/ap.nsf/Content/revisionnGMSFeb20062 (accessed 12.06.2006)

BMA, Royal Pharmaceutical Society of Great Britain (RPSGB; 2006) Statins: Additional information. In: *British National Formulary.* BMA and RPSGB, London. Available at http://www.bnf.org/bnf/bnf/51/33422.htm (accessed 12.06.2006)

Buse JB, Tan MH, Prince MJ, Erickson PP (2004) The effects of oral anti-hyperglycaemic medications on serum lipid profiles in patients with type 2 diabetes. *Diabetes, Obesity & Metabolism* **6**(2): 133–56

Castelli WP (1998). Cholesterol and lipids in the risk of coronary artery disease – the Framingham Heart Study. *Canadian Journal of Cardiology* **4**(Suppl A): 5A–10A

Chu NV, Kong AP, Kim DD et al (2002) Differential effects of metformin and troglitazone on cardiovascular risk factors in patients with type 2 diabetes. *Diabetes Care* **25**(3): 542–9

Colhoun H (2005) After FIELD: should fibrates be used to prevent cardiovascular disease in diabetes? *Lancet* **366**(9500): 1829–31

Colhoun HM, Betteridge DJ, Durrington PN et al (2004) Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* **364**(9435): 685–96

Collins R, Armitage J, Parish S et al (2003) MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* **361**(9374): 2005–16

Department of Health (DoH; 2001) *National Service Framework for diabetes: Standards.* DoH, London

Donnelly R (2005) Managing cardiovascular risk in patients with diabetes. *British Journal of Diabetes & Vascular Disease* **5**(6): 325–9

Dormandy JA, Charbonnel B, Eckland DJ et al (2005) Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* **366**(9493): 1279–89

Fox CS, Coady S, Sorlie PD et al (2004) Trends in cardiovascular complications of diabetes. *Journal of the American Medical Association* **292**(20): 2495–9

Gaede P, Vedel P, Larsen N et al (2003) Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *New England Journal of Medicine* **348**(5): 383–93

Goldberg RB, Kendall DM, Deeg MA et al (2005) A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. *Diabetes Care* **28**(7): 1547–54

Granberry MC, Fonseca VA (2005) Cardiovascular risk factors associated with insulin resistance: effects of oral antidiabetic agents. *American Journal of Cardiovascular Drugs* **5**(3): 201–9

Keech A, Simes RJ, Barter P et al (2005) Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* **366**(9500): 1849–61

Kenny C (2006) How changes to the QOF will affect diabetes care. *Diabetes and Primary Care* **8**(1): 22–30

Laakso M, Lehto S, Penttila I, Pyorala K (1993) Lipids and lipoproteins predicting coronary heart disease mortality and morbidity in patients with non-insulin-dependent diabetes. *Circulation* **88**(4 Pt 1): 1421–30

Lehto S, Ronnemaa T, Haffner SM (1997) Dyslipidemia and hyperglycemia predict coronary heart disease events in middle-aged patients with NIDDM. *Diabetes* **46**(8): 1354–9

Oxford Centre for Diabetes, Endocrinology & Metabolism (OCDEM; 2006) *AFORRD: Protocol.* OCDEM, Oxford. http://www.dtu.ox.ac.uk/index.html?maindoc=/aforrd/protocol.html (accessed 12.06.2006)

McCormack PL, Keating GM (2005) Prolonged-release nicotinic acid: a review of its use in the treatment of dyslipidaemia. *Drugs* **65**(18): 2719–40

Mikhailidis DP, Wierzbicki AS, Daskalopoulou SS et al (2005) The use of ezetimibe in achieving low density lipoprotein lowering goals in clinical practice: position statement of a United Kingdom consensus panel. *Current Medical Research and Opinion* **21**(6): 959–69

National Institute for Clinical Excellence (NICE; now the National Institute for Health and Clinical Excellence; 2002) *Management of type 2 diabetes - management of blood pressure and blood lipids. Guideline H.* NICE, London

NICE (2006) *Statins for the prevention of cardiovascular events. Technology Appraisal 94.* NICE, London

Reynolds K, Goldberg RB (2006) Thiazolidinediones: beyond glycemic control. *Treatments in Endocrinology* **5**(1): 25–36

Rubins HB, Robins SJ, Collins D et al (2002) Diabetes, plasma insulin, and cardiovascular disease: subgroup analysis from the Department of Veterans Affairs high-density lipoprotein intervention trial (VA-HIT). *Archives of Internal Medicine* **162**(22): 2597–604

Saenz A, Fernandez-Esteban I, Mataix A et al (2006) Metformin monotherapy for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews* (Issue 2)

Sinclair AJ (2000) Diabetes in old age – changing concepts in the secondary care arena. *Journal of the Royal College of Physicians of London* **34**(3): 240–4

Syvanne M, Taskinen MR (1997) Lipids and lipoproteins as coronary risk factors in non-insulin-dependent diabetes mellitus. *Lancet* **350**(Suppl 1): SI20–3

Turner RC, Millns H, Neil HA et al (1998). Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS: 23). *British Medical Journal* **316**(7134): 823–8

Wulffele MG, Kooy A, de Zeeuw D et al (2004) The effect of metformin on blood pressure, plasma cholesterol and triglycerides in type 2 diabetes mellitus: a systematic review. *Journal of Internal Medicine* **256**(1): 1–14