Managing CV risk in type 2 diabetes: Towards best practice

Part 2: Oral glucose-lowering agents

Roger Gadsby

Article points

1. Type 2 diabetes is associated with a cluster of risk factors for cardiovascular disease, including hyperglycaemia, diabetic dyslipidaemia, hypertension and insulin resistance.
2. Currently only two oral glucose-lowering agents (metformin and pioglitazone) have been shown to reduce cardiovascular risk and improve morbidity and mortality in type 2 diabetes.
3. Selection of hypoglycaemic agents for type 2 diabetes should also be based on their impact on other metabolic factors that contribute to the disease process.

Key words

- Type 2 diabetes
- Cardiovascular disease
- Risk reduction
- Oral hypoglycaemic agents

Roger Gadsby is a GP, Nuneaton, and Senior Lecturer in Primary Care, Warwick Medical School, University of Warwick.

Approximately 50% of people with type 2 diabetes will already show evidence of cardiovascular (CV) complications at diagnosis (UK Prospective Diabetes Study Group, 1990). People with type 2 diabetes have a higher incidence of stroke, myocardial infarction, heart failure and acute coronary syndromes than those without diabetes (Haffner et al, 1998; Almdal et al, 2004). This three-part series provides an overview of the multifactorial interventions (lipid-lowering agents, oral glucose-lowering agents and antihypertensive agents) that, according to evidence-based medicine, can improve CV morbidity and mortality in type 2 diabetes. In part 2, Roger Gadsby looks at oral glucose-lowering agents.

In the past, the clinical management of type 2 diabetes has centred on the achievement of target HbA_{1c} levels. The landmark UK Prospective Diabetes Study (UKPDS) demonstrated that intensive blood glucose control substantially decreases the risk of debilitating microvascular complications in type 2 diabetes (UKPDS Group, 1998a). Currently only two oral glucose-lowering agents (metformin and pioglitazone) have been shown to reduce cardiovascular (CV) risk and improve morbidity and mortality in type 2 diabetes in CV outcome studies (*Table 1*; UKPDS Group, 1998a).

In a sub-group of overweight participants with newly diagnosed type 2 diabetes the UKPDS demonstrated that intensive glucose-lowering treatment with metformin was associated with a 32% risk reduction for diabetes-related endpoints (including myocardial infarction [MI] and stroke), and a 42% reduction in risk for diabetes-related deaths compared with conventional treatment with diet alone (UKPDS Group, 1998b). Metformin was the only glucose-lowering agent in the UKPDS to improve CV outcomes in this population. On the strength of these findings, metformin is the unequivocal first-line pharmacological therapy of choice in the majority of people with type 2 diabetes and the foundation of hypoglycaemic treatment.

Why does metformin have a beneficial CV outcome? It seems to have moderate effects on some 'non-traditional' CV risk factors such as markers of inflammation and hypercoagulation. These factors are not yet generally accepted as predictors of cardiovascular disease (CVD) and therefore are not specifically targeted (Chu et al, 2002).

Table 1. Summary of randomised large-scale clinical outcome studies in populations with type 2 diabetes.

Study	Number of participants	Number with diabetes	Drug (dose)	Comparator	Endpoint
UKPDS	4209	342 metformin 411 conventional	Metformin (850–2550 mg) intensive treatment	Conventional treatment (diet alone)	32% reduction in diabetes-related endpoints;* 42% reduction in diabetes-related deaths*
PROactive	5238	5238	Pioglitazone (15–45 mg)	Placebo	10% reduction in combined primary endpoint; 16% reduction in secondary principal endpoint (death, stroke and MI)*
PROactive sub-group	2445	2445	Pioglitazone (15–45 mg)	Placebo	28% reduction in risk of recurrent fatal or non-fatal MI;* 37% reduction in acute coronary syndrome*

*Significant reduction

MI, myocardial infarction; PROactive, PROspective pioglitAzone Clinical Trial In macroVascular Events; UKPDS, UK Prospective Diabetes Study

Page points

1. In the PROactive study, pioglitazone significantly reduced the principal secondary combination endpoint of death, stroke or myocardial infarction (MI) by 16%.
2. In people with previous MI, pioglitazone also significantly reduced the risk of recurrent fatal or non-fatal MI by 28% and significantly reduced the risk of acute coronary syndrome by 37%.
3. The favourable outcomes of pioglitazone treatment may be related to its beneficial effects on a number of metabolic risk factors for cardiovascular disease.

A recent systematic review revealed that overall there are no clinically significant benefits of metformin on 'traditional' CV risk factors in type 2 diabetes (that is, those recognised and treated by most physicians) such as blood pressure or lipid parameters (Wulffele et al, 2004). Therefore the findings of the UKPDS are still without full explanation.

The PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) study was designed to assess whether pioglitazone (15–45 mg daily) could improve CV outcomes in people with type 2 diabetes at high risk of CVD (Dormandy et al, 2005). Participants were already receiving optimised standard of care according to the International Diabetes Federation (IDF; Europe) guidelines (IDF, 2005), including glucose-lowering agents, lipid-lowering agents (the majority being on statins), antihypertensive agents (mainly angiotensin-converting enzyme [ACE] inhibitors and β-blockers) and antiplatelet agents.

Treatment with pioglitazone significantly reduced the principal secondary combination endpoint of death, stroke or MI by 16% (Dormandy et al, 2005). The primary combination endpoint of seven different macrovascular events of varying clinical importance was reduced by 10% but this did not reach statistical significance.

A sub-group analysis revealed that in those who had previous MI, pioglitazone significantly reduced the risk of recurrent fatal or non-fatal MI by 28% and also significantly reduced the risk of acute coronary syndrome by 37% (Erdmann, 2005b).

The favourable outcomes associated with pioglitazone treatment in the PROactive study may relate to its beneficial effects on a number of metabolic risk factors for CVD. When added to already optimised medication, pioglitazone produced beneficial effects on the following risk factors (Dormandy et al, 2005).

- HbA_{1c} was reduced from 7.8% to 7.0% (a decrease of 0.8 percentage points).
- HDL-cholesterol was increased by 0.2 mmol/l (an increase of 8.9%).
- Triglycerides (TG) were decreased by 0.2 mmol/l (a decrease of 13.2%).
- LDL-cholesterol:HDL-cholesterol ratio was reduced from 2.6 to 2.3.
- Systolic blood pressure and diastolic blood pressures were reduced by a median of 3 mmHg and 2 mmHg respectively.

Pioglitazone has also been shown to improve key CV parameters in type 2 diabetes, although within the glitazone class there are some significant differences between the agents (*Table 2*; Dormandy et al, 2005). The differential effect of the glitazones on lipid profiles was highlighted in the first head-to-head,

Table 2. An overview of the effects of metformin, pioglitazone and rosiglitazone on cardiovascular (CV) risk factors in type 2 diabetes.*

Traditional CV risk factors	Metformin	Pioglitazone	Rosiglitazone
Glycaemic control			
HbA_{1c} (%)	↓ (-1.5)[a]	↓ (-1 to -1.5)[b]	↓ (-1 to -1.5)[b]
Lipid parameters			
TG (mmol/l)	↔ (-0.1)[c]	↓ (-0.5)[b]	↔ (-0.1)[b]
HDL-c (mmol/l)	↔ (+0.0)[c]	↑ (+0.1)[b]	↑ (+0.7)[b]
LDL-c (mmol/l)	↓ (-0.2)[c]	↑↓	↑ (+0.4)[b]
LDL-c particle size (nm)	↔ (+0.1)[d]	↑ (+0.5)[e]	↑ (+0.3)[e]
Total-c (mmol/l)	↓ (-0.3)[c]	↔ (-0.0)[b]	↑ (+0.6)[b]
Blood pressure	↓	↓	↓
SBP and DBP (mmHg)	(SBP, -1.1; DBP, -1.0)[c]	lowest: (SBP, -1.6; DBP, -1.4)[f] highest: (SBP, -10; DBP, -8)[g]	lowest: (SBP, -0.7; DBP, -0.8)[b] highest: (SBP, -5.4; DBP, -4.1)[h]
Microalbuminuria			
Urinary albumin: creatinine ratio	↔ (-1 %)[i]	↓ (-19 %)[i]	↓ (-33 %)[j]
Non-traditional CV risk factors			
Vascular haemostasis			
PAI-1 (ng/ml)	↑↓	↓ (-10.4)[e]	↓ (-11.7)[e]
Platelet reactivity	↑↓	↓	↓
Inflammatory markers			
CRP (mg/l)	↓ (-2.0)[d]	↓ (-2.0)[e]	↓ (-2.5)[e]
TNF-α (pg/ml)	Not available	↓ (-0.7)[k]	↔[l]
Adiponectin (µg/ml)	↔[m]	↑ (+8.7)[k]	↑ (+9.0)[n]

*The data are from a variety of randomised, controlled clinical studies, some of which have been meta-analysed to provide a more consistent view. CRP, C-reactive protein; CV, cardiovascular; DBP, diastolic blood pressure; HDL-c, HDL-cholesterol; LDL-c, LDL-cholesterol; PAI-1, plasminogen activator inhibitor-1; SBP, systolic blood pressure; TG, triglycerides; TNF-α, tumour necrosis factor-α; Total-c, total cholesterol

↑ = increase; ↓ = decrease; ↔ = no significant difference; ↑↓ = inconsistent effects

[a] Schernthaner et al, 2004; [b] Chiquette et al, 2004 – meta-analysis of randomised controlled trials comparing the effect of pioglitazone and rosiglitazone on CV risk factors in type 2 diabetes; [c] Wulffele et al, 2004 – systematic review of randomised controlled trials examining the effects of metformin on blood pressure and lipid parameters in type 2 diabetes; [d] Chu et al, 2002; [e] Goldberg et al, 2005; [f] Belcher et al, 2004; [g] Gerber et al, 2003; [h] Sarafidis et al, 2004; [i] Erdmann, 2005a; [j] Sarafidis et al, 2005; [k] Miyazaki et al, 2004; [l] Mohanty et al, 2004; [m] Jung et al, 2005; [n] Osei et al, 2004

Page points

1. It is well documented that pioglitazone is associated with a more favourable lipid profile than rosiglitazone.
2. The fact that glitazones can control the levels of proteins involved in glucose homeostasis, lipid metabolism, vascular tone and inflammation may explain their wide array of effects.

randomised, controlled study of rosiglitazone and pioglitazone in people with type 2 diabetes and dyslipidaemia who were not taking any lipid-lowering agents (Goldberg et al, 2005). Pioglitazone was associated with significant improvements in TG, HDL-cholesterol, LDL-cholesterol particle concentration and size compared with rosiglitazone. Overall, it is now well documented that pioglitazone is associated with a more favourable lipid profile than rosiglitazone (Chiquette et al, 2004).

The fact that the actions of the glitazones can control the levels of proteins involved in glucose homeostasis, lipid metabolism, vascular tone and inflammation may explain the wide array of effects demonstrated by this class of agent (Yki-Jarvinen, 2004). For example, the glitazones have also been shown to improve

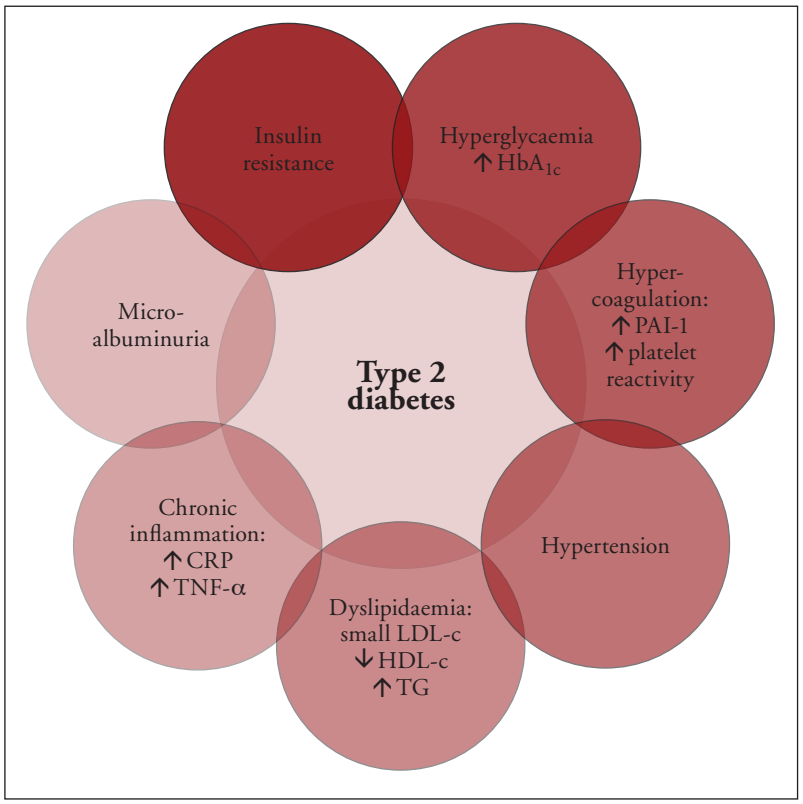

Figure 1. The cluster of cardiovascular risk factors associated with type 2 diabetes. CRP, C-reactive protein; HDL-c, HDL-cholesterol; LDL-c, LDL-cholesterol; PAI-1, plasminogen activator inhibitor-1; TG, triglycerides; TNF-α, tumour necrosis factor-α; ↑ = increase; ↓ = decrease.

Page points

1. It is now clear that type 2 diabetes is a highly complex condition associated with a cluster of other risk factors that contribute significantly to the burden of cardiovascular disease.
2. The challenge facing primary care physicians is to achieve the best possible standard of care for people with type 2 diabetes in terms of glycaemic control and cardiovascular (CV) risk, in order to improve CV morbidity and mortality.

clinical CVD markers (for example, by Sidhu et al, 2004).

Carotid intima–media thickness (CIMT) is used clinically as a surrogate marker for CV risk. A thick carotid intima has been shown to correlate with future CV events (Bots et al, 1997). The glitazones have been shown to attenuate the progression of CIMT, suggesting a direct role in modulating the atherosclerotic process (Sidhu et al, 2004; Langenfeld et al, 2005). The exact mechanisms for these effects are not entirely clear and are likely to involve multiple pathways, although it has been suggested that inhibition of neointimal tissue proliferation plays a key role (Takagi et al, 2003; Marx et al, 2005). Further research and clinical studies are required to more fully understand the modes of action of glitazones in this context.

An overview of the effects of metformin and the glitazones on traditional and non-traditional CV risk factors is given in *Table 2*.

Other oral glucose-lowering agents

It is noteworthy that many investigations have examined the potential for additional cardioprotective effects of glucose-lowering agents, but not all agents have been studied to the same extent (Buse et al, 2004; Granberry and Fonseca, 2005). Recent systematic literature reviews have concluded that the α-glucosidase inhibitors and the insulin secretagogues do not confer any significant effects on the cluster of CV risk factors associated with type 2 diabetes (*Figure 1*; Buse et al, 2004; Granberry and Fonseca, 2005; Van de Laar et al, 2005). However, only sparse data are available on the CV profiles of these agents.

Best practice

It is now clear that type 2 diabetes is a highly complex condition associated with a cluster of other risk factors that contribute significantly to the burden of CVD, namely diabetic dyslipidaemia, hypertension, insulin resistance and hyperglycaemia (McCallum and Fisher, 2005). The relationship between these established risk factors and CV outcomes in type 2 diabetes is well known and supported by a robust evidence base provided by large, randomised clinical trials conducted over the last 10 years (for example, those discussed in McCallum and Fisher, 2005).

The challenge facing primary care physicians is to achieve the best possible standard of care for people with type 2 diabetes in terms of glycaemic control and CV risk, in order to improve CV morbidity and mortality. Physicians must now look beyond blood glucose control in order to avoid the otherwise inevitable consequences of disease progression in this high-risk group. Although hypoglycaemic drugs act primarily as glucose-lowering agents, it is increasingly being recognised that some agents may confer additional cardioprotective effects (UKPDS Group, 1998a).

As a result of the findings of the UKPDS Group (1998b) metformin continues to provide the foundation of hypoglycaemic treatment in people with type 2 diabetes. If generic metformin cannot be tolerated because of gastrointestinal side effects it is worth trying modified-release metformin, which causes fewer gastrointestinal

side effects (Blonde et al, 2004). If modified-release metformin is not tolerated for initial monotherapy, then either a glitazone or sulphonylurea will need to be used. (In the author's opinion, people in whom a sulphonylurea might be considered as initial monotherapy would be those who are very symptomatic, who are not overweight and in whom β-cell dysfunction was thought to be the main pathophysiological abnormality.)

In due time, a second therapy will be required in order to maintain glycaemic control at recommended target levels. Current guidelines from the National Institute for Health and Clinical Excellence (NICE; formerly National Institute for Clinical Excellence; 2002) recommend that a sulphonylurea be the second agent that is added to metformin monotherapy. Given the findings from more recently reported randomised, controlled studies, many physicians would now consider a glitazone to be an ideal addition to metformin monotherapy in overweight people in whom insulin resistance is thought to be the major pathophysiological problem. The PROactive study with its suggestion of CV protection with pioglitazone supports this complementary combination.

Once two agents in combination no longer control hyperglycaemia, a third oral antidiabetic agent can be added to delay progression to insulin therapy (Higgs and Krentz, 2004). The combination of sulphonylurea, metformin and rosiglitazone as triple oral therapy will be of benefit to people with diabetes who are frightened by the thought of injecting insulin and those for whom going on to insulin would cause employment problems, such as public service and heavy goods vehicle drivers. The advent of inhaled insulin may be of benefit to those who are terrified of insulin injections.

It should be noted that glitazones are currently contraindicated for use in combination with insulin in the UK. Pioglitazone is not currently licensed for use in triple-therapy combination with other oral glucose-lowering agents; however, rosiglitazone is.

The American Diabetes Association (ADA) in conjunction with the European Association for the Study of Diabetes (EASD) has recently published a consensus algorithm for the management of hyperglycaemia in type 2 diabetes, to help guide healthcare providers in choosing the most appropriate interventions for their patients (Nathan et al, 2006). In contrast to the current NICE guidelines, within the ADA/EASD algorithm there is no strong consensus regarding the second-line medication to add in after metformin, other than to choose from insulin, a sulphonylurea or a glitazone. The ADA/EASD guidelines also state that, in general, antihyperglycaemic agents with different mechanisms of action will have the greatest synergy and this should also be a consideration. Nathan et al state that, in addition to their variable effects on glycaemia, specific effects of individual therapies on CV risk factors, such as hypertension or dyslipidaemia, were also considered important when reaching a consensus algorithm.

Future strategies

Hypoglycaemic therapies for the treatment of type 2 diabetes should no longer be viewed solely as blood glucose-lowering agents, but rather as agents that can impact on the underlying pathophysiology of the condition. Despite this, the terms 'antidiabetic agent' and 'glucose-lowering agent' are used synonymously. A redefinition of these terms is appropriate, the author believes. A 'glucose-lowering agent' improves glycaemic control but has no additional CV effects. The term 'antidiabetic agent' encompasses glucose-lowering agents that also have beneficial

Page points

1. Ongoing clinical studies may potentially lead to a paradigm shift in treatment strategies for type 2 diabetes in the future.
2. The DREAM trial aimed to determine whether early treatment with an angiotensin-converting enzyme inhibitor or a glitazone can reduce the development of diabetes and atherosclerosis in people with impaired fasting glucose or impaired glucose tolerance (IGT).
3. The ACT NOW study will examine whether early pioglitazone therapy (45 mg/day) can prevent or delay the onset of type 2 diabetes in people with IGT and one or more components of the metabolic syndrome.
4. ACT NOW will also evaluate glycaemic control, insulin sensitivity, cardiovascular risk factors, β-cell function and changes in body composition.

CV effects which may be mediated through their actions on the underlying pathophysiology of diabetes.

The Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes (RECORD) study aims to evaluate the long-term impact of rosiglitazone on CV outcomes in people with type 2 diabetes with inadequate blood glucose control (HbA_{1c} 7.1–9.0%) who are taking metformin or sulphonylurea alone, without a pre-requirement to include people with a previous CV event (Home et al, 2005). The results of RECORD (expected in 2009) will determine whether the beneficial effects of pioglitazone observed in the PROactive study are due to a class effect of the glitazones or a finding that is unique to pioglitazone.

Furthermore, A Diabetes Outcome Progression Trial (ADOPT) aims to compare the long-term efficacy of rosiglitazone monotherapy with that of metformin or a sulphonylurea (glibenclamide) on glycaemic control and CV risk markers (but not morbidity and mortality outcomes) in people recently diagnosed with type 2 diabetes (Viberti et al, 2002). The results of this primary CV prevention study will provide the first comparative information on the effect of different classes of glucose-lowering agents on the progression of type 2 diabetes and their influence on risk factors associated with long-term complications.

Ongoing clinical studies may potentially lead to a paradigm shift in treatment strategies for people with type 2 diabetes. The Diabetes REduction Assessment with ramipril and rosiglitazone Medications (DREAM) trial aimed to determine whether early treatment with an ACE inhibitor or a glitazone can reduce the development of diabetes and atherosclerosis in people with impaired fasting glucose or impaired glucose tolerance (IGT, a pre-diabetic state; Gerstein et al, 2004). (Editor's note: Page 156 provides details of the first set of DREAM results, which were not available at the time of writing.)

In the DREAM trial, a total of 5269 people have been randomised to ramipril (15 mg/day) or placebo and rosiglitazone (8 mg/day) or placebo according to a 2-by-2 factorial design and were followed for a minimum of 3 years. Participants were assessed regularly for the primary outcome (new-onset type 2 diabetes or all-cause mortality) as well as predefined secondary outcomes. A subset of individuals (around 20% of participants) is undergoing annual carotid ultrasound to assess the effects of treatment on the progression of atherosclerosis.

Furthermore, the Actos Now for the Prevention of Diabetes (ACT NOW) study is examining whether early treatment with pioglitazone (45 mg/day) can prevent or delay the onset of type 2 diabetes in people with IGT and one or more components of the metabolic syndrome (Texas Diabetes Institute, 2005). In addition to assessing progression to diabetes, ACT NOW will also evaluate glycaemic control, insulin sensitivity, CV risk factors, β-cell function and changes in body composition. Although the thought of preventing or delaying the onset of diabetes is a thrilling one, pharmacological management of individuals with IGT will be challenging from both practical and budgetary perspectives.

Conclusion

For the majority of people diagnosed with type 2 diabetes, metformin is the unequivocal first-line hypoglycaemic agent of choice on the basis of glycaemic control, safety, outcomes and cost. However, because of the progressive nature of the condition, a second agent may be needed within 1–2 years to maintain target glycaemic control.

To make an informed decision with regard to the appropriate hypoglycaemic agent to add in, physicians should be aware of the distinction between a glucose-lowering and an antidiabetic agent. The goal of an effective antidiabetic agent is not only to achieve glycaemic control but also to impact on the natural history of the condition. Hypoglycaemic agents differ widely in their potential impact on CV risk factors. The question is whether or not these effects are significant enough to be incorporated into treatment selection decisions. Clearly, this question can only be answered by performing large, randomised outcome studies. ■

Conflict of interest

The author has participated in advisory boards for Takeda UK.

Almdal T, Scharling H, Jensen JS, Vestergaard H (2004) The independent effect of type 2 diabetes mellitus on ischemic heart disease, stroke, and death: a population-based study of 13,000 men and women with 20 years of follow-up. *Archives of Internal Medicine* **164**(13): 1422–6

Belcher G, Lambert C, Goh KL et al (2004) CV effects of treatment of type 2 diabetes with pioglitazone, metformin and gliclazide. *International Journal of Clinical Practice* **58**(9): 833–7

Blonde L, Dailey GE, Jabbour SA et al (2004) Gastrointestinal tolerability of extended-release metformin tablets compared to immediate-release metformin tablets: results of a retrospective cohort study. *Current Medical Research and Opinion* **20**(4): 565–72

Bots ML, Hoes AW, Koudstaal PJ et al (1997) Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. *Circulation* **96**(5): 1432–7

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 and Metabolism* **6**(2): 133–56

Chiquette E, Ramirez G, Defronzo R (2004) A meta-analysis comparing the effect of thiazolidinediones on CV risk factors. *Archives of Internal Medicine* **164**(19): 2097–104

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

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

Erdmann E (2005a) Microalbuminuria as a marker of CV risk in patients with type 2 diabetes. *International Journal of Cardiology* **107**(2): 152–8

Erdmann E (2005b) *The effect of pioglitazone on recurrent myocardial infarction in 2445 patients with type 2 diabetes & previous myocardial infarction*. Available at http://www.proactive-results.com/ahappt/AHA_files/frame.htm (accessed 13.09.2006)

Gerber P, Lubben G, Heusler S, Dodo A (2003) Effects of pioglitazone on metabolic control and blood pressure: a randomised study in patients with type 2 diabetes mellitus. *Current Medical Research and Opinion* **19**(6): 532–9

Gerstein HC, Yusuf S, Holman R et al (2004) Rationale, design and recruitment characteristics of a large, simple international trial of diabetes prevention: the DREAM trial. *Diabetologia* **47**(9): 1519–27

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) CV risk factors associated with insulin resistance: effects of oral antidiabetic agents. *American Journal of Cardiovascular Drugs* **5**(3): 201–9

Haffner SM, Lehto S, Ronnemaa T et al (1998) Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *New England Journal of Medicine* **339**(4): 229–34

Higgs ER, Krentz AJ; on behalf of the Association of British Clinical Diabetologists (2004) ABCD position statement on glitazones. *Practical Diabetes International* **21**(8): 293–5

Home PD, Pocock SJ, Beck-Nielsen H et al (2005) Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD): study design and protocol. *Diabetologia* **48**(9): 1726–35

Jung HS, Youn BS, Cho YM et al (2005) The effects of rosiglitazone and metformin on the plasma concentrations of resistin in patients with type 2 diabetes mellitus. *Metabolism: Clinical and Experimental* **54**(3): 314–20

International Diabetes Federation (IDF; 2005) *Global Guidelines for Type 2 Diabetes*. IDF, Brussels

Langenfeld M, Forst T, Hohberg C et al (2005) Pioglitazone decreases carotid intima-media thickness independently of glycemic control in patients with type 2 diabetes mellitus. *Circulation* **111**(19): 2525–31

Marx N, Wohrle J, Nusser T et al (2005) Pioglitazone reduces neointima volume after coronary stent implantation: a randomized, placebo-controlled, double-blind trial in nondiabetic patients. *Circulation* **112**(18): 2792–8

McCallum RW, Fisher M (2005) From 4S to FIELD and PROactive: 10 years of CV trials in people with diabetes. *British Journal of Diabetes and Vascular Disease* **5**(4): 218–25

Miyazaki Y, Mahankali A, Wajcberg E et al (2004) Effect of pioglitazone on circulating adipocytokine levels and insulin sensitivity in type 2 diabetic patients. *Journal of Clinical Endocrinology and Metabolism* **89**(9): 4312–19

Mohanty P, Aljada A, Ghanim H et al (2004) Evidence for a potent antiinflammatory effect of rosiglitazone. *Journal of Clinical Endocrinology and Metabolism* **89**(6): 2728–35

Nathan DM, Buse JB, Davidson MB et al (2006) Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy: A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* **29**(8): 1963–72

National Institute for Health and Clinical Excellence (NICE; 2002) *Management of Type 2 Diabetes: Managing blood glucose levels (Guideline G)*. NICE, London

Osei K, Gaillard T, Kaplow J et al (2004) Effects of rosiglitazone on plasma adiponectin, insulin sensitivity, and insulin secretion in high-risk African Americans with impaired glucose tolerance test and type 2 diabetes. *Metabolism* **53**(12): 1552–7

Sarafidis PA, Lasaridis AN, Nilsson PM et al (2004) Ambulatory blood pressure reduction after rosiglitazone treatment in patients with type 2 diabetes and hypertension correlates with insulin sensitivity increase. *Journal of Hypertension* **22**(9): 1769–77

Sarafidis PA, Lasaridis AN, Nilsson PM et al (2005) The effect of rosiglitazone on urine albumin excretion in patients with type 2 diabetes mellitus and hypertension. *American Journal of Hypertension* **18**(2 Pt 1): 227–34

Schernthaner G, Matthews DR, Charbonnel B et al (2004) Efficacy and safety of pioglitazone versus metformin in patients with type 2 diabetes mellitus: a double-blind, randomized trial. *Journal of Clinical Endocrinology and Metabolism* **89**(12): 6068–76

Sidhu JS, Kaposzta Z, Markus HS, Kaski JC (2004) Effect of rosiglitazone on common carotid intima-media thickness progression in coronary artery disease patients without diabetes mellitus. *Arteriosclerosis, Thrombosis and Vascular Biology* **24**(5): 930–4

Takagi T, Yamamuro A, Tamita K et al (2003) Pioglitazone reduces neointimal tissue proliferation after coronary stent implantation in patients with type 2 diabetes mellitus: an intravascular ultrasound scanning study. *American Heart Journal* **146**(2): E5

Texas Diabetes Institute (2005) *Actos Now for Prevention of Diabetes (ACT NOW)*. Available at http://www clinicaltrial.gov/ct/show/NCT00220961?order=1 (accessed 13.09.2006)

UK Prospective Diabetes Study (UKPDS) Group (1990) UK Prospective Diabetes Study 6. Complications in newly diagnosed type 2 diabetic patients and their association with different clinical and biochemical risk factors. *Diabetes Research* **13**(1): 1–11

UKPDS Group (1998a) Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* **352**(9131): 837–53

UKPDS Group (1998b) Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* **352**(9131): 854–65

Van de Laar FA, Lucassen PL, Akkermans RP et al (2005) Alpha-glucosidase inhibitors for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews*, Issue 2, Article No. CD003639

Viberti G, Kahn SE, Greene DA et al (2002) A diabetes outcome progression trial (ADOPT): an international multicenter study of the comparative efficacy of rosiglitazone, glyburide, and metformin in recently diagnosed type 2 diabetes. *Diabetes Care* **25**(10): 1737–43

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

Yki-Jarvinen H (2004) Thiazolidinediones. *New England Journal of Medicine* **351**(11): 1106–18