PROactive 07: pioglitazone in the treatment of type 2 diabetes: results of the PROactive study

Erland Erdmann[1]
John Dormandy[2]
Robert Wilcox[3]
Massimo Massi-Benedetti[4]
Bernard Charbonnel[5]

[1]University of Cologne, Cologne, Germany; [2]Department of Clinical Vascular Research, St Georges Hospital, London, UK; [3]Department of Cardiovascular Medicine, Queen's Medical Centre, University Hospital, Nottingham, UK; [4]University of Perugia, Medicine and Metabolic Diseases, Perugia, Italy; [5]Clinique d'Endocrinologie, Hôtel Dieu, Nantes Cedex 1, France

Abstract: Patients with type 2 diabetes face an increased risk of macrovascular disease compared to those without. Significant reductions in the risk of major cardiovascular events can be achieved with appropriate drug therapy, although patients with type 2 diabetes remain at increased risk compared with non-diabetics. The thiazolidinedione, pioglitazone, is known to offer multiple, potentially antiatherogenic, effects that may have a beneficial impact on macrovascular outcomes, including long-term improvements in insulin resistance (associated with an increased rate of atherosclerosis) and improvement in the atherogenic lipid triad (low HDL-cholesterol, raised triglycerides, and a preponderance of small, dense LDL particles) that is observed in patients with type 2 diabetes. The recent PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) study showed that pioglitazone can reduce the risk of secondary macrovascular events in a high-risk patient population with type 2 diabetes and established macrovascular disease. Here, we summarize the key results from the PROactive study and place them in context with other recent outcome trials in type 2 diabetes.
Keywords: pioglitazone, macrovascular disease, type 2 diabetes, secondary prevention

Introduction

People with type 2 diabetes have a higher risk of macrovascular disease than those without diabetes (Haffner et al 1998; NCEP 2002; Juutilainen et al 2005; Idris et al 2006). Furthermore, prognosis after a first myocardial infarction (MI) or stroke is particularly poor in patients with type 2 diabetes (Miettinen et al 1998; Mukamal et al 2001; Idris et al 2006). As such, type 2 diabetes is associated with excess mortality in all age groups, which is largely attributable to cardiovascular disease (CVD) (Roper et al 2001).

Outcome studies in patients with type 2 diabetes using antihypertensive agents, lipid-modifying drugs, and antiplatelet therapy show that significant reductions in the risk of major CV events are possible with appropriate management. Furthermore, outcome studies with glucose-lowering agents show a trend towards reduced risk of macrovascular events (UKPDS33 1998). Nevertheless, these studies also show that excess risk remains in patients with type 2 diabetes relative to those without diabetes, despite contemporary interventions. This highlights the need for novel therapies for this high-risk group, especially those who also have established macrovascular disease.

Pioglitazone is an agonist for the peroxisome proliferator-activated receptor γ (PPARγ), which regulates multiple genes controlling carbohydrate and lipid metabolism and is licensed as a glucose-lowering agent for the treatment of type 2 diabetes (Yki-Järvinen 2004). Pioglitazone has multiple, potentially antiatherogenic properties, including effects on insulin sensitivity, lipid profiles, inflammatory markers, blood pressure, and components of the coagulation cascade that suggest it

Correspondence: Erland Erdmann
Department III of Internal Medicine, University of Cologne, Josef-Stelzman Str. 9, 50924 Cologne, Germany
Tel +49 221 478 4503
Fax +49 221 478 6275
Email erland.erdmann@uni-koeln.de

might have a beneficial impact on macrovascular outcomes. This has been investigated in the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) study and final results have been published recently. This study, in more than 5000 high-risk patients with type 2 diabetes and a history of macrovascular disease, investigated whether pioglitazone added to standard contemporary multifactorial treatment could improve mortality and morbidity associated with major CVD progression (Dormandy et al 2005). This review summarizes the key results from PROactive and puts them in context with other outcome trials in type 2 diabetes.

Why should pioglitazone improve macrovascular outcomes?

Several lines of evidence suggest that pioglitazone has antiatherogenic properties and the potential to improve macrovascular outcomes in patients with type 2 diabetes. Firstly, pioglitazone produces long-term improvements in insulin sensitivity (Pavo et al 2003; Tan et al 2004a; Roden et al 2005) and insulin resistance is associated with an increased rate of atherosclerosis (Nigro et al 2006). Furthermore, pioglitazone improves multiple established modifiable risk factors for CVD, eg, atherogenic diabetic dyslipidemia (low HDL-cholesterol, raised triglycerides, and a preponderance of small, dense LDL particles) and blood pressure (Taskinen 2003; Buse et al 2004; Lawrence et al 2004; Perez et al 2004; Goldberg et al 2005; Derosa et al 2005a).

In line with its current role as a glucose-lowering therapy, pioglitazone produces long-term improvements in glycemic control, as evident in the sustained improvements in HbA_{1c} and fasting plasma glucose seen in patients with type 2 diabetes in clinical trials up to 2 years in duration (Hanefeld et al 2004; Schernthaner et al 2004; Tan et al 2004c; Charbonnel et al 2005a, b). However, it should be noted that it has not been firmly established that improving glycemia per se can significantly improve macrovascular outcomes in type 2 diabetes, although data from the United Kingdom Prospective Diabetes Study (UKPDS) suggest a trend (UKPDS33 1998; Stratton et al 2000). In type 1 diabetes, on the other hand, intensive glucose-lowering therapy is associated with reductions in markers of inflammation, atherosclerosis and CVD, as well as a significant reduction in macrovascular events (Nathan et al 2003, 2005; Schaumberg et al 2005; The DCCT Research Group 1993).

Pioglitazone also improves multiple non-traditional risk markers and emerging risk factors for CVD. Notably,

pioglitazone significantly reduces C-reactive protein (CRP) levels and improves the levels of a host of other cytokines, inflammatory mediators, and markers of endothelial dysfunction with a potential role in atherosclerosis (for example adiponectin, the matrix metalloproteinase, MMP-9, and plasminogen activator inhibitor-1 [PAI-1]) (Satoh et al 2003; Derosa et al 2005b; Miyazaki et al 2004; Pfutzner et al 2005). Pioglitazone has also been shown to reduce carotid intima media thickness, a surrogate marker for atherosclerosis, in a glucose-independent manner (Langenfeld et al 2005; Pfutzner et al 2005). Pioglitazone and other thiazolidinediones also reduce restenosis and neointimal tissue proliferation after coronary stent implantation in patients with or without type 2 diabetes (Takagi et al 2000, 2003; Choi et al 2004; Marx et al 2005). Studies in the isolated rat heart model suggest another potential benefit that may be relevant to improving outcomes – pioglitazone mimics ischemic preconditioning, which may protect the myocardium against subsequent prolonged episodes of lethal ischemia (Wynne et al 2005).

The PROactive study was designed to examine whether the incidence of macrovascular events is reduced in patients given pioglitazone or placebo in combination with their usual medication for diabetes and CVD. The primary composite endpoint of the surrogate vascular endpoints of all-cause mortality, MI, acute coronary syndrome (ACS), coronary intervention, major leg amputation, bypass surgery, or leg revascularization was chosen so as to capture all CV events.

PROactive study design

The PROactive study design is well documented elsewhere (Charbonnel et al 2004; Dormandy et al 2005; www.proactive-results.com). Briefly, it was a prospective, multicenter, European (19 countries), randomized, double-blind outcome study in patients with type 2 diabetes (35–75 years). All patients had a history of pre-existing extensive macrovascular disease (MI, stroke, percutaneous coronary intervention or coronary artery bypass surgery ≥6 months before study entry, ACS ≥3 months before study entry, or objective evidence of coronary artery disease or obstructive arterial disease in the leg) making the patient population at very high-risk for macrovascular disease.

Patients were randomized to receive pioglitazone (titrated from 15 mg to 45 mg; n = 2605) or matched placebo (n = 2633) in addition to existing therapies. These included blood glucose-lowering drugs (with or without insulin), and

Table 1 Concomitant glucose-lowering medication use during the study

	Pioglitazone			Placebo		
	Baseline (% pts)	Final visit (% pts)	Absolute change from baseline	Baseline (% pts)	Final visit (% pts)	% Absolute change from baseline
Any glucose-lowering medication	95.8	91.6	−4.2%	96.0	95.5	−0.5%
Any insulin	33.2	35.9	+2.7%	34.0	46.4	+12.4%
Any metformin	61.2	58.1	−3.1%	61.8	63.6	+1.8%
Sulfonylurea	62.3	53.3	−9.0%	61.8	52.2	−9.6%

Abbreviations: pts, patients.

lipid-lowering, antihypertensive, and antiplatelet therapies (Tables 1 and 2) – many patients were already receiving contemporary multifactorial therapy. The primary endpoint was the time from randomization to the first incidence of all-cause mortality, non-fatal MI (including silent MI), stroke, major leg amputation, ACS, cardiac intervention (bypass graft or percutaneous coronary intervention), or leg revascularization. This very challenging composite endpoint therefore included procedural endpoints and was designed to demonstrate benefit in multiple vascular beds – cardiac, cerebral, and peripheral. The main secondary endpoint was time to first incidence of all-cause mortality, non-fatal MI, or stroke – this represented the most clinically important and objectively confirmed events and is identical or similar to primary composite endpoints used in many other major CV outcome studies. Although not included in the original study design (Charbonnel et al 2004), this main secondary endpoint was prespecified in the statistical

analysis plan prior to unblinding (Dormandy et al 2006; www.proactive-results.com).

Throughout the study, investigators were encouraged to strive for a target HbA$_{1c}$ <6.5% and to increase lipid-altering, antiplatelet, and antihypertensive therapy to an optimum in line with IDF Europe guidelines (European Diabetes Policy Group 1999). The duration of the study was event-driven – however, due to faster than anticipated enrolment and a higher event rate than predicted, the study was amended to include a minimum duration of follow-up of 30 months.
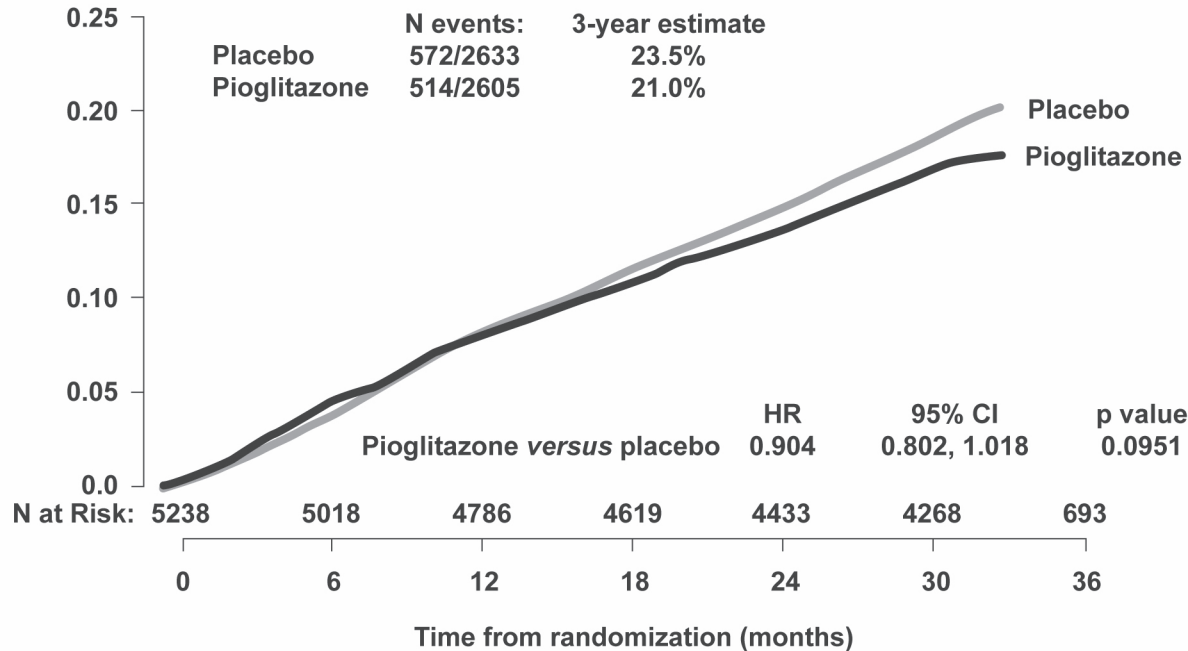
Main outcome results in PROactive

After a mean follow-up of 34.5 months, patients in the pioglitazone group experienced 803 events, of which 514 were first events, whereas those on placebo had 900 events, of which 572 were first events. For the primary composite endpoint, pioglitazone reduced the relative risk for an event

**Table 2** Concomitant cardiovascular medication use during the study

	Pioglitazone			Placebo		
	Baseline (% pts)	Final visit (% pts)	Absolute change from baseline	Baseline (% pts)	Final visit (% pts)	% Absolute change from baseline
Any cardiovascular medication	95.1	96.2	1.1%	94.8	96.5	1.7%
ACE inhibitors	62.6	64.8	2.2%	63.0	66.7	3.7%
β-blockers	54.6	57.9	3.3%	54.5	60.6	6.1%
Angiotensin II antagonists	6.5	9.6	3.1%	7.0	10.9	3.9%
Calcium channel blockers	34.2	35.4	1.2%	36.6	39.5	2.9%
Nitrates	39.1	35.8	−3.3%	39.7	34.8	−4.9%
Thiazide diuretics	15.4	18.5	+3.1%	16.3	20.2	+3.9%
Loop diuretics	14.3	22.0	+7.7%	14.4	19.8	+5.4%
Cardiac glycosides	5.0	4.4	−0.6%	4.8	3.6	−1.2%
Antiplatelet medication	85.3	88.2	+2.9%	82.6	87.7	+5.1%
Aspirin	74.5	76.2	+1.7%	71.7	73.9	+2.2%
Lipid-altering medication	50.7	61.8	11.1%	52.6	62.7	10.1%
Statins	42.5	55.0	+12.5%	43.2	55.5	+12.3%
Fibrates	10.1	8.6	−1.5%	11.2	10.1	−1.1%

Abbreviations: pts, patients.

A   Kaplan-Meier event rate

B   Kaplan-Meier event rate
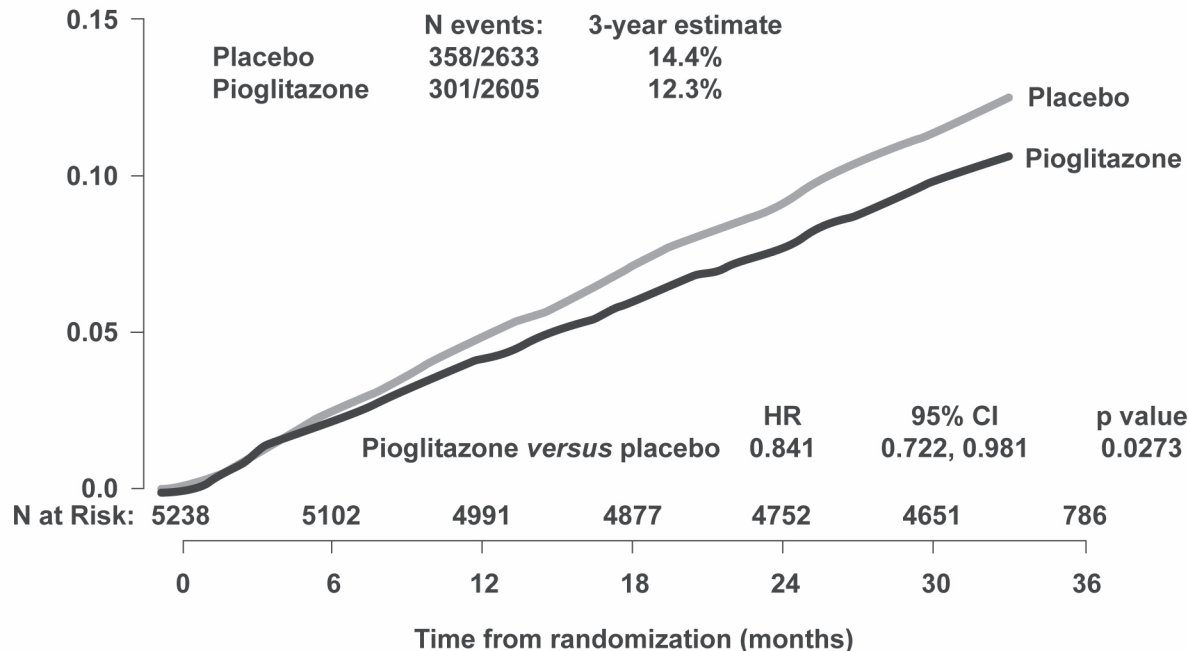
Figure 1 Main outcome results in PROactive. **A.** Primary composite endpoint (all-cause mortality, non-fatal MI (including silent MI), stroke, major leg amputation, acute coronary syndrome, cardiac intervention, or leg revascularization); **B.** Main secondary composite endpoint (all-cause mortality, non-fatal MI, or stroke). Both figures reproduced with permission from Dormandy JA, Charbonnel B, Eckland DJ, et al. 2005. PROactive investigators. 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*, 366:1279–89. Copyright © 2005 Elsevier.

by 10% compared with placebo, but this difference did not achieve statistical significance (Figure 1A). Nevertheless, there was a consistent reduction in most of the individual components of the primary endpoint – the risk of mortality, non-fatal MI, silent MI, stroke, major leg amputation, and ACS was lower with pioglitazone relative to placebo (Table 3). For the main secondary endpoint, pioglitazone was associated with a 16% relative risk reduction (Figure 1B).

Table 3 Effects of pioglitazone and placebo on individual components of the composite endpoints and total events during the study

Endpoint	Primary composite		Secondary composite		Total events	
	Pioglitazone	Placebo	Pioglitazone	Placebo	Pioglitazone	Placebo
Any event	514	572	301	358	803	900
Death	110	122	129	142	177	186
Non-fatal MI (excl silent MI)	85	95	90	116	108	132
Silent MI	20	23	—	—	23	25
Stroke	76	96	82	100	92	119
Major leg amputation	9	15	—	—	28	28
ACS	42	63	—	—	65	78
Coronary revascularization	101	101	—	—	195	240
Leg revascularization	71	57	—	—	115	92

Abbreviations: ACS, acute coronary syndrome; MI, myocardial infarction.

Adding pioglitazone to the medication of 1000 patients would, therefore, avoid 21 first MIs, strokes, or deaths over 3 years. In other words, the number needed to treat (NNT) would be 48 patients for 3 years to avoid one first major CV event.

The difference between the two main composite endpoints was explained mainly by an unexpected increase in the number of peripheral vascular procedures performed in the pioglitazone group. There was also no decrease in the number of coronary revascularization procedures included in the primary endpoint; however, there was a decrease in the number of coronary revascularization procedures in the pioglitazone group overall during the study (including those that were not the first event) (Table 3).

Twenty-five baseline variables were prespecified for subgroup analysis. Interaction tests within these subgroups did not reveal evidence of heterogeneity. Multivariate analysis of the association of entry characteristics to the main secondary endpoint showed associations with several factors, such as statin use, insulin use, smoking, and previous MI. Nevertheless pioglitazone was associated with a 16% reduction in relative risk even after adjustment for these factors.

Composite endpoints of cardiovascular events, referred to as major adverse cardiovascular events (MACE), are standard measures for comparing treatments in large cardiovascular outcome studies. In addition to the main secondary endpoint, analyses of other prespecified and post-hoc MACE endpoints have been presented recently for the overall patient population (Wilcox and Kupfer 2006). Pioglitazone treatment resulted in significant relative risk reductions in the prespecified endpoint of risk of fatal/non-fatal MI (excluding silent MI) (HR = 0.77, 95% CI [0.60,1.00]; p = 0.046), and prespecified endpoint of the composite of CV death, non-fatal MI (excluding silent MI), or non-fatal stroke (HR = 0.82, 95% CI [0.70, 0.97]; p = 0.02). A post-hoc analysis also showed a significant relative risk reduction for the composite of all-cause mortality, non-fatal MI (excluding silent MI), non-fatal stroke, or ACS (HR = 0.83, 95% CI [0.72, 0.96]; p = 0.010).

Metabolic and laboratory results

Laboratory data showed significant improvements in HbA$_{1c}$ (–0.5%), triglycerides (–13.2%), HDL-cholesterol (+8.9%) and LDL-/HDL-cholesterol ratio (–5.3%) with pioglitazone relative to placebo (Table 4). The improvement in glycemic control occurred despite a 50% reduction in rate of progression to permanent insulin use (defined as daily insulin use for a period of ≥90 days, or ongoing use at death/final visit) in the pioglitazone group compared with placebo – 183 patients on pioglitazone progressed to permanent insulin use during the study compared with 362 on placebo (Massi-Benedetti et al 2006). The decreased need for insulin in the pioglitazone group was irrespective of baseline treatment. Furthermore, among patients receiving insulin at baseline, insulin doses progressively decreased in the pioglitazone group during the study, but progressively increased with placebo and were significantly different by study end (Scheen and Charbonnel 2006). There were no differences in changes in the use of other medications during the study, apart from a slight decrease in metformin use in the pioglitazone group compared with placebo (Table 1). Significant improvements in HbA$_{1c}$ of similar magnitude to the overall pioglitazone group were seen in patients who were on insulin at baseline (Scheen and Charbonnel 2006) or on dual oral agent therapy with metformin plus sulfonylureas at baseline (when pioglitazone was added as a third agent) (Charbonnel and Scheen 2006).

Systolic blood pressure was significantly improved in the pioglitazone group compared with placebo (between-group

Table 4 Change in metabolic parameters from baseline to final visit

	Pioglitazone	Placebo	p-value
HbA$_{1c}$ (% absolute change)	−0.8 [−1.6, −0.1]	−0.3 [−1.1, 0.4]	<0.001
Triglycerides (% change)	−11.4 [−34.4, 18.3]	1.8 [−23.7, 33.9]	<0.001
LDL-cholesterol (% change)	7.2 [−11.2, 27.6]	4.9 [−13.9, 23.8]	0.0034
HDL-cholesterol (% change)	19.0 [6.6, 33.3]	10.1 [−1.7, 21.4]	<0.001
LDL/HDL (% change)	−9.5 [−27.3, 10.1]	−4.2 [−21.7, 15.8]	<0.001

Data are median [interquartile range].

difference of −3 mmHg), with only a slight increase in the use of antihypertensive agents. Analyses of laboratory assessments for liver function (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and alkaline phosphatase [AP]) have also been presented recently (Heine et al 2006). The results showed a general shift toward normalization of ALT and AST values in the pioglitazone group from baseline to final visit compared with no change or an increase in the placebo group (p < 0.001 for difference between groups at final visit). Changes in ALT with pioglitazone may reflect a reduction in liver fat due to improvement in hepatic insulin sensitivity.

Subgroup analyses

The first prespecified subgroup analysis involved the cohort of 2445 patients with a previous MI ≥ 6 months prior to randomization (Erdmann et al 2007). Prespecified endpoints were time to fatal or non-fatal MI (excluding silent MI), time to CV death or non-fatal MI, and time to CV death, non-fatal MI, or stroke. Time to fatal or non-fatal MI was significantly reduced by 28% in the pioglitazone group relative to placebo (Figure 2A). Risk of CV death or non-fatal MI, and risk of CV death, non-fatal MI, or stroke were both reduced by 15% with pioglitazone relative to placebo, but neither reached statistical significance. In addition, several post-hoc exploratory endpoints were analyzed for this subgroup. Risk of experiencing an event in a cardiac composite endpoint of cardiac death, non-fatal MI (excluding silent MI), ACS, and coronary revascularization was significantly reduced by 19% in the pioglitazone group relative to the placebo group (Figure 2B). There was no significant reduction in relative risk when silent MI was included in this composite endpoint or in any of its individual components, except for risk of an ACS, which was significantly reduced by 37% with pioglitazone relative to placebo.

Another prespecified subgroup analysis compared outcomes in patients with (n = 984) or without (n = 4254) prior stroke (Wilcox et al 2007). Risk of a recurrent stroke was significantly reduced by 47% with pioglitazone relative to placebo in patients with prior stroke (HR = 0.53; 95% CI [0.34, 0.85]; p = 0.0085), whereas no significant difference in the relative risk of stroke was seen in patients without a prior stroke. For the composite of CV death, MI, or stroke there was also a significant relative risk reduction with pioglitazone in patients with prior stroke (HR = 0.72; 95% CI [0.52, 1.00]; p = 0.0467).

Were there any potential safety or tolerability issues in PROactive?

The overall frequency of serious adverse events was slightly lower in the pioglitazone group, even after events contributing to the primary composite endpoint were excluded. The incidence of adverse events reported as "heart failure" has received considerable attention in the critical appraisal of the results from PROactive (Yki-Järvinen 2005). Regarding serious heart failure as reported by the investigators, 5.7% of pioglitazone-treated patients were reported with heart failure leading to hospitalization compared with 4.1% of placebo-treated patients; however, rates of mortality due to heart failure were similar between the two groups (0.96% [n = 25 out of 2605] vs 0.84% [n = 22 out of 2633] for pioglitazone and placebo, respectively). Despite more reports of heart failure in the pioglitazone group, overall CV outcomes were improved and the number of CV endpoints after serious heart failure was also similar between treatment groups (Erdmann et al 2006). Furthermore, most investigator-reported cases of serious heart failure resolved and were not treatment-limiting. Only 34 of the 113 patients in the pioglitazone group and 17 out of 89 patients in the placebo group who were on therapy at the time of diagnosis of heart failure discontinued study drug. Therefore, only a little more than 1% of patients in the pioglitazone group discontinued study drug for this reason. Edema in the absence of heart failure was reported in 21.6% of patients treated with pioglitazone compared with 13.0% on placebo. An independent review of the heart failure cases was conducted by assessing the strength of evidence of the patients having a history of heart failure before entering the study and also for each reported case of serious heart failure. This confirmed the accuracy of the original investigator diagnoses of greater rates of non-serious and serious heart failure in the

A Kaplan-Meier event rate

Time from randomization (months)

B Kaplan-Meier event rate

Time from randomization (months)
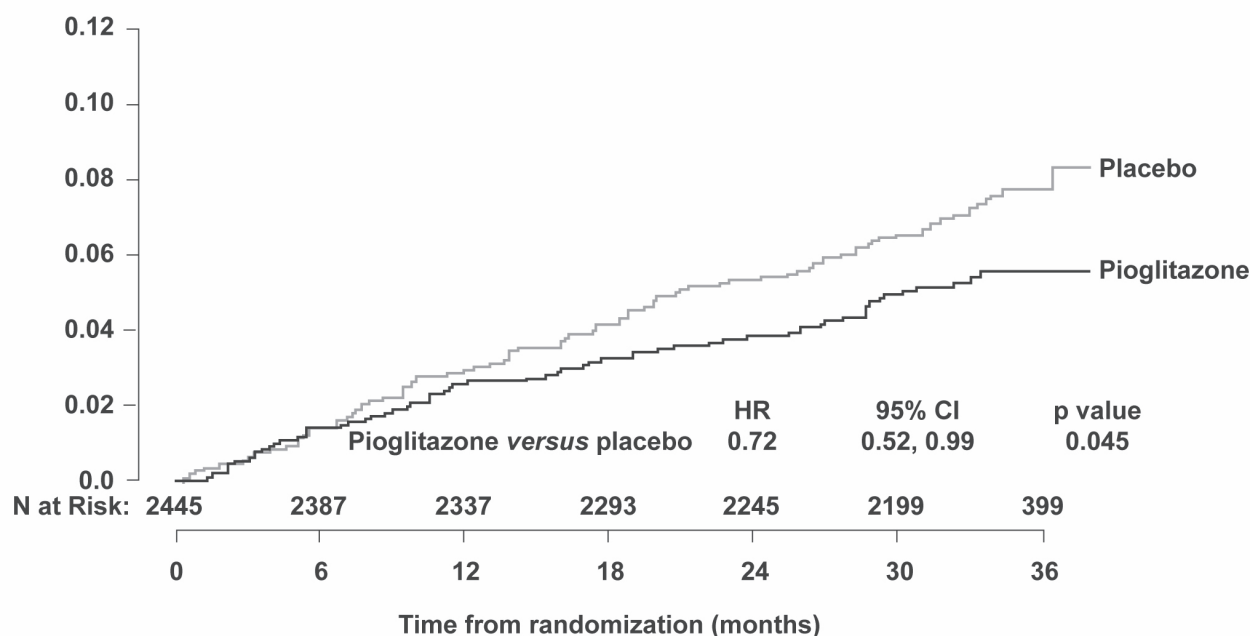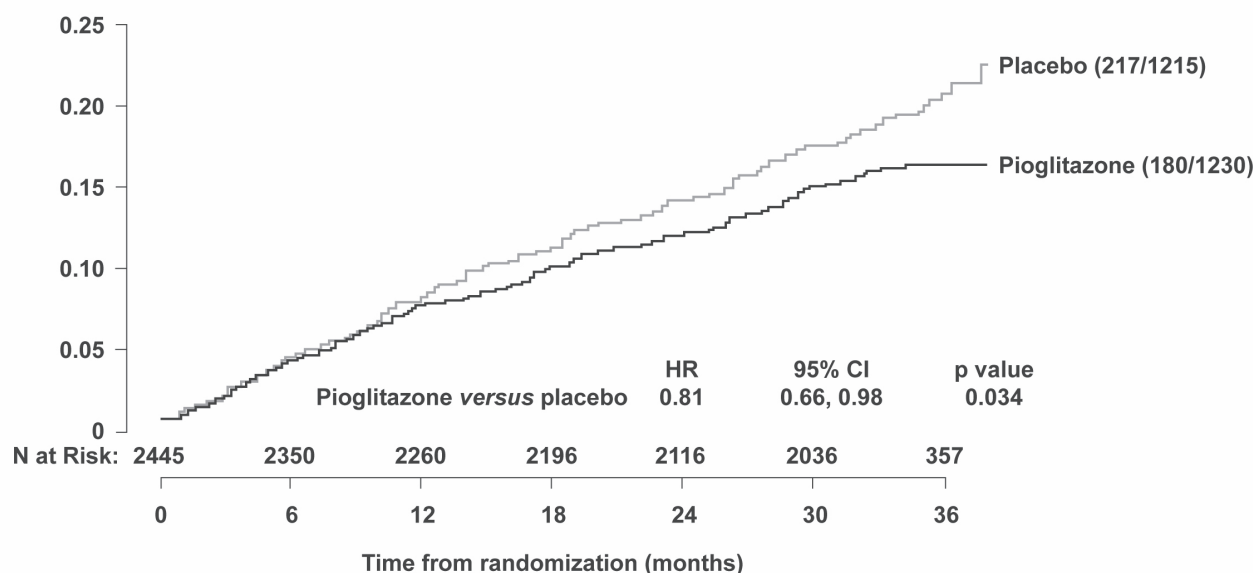
Figure 2 Outcomes in the subgroup of patients with a previous myocardial infarction (MI). **A.** Prespecified endpoint of fatal/non-fatal MI (excluding silent MI); **B.** Exploratory composite cardiac endpoint (cardiac death, non-fatal MI, coronary revascularization, or acute coronary syndrome). Figure 2A reproduced with permission from Erdmann E, Dormandy JA, Charbonnel B, et al; on behalf of the PROactive investigators 2007. The effect of pioglitazone on recurrent myocardial infarction in 2445 patients with type 2 diabetes and previous myocardial infarction – Results from PROactive (PROactive 05). *J Am Coll Cardiol*, 49:1772–80. Copyright © 2007 Elsevier.

pioglitazone arm, but comparable rates of mortality due to heart failure (Rydén et al 2007).

It should be emphasized that there is no evidence available in the literature to suggest that pioglitazone or other thiazolidinediones have any adverse effect on cardiac function. In clinical practice, initiation of pioglitazone therapy (alone or as an addition to pre-existing therapies, such as other oral agents and/or insulin) does not appear to be associated with

increased hospitalization due to heart failure over a 10-month follow-up compared with initiation of sulfonylureas as a standard reference diabetes therapy (Karter et al 2005). Initiation of insulin, on the other hand, is associated with a significant increase. Furthermore, 52 weeks of therapy with rosiglitazone was shown to have no adverse effect on cardiac structure or function (left ventricular [LV] mass index, ejection fraction, and left ventricular end-diastolic volume) (St John Sutton

et al 2002). In fact, pioglitazone has been shown actually to improve LV diastolic function without LV mass regression in hypertensive patients in proportion to the amelioration of insulin resistance (Horio et al 2005). Animal models support these observations. Pioglitazone improved LV remodeling and function in mice with post-MI heart failure, an effect that was associated with an attenuated LV expression of inflammatory cytokines (Shiomi et al 2002). Such studies have led to the suggestion that thiazolidinediones may, in fact, have therapeutic potential in patients with advanced heart failure, rather than being a cause for concern (Nikolaidis and Levine, 2004). However, it should be noted that edema is more frequent in patients treated with pioglitazone plus insulin – fluid retention is a dose-dependent side-effect of both drugs.

In PROactive, average weight gain from baseline with pioglitazone was 3.6 kg (compared with –0.6 kg for placebo). However, weight gain led to permanent discontinuation in only 0.8% of patients compared with 0.2% on placebo. Weight gain with thiazolidinediones is a consistent finding and may reflect a combination of both fat increase and fluid retention (Hollenberg 2003). Any possible detrimental effect of increased body fat is offset by potentially beneficial qualitative effects – thiazolidinediones shift fat distribution away from the more metabolically active visceral depots to less active subcutaneous depots (an effect associated with improvements in hepatic and peripheral insulin sensitivity) (Miyazaki et al 2002). The overall incidence of cancer in PROactive was equivalent in the pioglitazone and placebo groups (3.7% vs 3.8%, respectively). Although there was a slight increase in the number of bladder tumors (n = 14 vs 6) and a slight decrease in breast tumors (n = 3 vs 11) reported in the pioglitazone group, an external independent review of blinded data concluded that any causal link was unlikely.

How does PROactive compare with other outcome studies in type 2 diabetes?

Several intervention trials using antihypertensive agents, lipid-modifying drugs (principally statins), glucose-lowering agents, or multifactorial intervention strategies have looked at macrovascular outcomes in patients with type 2 diabetes. However, much of the data pertaining to patients with diabetes are post-hoc or, in some instances, predefined subgroup analyses from larger cohorts (Table 5). Comparison between the results of PROactive and previous outcome studies is complicated by differences in predefined endpoints, study population, study duration, concomitant medication use, and a range of other methodological issues.

To date, no prospective studies have been able to establish conclusively whether improving hyperglycemia per se in patients with type 2 diabetes can improve macrovascular outcomes. However, the UKPDS showed a clear trend towards a reduction in primary macrovascular events (based on a secondary endpoint of fatal/non-fatal MI) in patients whose hyperglycemia was more intensively managed with pharmacologic therapy (using sulfonylureas or insulin) compared with conventional management using lifestyle interventions (UKPDS33 1998). Subsequent observational analyses showed that each 1% reduction in HbA_{1c} was associated with a 14% relative reduction in risk for MI (Stratton et al 2000). However, in a substudy of overweight patients, tight glycemic control with metformin significantly reduced the two secondary endpoints of MI and any macrovascular disease (UKPDS34 1998), suggesting an effect independent of glucose control in this patient group. Secondary endpoint measures from a prospective placebo-controlled diabetes prevention study suggested that acarbose (an α-glucosidase inhibitor that reduces postprandial hyperglycemia) may reduce the development of major CV events in people with impaired glucose tolerance, although the total number of events was low (Chiasson et al 2003). In type 1 diabetes, the benefits of reducing hyperglycemia appears to be less ambiguous, and the recent 17-year follow-up of the Diabetes Control and Complications Trial (DCCT) showed that intensive treatment caused a significant 57% reduction in macrovascular events among intensively-treated patients that was explained principally by a sustained decrease in HbA_{1c} (HbA_{1c} decreases at Year 11 were the same in both the intensive and conventional treatment groups; Nathan et al 2005).

Statin use in PROactive was not completely optimal for such a high-risk patient group (approximately 43% at baseline increasing to 55% at study end in both groups). Nevertheless, it reflects or possibly even exceeds the levels seen in contemporary practice among patients with diabetes with or without established coronary heart disease (CHD) and other high-risk patients (Brown et al 2004; Ko et al 2004; Emberson et al 2005; Bhatt et al 2006).

The 5-year Cholesterol And Recurrent Events (CARE) trial looked at secondary prevention in patients with a previous MI and had major coronary events (CHD death, non-fatal MI, or coronary revascularization) as a primary endpoint (Goldberg et al 1998). This provides similar criteria for comparison with the previous MI subgroup in PROactive using the post-hoc exploratory composite

Table 5 Placebo-controlled outcome trials

Trial	Population	n	Study duration	Intervention	Positives	Negatives
PROactive (Dormandy et al 2005)	Secondary prevention in type 2 diabetes and established macrovascular disease	5238	34.5 months	Pioglitazone	• Significant 16% relative risk reduction in the endpoint of all-cause mortality, stroke, and MI • Prevention of recurrent stroke and MI • Effects were observed on top of guideline-directed background CV and diabetes medication	• Primary endpoint did not reach significance • Study duration relatively short (3 years) • Higher rates of serious heart failure with pioglitazone (but fatal heart failure rates were similar)
UGDP (Meinert et al 1970)	Primary prevention in patients with type 2 diabetes	823	5.5 years	Tolbutamine Insulin	• First large-scale intervention study	• Failed to show any benefit of glucose control on vascular events in type 2 diabetes • Inconclusive findings in the insulin groups in terms of delaying or preventing CV complications • Increased relative risk of cardiac events with tolbutamine • No significant difference in incidence of overall mortality in all of the groups • Small patient number and poor patient follow-up
UKPDS (UKPDS 34 1998)	Primary prevention in newly diagnosed drug-naïve with type 2 diabetes	342 (out of 5102)	10.7 years	Metformin	• Metformin significantly reduced MI (by 39%) and any diabetes-related endpoint (by 32%) relative to lifestyle management	• The number of patients allocated to metformin was less than 10% of the total patient population in the UKPDS and effects were only assessed in a population of obese people • The reduction in micro-vascular events was not statistically significant (unlike the results seen in the main study)
CARDS (Colhoun et al 2004)	Primary prevention in patients with type 2 diabetes and CV risk	2838	3.9 years	Atorvastatin	• Trial terminated 2 years earlier as the prespecified early stopping rule for efficacy had been met • 37% decrease in CV events and 48% decrease in stroke with atorvastatin relative to placebo	• Most participants had long-standing diabetes with multiple additional risk factors that were substantially undertreated

(Continued)

Table 5 *(Continued)*

| Trial	Population	n	Study duration	Intervention	Positives	Negatives
FIELD (Keech et al 2005)	Primary and secondary prevention in patients with type 2 diabetes and varying levels of dyslipidemia	9795	5 years	Fenofibrate	• Largest intervention study in diabetes to date • Significant relative reduction in non-fatal MI (by 24%) • Significant 11% relative risk reduction in main secondary outcome (composite of MI, stroke, CVD death, and coronary and carotid revascularization)	• Primary endpoint (non-fatal MI or CHD death did not reach significance • There was a 19% relative increase in CHD mortality with fenofibrate therapy • Statin use during the study was a confounding factor • Fenofibrate appeared to confer benefit only in the primary prevention of CVD and increased relative risk in patients with prior CVD • Fenofibrate only reduced CVD events in patients <65 years
HOPE (HOPE study investigators 2000)	Secondary prevention in high-CV risk patients (subgroup analysis in patients with type 2 diabetes)	3577 (out of 9541)	4.5 years	Ramipril	• Significant 25% relative risk reduction with ramipril in the primary composite endpoint of CV death, MI or stroke • Significant relative risk reduction with ramipril in MI, stroke, total mortality and CV death	• The analysis in patients with diabetes, but without overt CVD did not reach statistical significance • There was a high discontinuation rate due to side effects
HOT (Hansson et al 1998)	Secondary prevention (subgroup analysis in patients with type 2 diabetes)	1501 (out of 18,790)	3.8 years	Aspirin (+ others)	• There was a 66% relative risk reduction in mortality and a 51% relative risk reduction in major CV events with aspirin	• No effect on stroke prevention • Non-fatal major bleeds were twice as common in the aspirin group
CARE (Goldberg et al 1998)	Secondary prevention in patients with previous MI (diabetes subgroup)	586 (out of 4159)	5 years	Pravastatin	• 22% relative risk reduction in CV events	• At the 3-year point, pravastatin produced no benefit
PROSPER (Shepherd et al 2002)	Secondary prevention in elderly patients with a history of/risk for CVD (diabetes subgroup)	623 (out of 5804)	3.2 years	Pravastatin		• Non-significant 27% increase in the relative risk of CV death, stroke, or MI with pravastatin • Number of patients with diabetes too small to permit accurate interpretation of any treatment effect • Patient population ≥70 years

(Continued)

Table 5 *(Continued)*

Trial	Population	n	Study duration	Intervention	Positives	Negatives
HPS (HPS Collaborative Group 2003)	Primary and secondary prevention in patients with CVD (diabetes subgroup)	2912 (out of 20,536)	5 years	Simvastatin	• 33% relative risk reduction in CV events	• 10% had type 1 diabetes
4S (Pyörälä et al 1997)	Secondary prevention in patients with CHD (diabetes subgroup)	483 (out of 4398)	5.4 years	Simvastatin	• 42% relative risk reduction in CHD events	• The event rate was very high (45%) in the placebo group
LIPID (LIPID Study Group 1998)	Secondary prevention in patients with known heart disease (diabetes subgroup)	782 (out of 9014)	6.1 years	Pravastatin		• Non-significant 16% relative risk reduction in CV events with pravastatin

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease.

endpoint of cardiac death, non-fatal MI, ACS, or coronary revascularization (Figure 3A). Patients in PROactive had a higher event rate than patients in CARE. At the 3-year point, pravastatin therapy in CARE produced no benefit in these patients, whereas in PROactive there was a significant 19% relative risk reduction with pioglitazone. An analysis of the 5963 patients with diabetes in the Heart Protection Study (HPS), around 50% of whom had a previous history of CVD, showed that simvastatin reduced the relative risk of major vascular events by approximately 17% after 3 years (Figure 3B). In the pravastatin in elderly individuals at risk of vascular disease (PROSPER) study (Shepherd et al 2002), which included individuals with a history of (or risk of) vascular disease, the length of follow-up (3.2 years) was very similar to that in PROactive. Among the 623 patients with diabetes, those treated with pravastatin appeared to have a non-significant 27% increase in the risk of an event (CV death, stroke, or MI), although there was a significant risk reduction in the population overall, and the authors considered the number of patients with diabetes too small to permit accurate interpretation of any treatment effect. The recent FIELD study was the largest intervention study to date in patients with type 2 diabetes (Keech et al 2005). The rather heterogeneous study population included patients with varying levels of dyslipidemia, only 22% of whom had a prior history of CVD. After a median 5 years of follow-up, the primary outcome (non-fatal MI or CHD death), was reduced by 11% with fenofibrate compared with placebo, but this did not achieve statistical significance. A significant 24% decrease in non-fatal MI was offset by a non-significant 19% increase in CHD mortality. However, patients were statin-naïve at baseline and significantly more patients in the placebo group commenced statin therapy during the study so this may have been a confounding factor. Interestingly, fenofibrate seemed to reduce events only in those patients with no previous CVD (19% decrease). In patients with prior CVD, there was a slight (2%) increase in relative risk. For the main secondary outcome (composite of MI, stroke, CVD death, and coronary and carotid revascularization), there was a statistically significant 11% reduction in risk overall.

The vast majority of patients in PROactive were receiving antihypertensive and antiplatelet therapy with comparable proportions in the two treatment groups, and all patients were treated to an HbA_{1c} goal of <6.5% (96% were using glucose-lowering agents) (Tables 1 and 2). The significant impact of antihypertensive therapy on macrovascular outcomes in type 2 diabetes has been demonstrated in several large-scale trials, including the UKPDS (primary prevention), the Heart Outcomes Prevention Evaluation (HOPE) study (mixed secondary/primary prevention) and GISSI-3 (secondary prevention) (Zuanetti et al 1997; UKPDS38 1998; HOPE 2000). An analysis from the HOPE study, which included 3577 patients with diabetes (approximately two-thirds with a

A   Major coronary events (%)
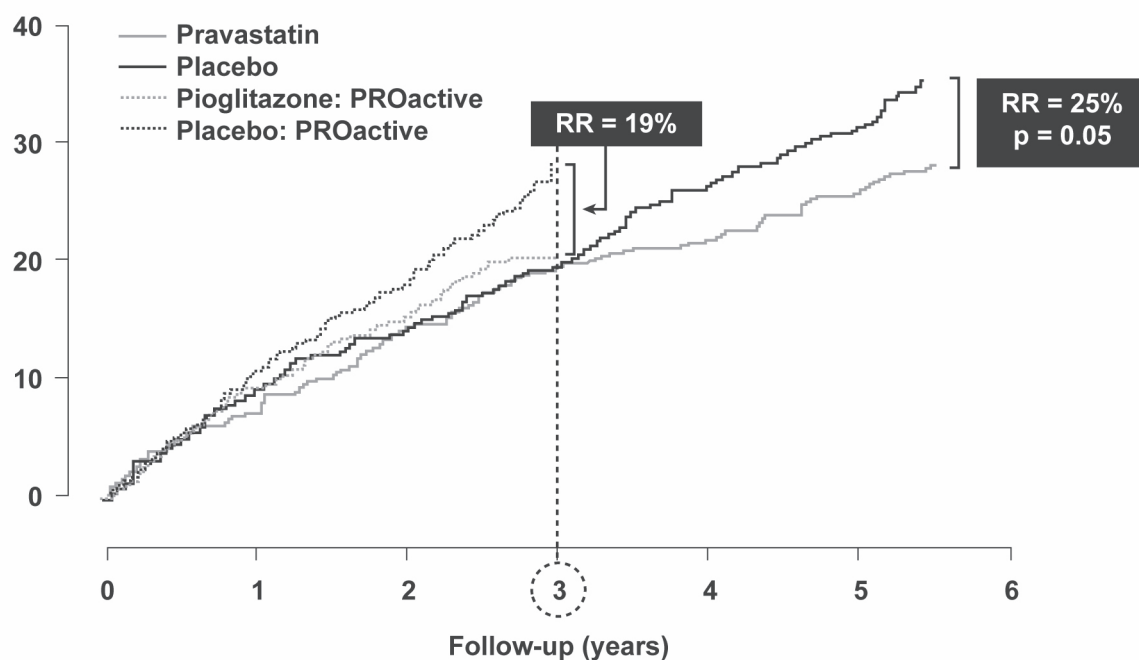
B   Major coronary events (%)
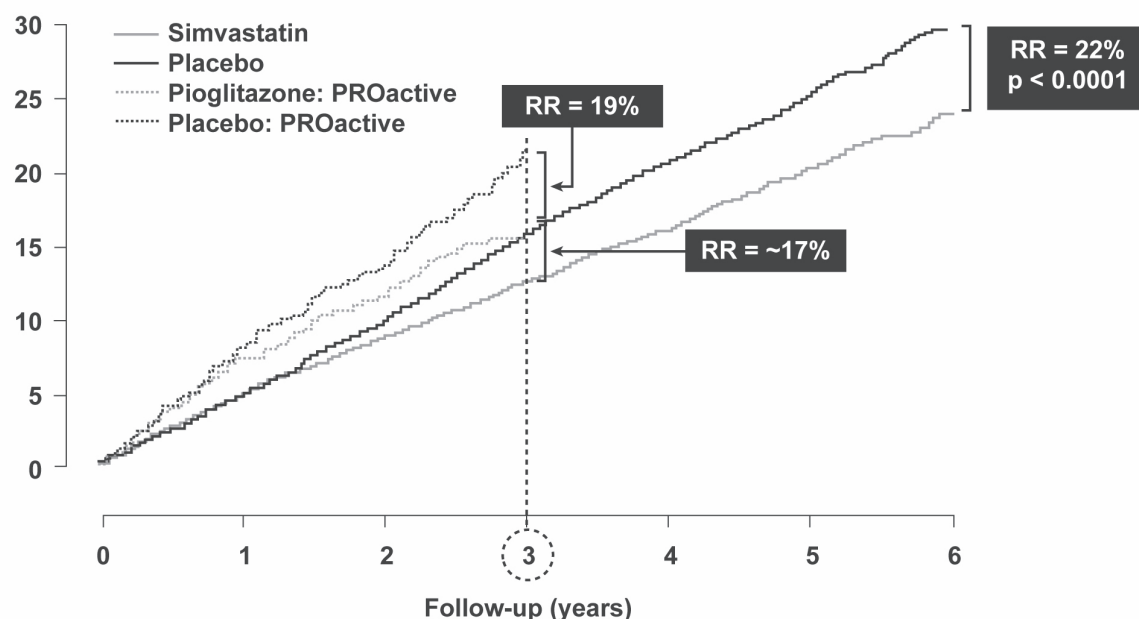
Figure 3 A. Major cardiac outcomes in the PROactive subgroup with previous myocardial infarction (MI) compared with outcomes in the CARE study. All patients in CARE had diabetes and a previous MI (from data of Goldberg 1998); **B.** Major vascular outcomes (major coronary events, stroke, and revascularization in patients with diabetes) in the HPS study (from data of Heart Protection Study Collaborative Group 2003). Figure 3A reproduced with permission from Goldberg RB, Mellies MJ, Sacks FM, et al. 1998 for the Care Investigators. Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels. Subgroup analyses in the cholesterol and recurrent events (CARE) trial. *Circulation*, 98:2513–9. Copyright © 1998 Lippincott Williams and Wilkins. Figure 3B reproduced with permission from Heart Protection Study Collaborative Group. 2003. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet*, 361:2005–16. Copyright © 2003 Elsevier.

history of CVD and one-third with ≥1 CV risk factor), compared treatment with the ACE inhibitor ramipril with placebo. By 3 years, a relative risk reduction of approximately 25% was seen in the ramipril group for the primary composite endpoint of CV death, MI, or stroke (HOPE 2000).

An analogy has been made between PROactive and the Steno-2 study, which had an almost identical primary endpoint (Gaede et al 2006). Steno-2 showed a 20% absolute risk reduction and a 53% relative risk reduction after intensified multifactorial intervention compared with standard multifactorial intervention (Gaede et al 2003, 2006). However, this was a comparatively small study (n = 180), with an 8-year follow-up in patients with microalbuminuria, the majority of whom had no pre-existing major CVD. Furthermore, significantly fewer patients in the control group received statins (n = 57 vs 14), antihypertensives, or antiplatelet therapy, whereas in PROactive, patients in both groups were receiving comparable multifactorial interventions at baseline and at study end (statins, fibrates, antihypertensives, and antiplatelet therapy). Any effect of pioglitazone should therefore be considered as additional to these interventions. Use of antihypertensives and antiplatelet therapy was similar between PROactive and the intensive group in Steno-2 (although statin use was lower in PROactive (43% increasing to 55% at study end)).

Conclusion
What are the implications of PROactive?
PROactive has shown that pioglitazone can significantly reduce the risk of secondary macrovascular events in a very high-risk patient population with established macrovascular disease, the majority of whom were receiving optimal treatment of established CV risk factors. As this patient population carries an excess risk, even with attention to established risk factors, pioglitazone may therefore provide an additional option to reduce residual events further as part of a multifactorial intervention strategy.

What questions remain unanswered after PROactive?
Several outcomes studies with thiazolidinediones are currently underway including IRIS (Insulin Resistance Intervention After Stroke) (http://iristrial.org) and RECORD (Rosiglitazone Evaluated of Cardiac Outcomes and Regulation of Glycemia in Diabetes) that aim to evaluate the long-term impact of these effects on CV outcomes and on long-term glycemic control in people with type 2 diabetes (Home et al 2005) and BARI 2D (Bypass Angioplasty Revascularization Investigation in Type 2 Diabetics; Sobel

et al 2003). The results of the Diabetes Reduction Approaches with ramipril and rosiglitazone Medications (DREAM) study were presented at the 2006 European Association for the Study of Diabetes (EASD) meeting and have been published in *The Lancet* (DREAM Trial Investigators 2006). In the enrolled population of 5,269 people with impaired glucose tolerance and/or impaired fasting glucose, rosiglitazone did not reduce all-cause mortality within 3 years of treatment (30 patients [1.1%] in the rosiglitazone group and 33 [1.3%] in the placebo group died). There was a trend for a higher number of events from the CV composite in the rosiglitazone group (75 [2.9%] events vs 55 [2.1%] in the placebo group; HR 1.37; 95% CI 0.97, 1.94; p = 0.08) that was driven by a higher rate of heart failure in the rosiglitazone group (0.5%; n = 14) than in the placebo group (0.1%, n = 2; HR 7.03; 95% CI 1.60, 30.9; p = 0.01). There were no cases of fatal heart failure during the study. It should be noted, however, that DREAM was a trial designed for primary prevention of manifest type 2 diabetes in patients with the metabolic syndrome and as such targeted towards glycemia outcomes and not towards prevention of CV risk.

PROactive has presented a range of questions that will hopefully be clarified with further analyses and through the results of these ongoing outcomes studies. For instance, it is unclear which effects of pioglitazone underlie its antiatherogenic effects – glucose-lowering, lipid regulation (effects on HDL-cholesterol, triglycerides, or LDL particle size), other pleiotropic factors (effects on inflammatory mediators, such as CRP), or a combination of factors. It is also unclear whether these results can be extrapolated to thiazolidinediones in general, considering some of their mechanistic distinctions, such as differing effects on lipid profiles (Goldberg et al 2005). Furthermore, it is not known whether a longer duration study would have resulted in a significant impact on the primary endpoint, or how effective pioglitazone would be in these patients if attention to antiplatelet therapy, blood pressure therapy, and, in particular, lipid-modifying therapy had been fully optimized. PROactive was a secondary prevention study, and we do not know if these results can be extrapolated to the wider population of patients with type 2 diabetes (such as in primary prevention), or indeed to those with prediabetes or high-risk patients without diabetes. Finally, the real impact (if any) of pioglitazone on heart failure is unclear at present.

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