Published in : Diabetic Medicine : A Journal of the British Diabetic Association (2009)
Status : Postprint (Author's version)

Long-term glycaemic effects of pioglitazone compared with placebo as add-ontreatment to metformin or sulphonylurea monotherapy in PROactive (PROactive18) [1]

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Abstract

Aims To assess the long-term glycaemic effects, concomitant changes in medications, and initiation of permanent insulin use (defined as daily insulin use for a period of ≥ 90 days, or ongoing use at death/final visit) with pioglitazone vs. placebo in diabetic patients receiving metformin or sulphonylurea monotherapy at baseline in the PROspective pioglitAzone Clinical Trial in macroVascular Events (PROactive). **Methods** In PROactive, patients with Type 2 diabetes and macrovascular disease were randomized to pioglitazone (force-titrated to 45 mg/day) or placebo, in addition to other existing glucose-lowering therapies. In a *post-hoc* analysis, we categorized patients not receiving insulin at baseline and treated by oral monotherapy into two main cohorts: addon to metformin alone (n = 514) and sulphonylurea alone (n = 1001). The follow-up averaged 34.5 months. **Results** There were significantly greater reductions in glycated haemoglobin (HbA_{1c}) with pioglitazone than with placebo and more pioglitazone-treated patients achieved HbA_{1c} targets, irrespective of the baseline oral glucose-lowering regimen and despite a decrease in the use of other glucose-lowering agents. Approximately twice as many in the placebo groups progressed to permanent insulin use than in the pioglitazone groups across the two cohorts: 3.4% for pioglitazone and 6.5% for placebo when added to metformin monotherapy and 6.3% and 14.8%, respectively, when added to sulphonylurea monotherapy. The overall safety of both dual therapies was good. **Conclusions** Intensifying an existing oral monotherapy regimen to a dual oral regimen by adding pioglitazone resulted in sustained improvements in glycaemic control and reduced progression to insulin therapy. The efficacy and safety of adding pioglitazone to either metformin monotherapy or sulphonylurea monotherapy were good.

Keywords : combination therapy ; metformin ; pioglitazone ; sulphonylurea ; Type 2 Diabetes

Abbreviations ADA, American Diabetes Association; DCCT, Diabetes Control and Complications Trial; EASD, European Association for the Study of Diabetes; IDF, International Diabetes Federation; PROactive, PROspective pioglitAzone Clinical Trial In macroVascular Events; UKPDS, United Kingdom Diabetes Prospective Study

Introduction

There is a need for strict glycaemic control in patientswith Type 2 diabetes due to the link between glucose levels and the high risk for macrovascular and microvascular complications. Although a range of oral glucose-lowering therapies are effective initially in improving glycaemic control, there are high secondary failure rates with metformin or sulphonylurea monotherapies over the longer-term, probably mainly due to a continuous decline in pancreatic ß-cell function, resulting in progressive deterioration in glycaemic control over time [1]. Therefore, there exists a need for therapies or combinations of medications that can sustain glycaemic control in the longer term [2,3]. In the recently updated consensus algorithm for the medical management of hyperglycaemia in Type 2 diabetes, pioglitazone is considered either in combination with lifestyle and

[1] PROactive is registered as an International Standard Randomised Controlled Trial (ISRCTN NCT00174993)

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metformin or possibly in triple therapy combined with metformin and a sulphonylurea [4]. The PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) assessed the effects of pioglitazone in addition to existing glucose-lowering and cardiovascular medications, on macrovascular events and total mortality in 5,238 patients with Type 2 diabetes [5,6]. Here, we report the glycaemic control data, concomitant changes in medication and initiation of permanent insulin in patients not receiving insulin at baseline from the PROactive cohort and initially treated with either metformin monotherapy or sulphonylurea monotherapy. It gives a unique opportunity to assess both efficacy and safety of either pioglitazone-metformin or pioglitazone-sulphonylurea dual therapies in a large cohort of Type 2 diabetic patients at high risk of cardiovascular disease.

Patients and Methods

Population and study design

PROactive was a randomized, double-blind, multicentre study performed in 19 European countries in 5328 patients aged 35-75 years with Type 2 diabetes and a history of macrovascular disease. Specific details of the entry criteria of established history of macrovascular disease and details of the other inclusion and exclusion criteria were reported by Dormandy et al. [5].

The study design has also been reported in detail elsewhere [5]. Patients were randomized to pioglitazone (15 mg titrated to 45 mg, if tolerated) or placebo for a mean of 34.5 months, in addition to existing therapy, such as diet and exercise and glucose-lowering agents, antihypertensives lipid-altering and antithrombotic agents. Over 90% of patients continuing on pioglitazone received 45 mg.

Efficacy endpoints

Glycaemic control data were prespecified as an additional measure of interest in the statistical analysis plan [7]. Here, we report changes in HbA_{1c} from baseline, the proportion of patients reaching the HbA_{1c} targets defined by the American Diabetes Association (< 7.0%) [8] and the International Diabetes Federation (IDF) (< 6.5%) [9] at the end of the study and concomitant changes in glucose-lowering medication. All blood samples were analysed at a central laboratory (ICON Laboratories, Dublin, Ireland). Glycated haemoglobin (HbA_{1c}) was measured using an ion-exchange HPLC assay (VARIANT HbA_{1c} program, BioRad Laboratories, Hercules, CA, USA) standardized against the DCCT reference method, with a normal reference range of 4.7-6.4% HbA_{1c}, assay sensitivity of 3.56% and intra- and inter-assay variability of <1.0 %. HbA_{1c} was measured at baseline and every 6 months.

In addition, the pre-specified analysis of time to the start of permanent insulin use (defined as daily insulin use for a period of ≥90 days, or ongoing use at death/final visit) in these patients not receiving insulin therapy at baseline is reported [5,7]). No specific goals were set for initiation of insulin. However, investigators were encouraged to follow the IDF guidelines [9]. Pioglitazone was not stopped when insulin therapy was initiated. The present *post-hoc* analysis compared both efficacy and safety of pioglitazone add-on vs. placebo add-on in 1. patients treated with metformin monotherapy (n = 514) and 2. patients treated with sulphonylurea monotherapy (n = 1001). In PROactive, only a limited number (n = 93) of patients were treated with other oral monotherapies, which does not allow appropriate assessment. The effects of adding pioglitazone vs. placebo in patients of PROactive already receiving a metformin-sulphonylurea combination therapy at baseline are analysed in a separate paper [10].

Safety endpoints

Investigators classified each adverse event into one of three categories: (i) serious adverse events (those resulting in death, life-threatening, needing or prolonging in-patient admission, resulting in persistent or significant disability, or needing intervention, which included potential endpoint events as well as other serious adverse events; (ii) nonserious adverse events of special interest, ie, hypoglycaemia, cardiac failure (new or worsening), oedema (in the absence of other signs of heart failure), bone fractures and other non-serious events that led to permanent cessation of study medication: or (iii) other non-serious adverse events, ie, those that were neither serious nor of special interest (not reported here). Serious hypoglycaemia was defined as that requiring hospital admission, serious heart failure was defined as requiring or prolonging a hospital stay, was fatal or life-threatening or resulted in persistent significant disability or incapacity and serious bone fractures were defined as those that were reported as a serious adverse event, and therefore meeting at least one of the standard criteria for seriousness.

Statistical methods

Statistical methods used for the sample size calculation and endpoint analysis for PROactive have been reported previously [5]. The data presented here are from the intention-to-treat population of patients who were receiving either metfomin monotherapy or sulphonylurea monotherapy at the time of entry into the study. Concomitant glucose-lowering medication was summarized by visit, regimen and treatment group. The change in HbA_{1c} from

baseline was calculated for each medication regimen and study visit; differences between the two treatment groups were compared using analysis of variance.

The comparative effect of the study treatments on time to permanent insulin use was estimated by calculating the hazard ratio and corresponding 95% confidence interval [CI] from a Cox proportional hazards survival model, with treatment as the only covariate. The standard threshold of $P < 0.05$ was used to define a "significant" result.

Results

Patient Baseline demographics and characteristics (Table 1) Baseline demography and patient characteristics in those from PROactive who were receiving metformin only or sulphonylurea only are given in Table 1. Known duration of diabetes was approximately 2 years lower in metformin-treated than in sulphonylureatreated patients. BMI was higher (almost 32 vs. 30 kg/m²) in patients on metformin monotherapy compared with patients on sulphonylurea monotherapy. Approximately half of all patients met two or more of the cardiovascular qualifying criteria in the two groups. Cardiovascular medication use was almost similar in the two cohorts (slightly more treated dyslipidaemia in the metformin subgroup). Although macrovascular disease antecedents were similar in the two subgroups, slightly less patients had microangiopathy complications in the metformin group than in the sulphonylurea group at baseline, perhaps because of a shorter duration of diabetes.

Table 1 *Patient characteristics and laboratory data in those with Type 2 diabetes and cardiovascular disease receiving metformin monotherapy or sulphonylurea monotherapy at baseline in PROactive*

	Metformin only		Sulphonylurea only	
	Pioglitazone (*n* = 253)	Placebo (*n* = 261)	Pioglitazone (*n* = 508)	Placebo (*n* = 493)
Male, *n* (%)	176 (70)	174 (67)	345 (68)	348 (71)
Caucasian, *n* (%)	247 (98)	256 (98)	503 (99)	486 (99)
Age (years), mean ± SD	60.8 ± 7.6	60.3 ± 7.9	63.2 ± 7.7	62.9 ± 7.8
Duration of diabetes (years), mean ± SD	5.1 ± 5.1	5.6 ± 5.4	7.3 ± 6.0	6.9 ± 6.1
Body mass index (kg/m^2), mean ± SD	31.9 ± 4.7	32.0 ± 5.3	29.7 ± 4.6	29.9 ± 4.3
History of hypertension, *n* (%)	190 (75)	200 (77)	376 (74)	371 (75)
Treated dyslipidaemia, *n* (%)	147 (58)	158 (61)	217 (43)	233 (47)
Macrovascular disease[a], *n* (%)	247 (98)	254 (97)	504 (99)	487 (99)
MI, *n* (%)	128 (51)	119 (46)	260 (51)	256 (52)
Stroke, *n* (%)	48 (19)	52 (20)	102 (20)	81 (16)
Microvascular disease[b], *n* (%)	64 (25)	60 (23)	173 (34)	146 (30)
HbA_{1c} (%), mean ± SD	7.6 ± 1.3	7.6 ± 1.2	7.8 ± 1.3	7.7 ± 1.4

[a]Established history of macrovascular disease includes one or more of the following: myocardial infarction, stroke, percutaneous coronary intervention, or coronary artery bypass graft ≥6 months before entry into the study; acute coronary syndrome ≥3 months before entry into the study; objective evidence of coronary artery disease; or symptomati< peripheral arterial obstructive disease [5]
[b]Investigator-diagnosed retinopathy, nephropathy, neuropathy There were no significant differences between pioglitazone and placebo in all of the treatment cohorts
HbA_{1c}, glycated haemoglobin; MI, myocardial infarction; PROactive, PROspective pioglitAzone Clinical Trial In macro Vascular Events; SD, standard deviation.

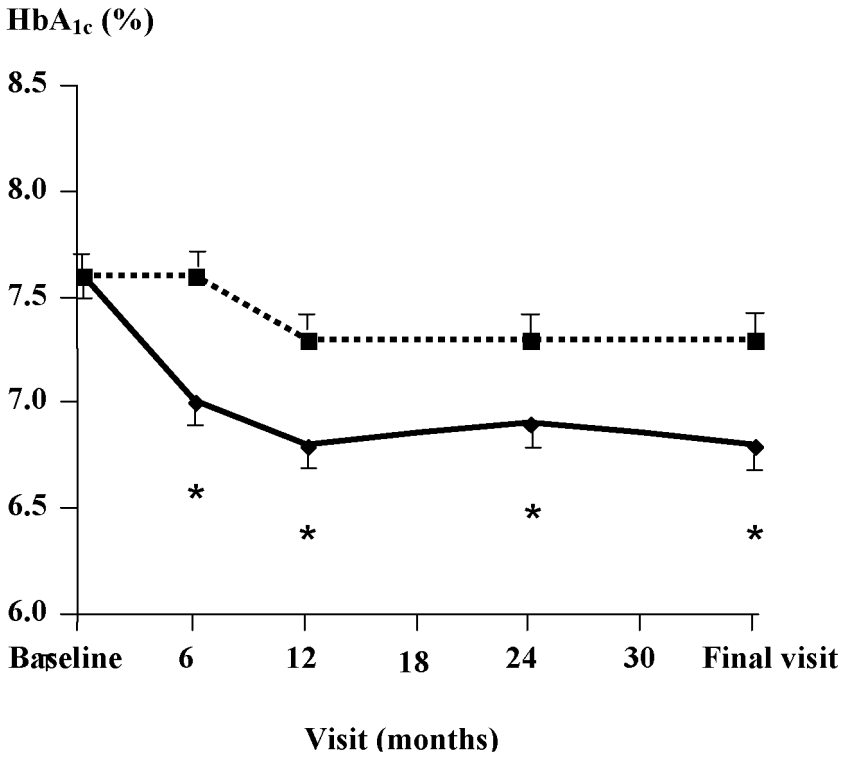
Glycaemic control results (Fig. 1, Table 2)

Pioglitazone add-on therapy in the two cohorts resulted in significantly better glycaemic control at final visit compared with the respective placebo group ($P < 0.01$). The decreases in HbA_{1c} for pioglitazone relative to placebo were 0.5% in the metformin monotherapy and 0.5% in the sulphonylurea monotherapy cohorts at final visit. The significant differences between the pioglitazone and placebo groups were sustained throughout the duration of the study in both cohorts (Fig. 1). The proportion of patients achieving HbA_{1c} targets of <6.5% (IDF) and <7.0% (ADA) was similar in the two cohorts (Table 2), with a significantly greater proportion of patients achieving both HbA_{1c} targets in the pioglitazone groups vs. the placebo groups, irrespective of baseline oral glucoselowering monotherapy.

Published in : Diabetic Medicine : A Journal of the British Diabetic Association (2009)
Status : Postprint (Author's version)

FIGURE 1 *Mean (±sem) changes in glycated haemoglobin (HbA_{1c}) over time with pioglitazone (solid lines and diamonds) or placebo (dashed lines and squares) in (a) the metformin monotherapy cohort, and (b) the sulphonylurea monotherapy cohort from the PROactive study (*p<0.0001)*

a



b

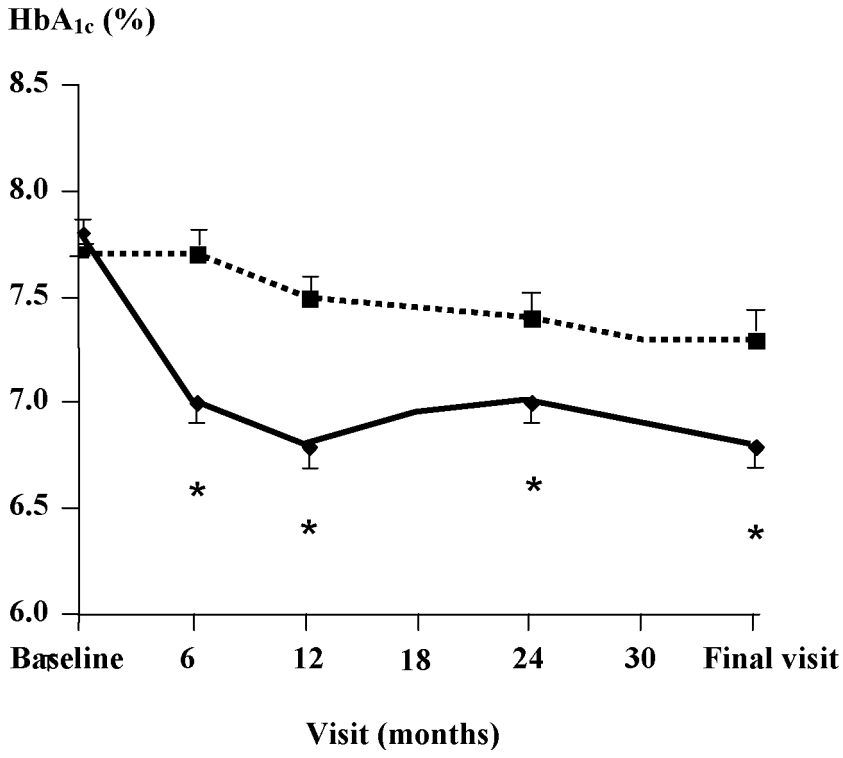


Table 2 *Mean changes in glycated haemoglobin (HbA_{1c}), proportion of patients reaching the ADA and IDF targets of HbA_{1c}, and HbA_{1c} thresholds associated with a change in treatment regimen*

	Metformin only		Sulphonylurea only	
	Pioglitazone (*n* = 253)	Placebo (*n* = 261)	Pioglitazone (*n* = 508)	Placebo (*n* = 493)
Mean ± SD change in HbA_{1c} level (%) (from baseline to final visit)	-0.8 ± 1.2	-0.3 ± 1.5‡	-0.9 ± 1.3	-0.4 ± 1.3‡
N & % of patients achieving HbA_{1c} <7.0% (ADA)[a]	156 (68.1%)	108 (46.8%)‡	287 (64.1%)	166 (38.9%)‡
N & % of patients achieving HbA_{1c} <6.5% (IDF)[a]	84 (36.7%)	56 (24.2%)†	189 (42.2%)	95 (22.2%)‡
Number and % of permanent insulin use at final visit	8 (3.4%)	16 (6.5%)‡	30 (6.3%)	67 (14.8%)‡
Mean ± SD HbA_{1c} at time of insulin initiation in patients who progressed to insulin use (*n*)	9.0 ± 2.2 (9)	9.3 ± 1.6(20)	8.3 ± 1.5 (35)	8.5 ± 1.6(78)

[a]The denominators used for the percentages are the numbers of patients with an HbA_{1c} measurement at final visit
† p<0.01 between-group difference; ‡ p<0.001 between-group difference
ADA, American Diabetes Association; HbA_{1c}, glycated haemoglobin; IDF, International Diabetes Federation; SD, standard deviation.

Progression to permanent insulin use (Fig. 2, Table 2)

. A twofold increase in insulin use in the placebo groups was irrespective of the baseline oral regimen (Table 2), with an incidence of 3.4% for pioglitazone and 6.5% for placebo when added to metformin monotherapy and 6.3% and 14.8%, respectively, when added to sulphonylurea monotherapy. Kaplan-Meier curves for permanent insulin use are given in Fig. 2**.**

The level of HbA_{1c} at which insulin therapy was initiated was 8.5% in the sulphonylurea monotherapy group and 9.2% in the metformin monotherapy group (*P* = 0.1227). However, it was comparable between pioglitazone and placebo (Table 2). Changes from baseline in glucose-lowering medication (Table 3) The improved glycaemic control with pioglitazone was accompanied by a lower proportion of patients (approximately half as many) switching to or adding another oral agent or insulin to their monotherapy treatment regimen than in the placebo group. Changes in the dose of oral glucose-lowering medication were more marked in the addon pioglitazone group than in the add-on placebo group. The mean daily insulin dose was lower with pioglitazone than with placebo in the sulphonylurea monotherapy group, but not in the metformin monotherapy group (Table 3).

Table 3 *Glucose-lowering drug use at final visit in the pioglitazone and placebo groups*

	Metformin only		Sulphonylurea only	
	Pioglitazone (*n* = 238)	Placebo (*n* = 247)	Pioglitazone (*n* = 476)	Placebo (*n* = 453)
Metformin only, *n* (%)	168 (71)	151 (61)	9 (2)	11 (2)
Sulphonylurea only, *n* (%)	5 (2)	7 (3)	326 (68)	228 (50)
Other oral monotherapies, *n* (%)	0 (0)	0 (0)	2 (0.4)	3 (1)
Metformin + sulphonylurea, *n* (%)	33 (14)	60 (24)	51 (11)	113 (25)
Other oral combinations, *n* (%)	4 (2)	6 (3)	13 (3)	19 (4)
No data available, *n* (%)	20 (8)	7 (3)	45 (9)	12 (3)
Insulin (alone or in combination), *n* (%)	8 (3)	16 (6)	30 (6)	67 (15)‡
Mean daily insulin dose, U ± SD	37.3 ± 18.9	36.2 ± 23.1	27.7 ± 17.6	41.6 ± 28.4*
Mean metformin dose, mg/day ± SD *(n)*	1687 ± 708 (210)	1721 ± 639 (228)		
Mean glibenclamide dose, mg/day ± SD *(n)*			8.4 ± 5.6 (61)	9.9 ± 4.5 (62)
Mean gliclazide dose, mg/day ± SD *(n)*			113.1 ± 82.4 (212)	135.2 ± 94.0 (201)*
Mean glimepiride dose, mg/day ± SD (*n*)			2.7 ± 1.5 (97)	3.5 ± 1.8 (91)†

* p<0.05 between-group difference; † p<0.0l between-group difference; ‡ p<0.00l between-group difference
SD, standard deviation

Published in : Diabetic Medicine : A Journal of the British Diabetic Association (2009)
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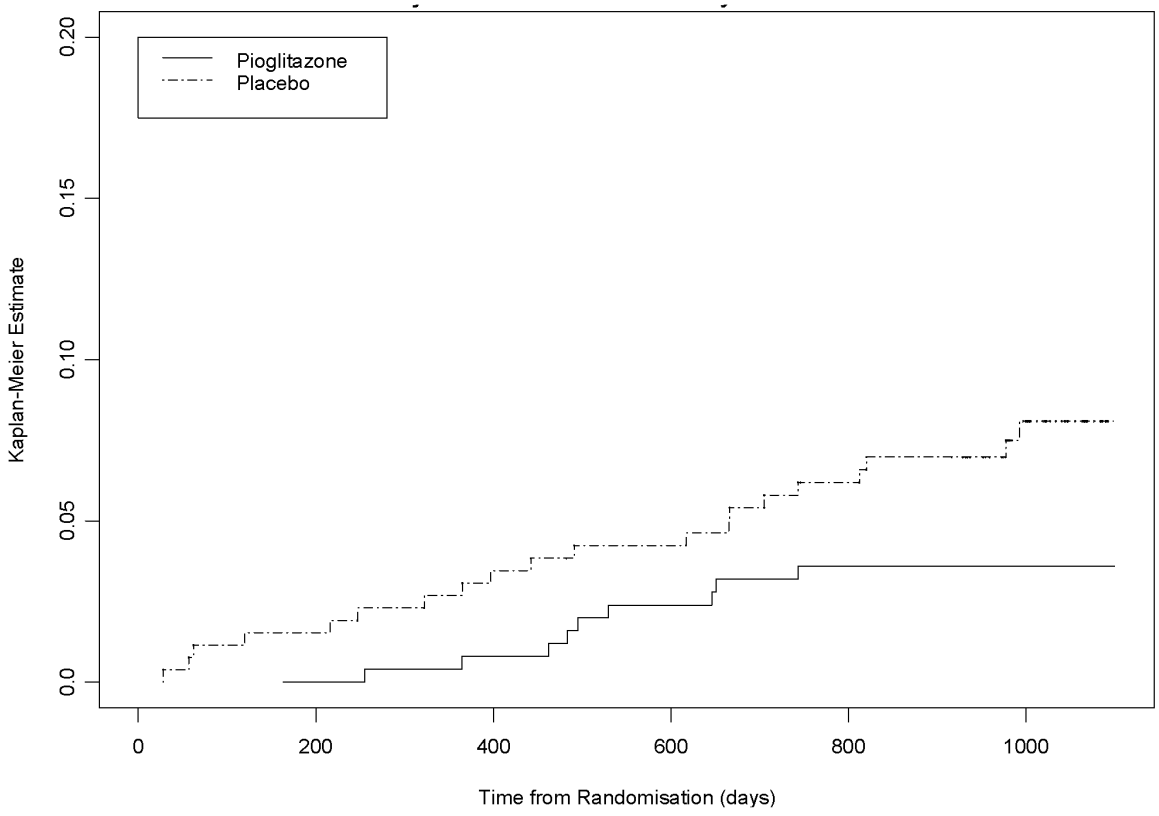
FIGURE 2 *Kaplan-Meier rates for time to permanent insulin use in pioglitazone-treated patients (solid lines) and placebo-treated patients (dashed lines) receiving (a) metformin monotherapy, and (b) sulphonylurea monotherapy.*

a



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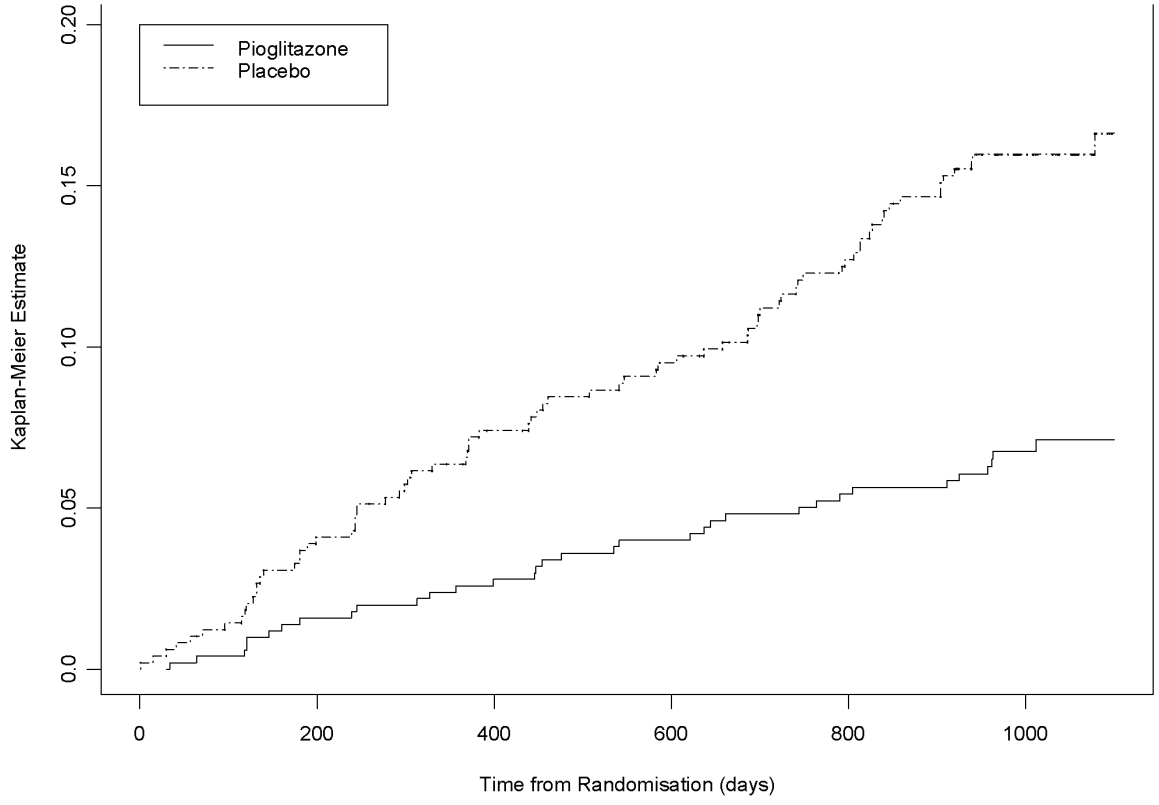

Safety and tolerability (Table 4)

A comparable proportion of pioglitazone- and placebo-treated patients had serious adverse events in the two cohorts. As expected with better glycaemic control, more patients in the pioglitazone group had hypoglycaemia (Table 4). However, serious hypoglycaemia occurred only in one pioglitazone-treated patient in the metformin group and one placebo-treated in the sulphonylurea group. Body weight increased by 3.9 kg in the pioglitazone plus metformin monotherapy group (vs. a decrease of 1.3 kg in the placebo group, $P < 0.001$) and by 2.6 kg with pioglitazone added to sulphonylurea monotherapy (vs. a decrease of 1.3 kg in the placebo group, $P < 0.001$) ($P = 0.013$ for between-group difference). Oedema (investigator-defined) and serious heart failure rates were slightly higher in the pioglitazone group than the placebo group when given with any glucose-lowering monotherapy (Table 4). However, fatal heart failure rates were low and similar between cohorts and between treatment groups. Bone fracture rates were slightly higher when adding pioglitazone than when adding placebo in the sulphonylurea monotherapy groups, but not in the metformin monotherapy groups. Serious fractures were very rare (Table 4). There were no other between-group differences in adverse events. Fifteen patients (5.9%) in the pioglitazone plus metformin group, 11 (4.2%) in the placebo plus metformin group, 21 (4.1%) in the pioglitazone plus sulphonylurea group and 21 (4.3%) in the placebo plus sulphonylurea group had a neoplasm. There were no imbalances between groups in individual cancers.

Table 4 *Safety data in the two subgroups receiving monotherapy with metformin or sulphonylurea at baseline*

	Metformin only		Sulphonylurea only	
	Pioglitazone (*n* = 253)	Placebo (*n* = 261)	Pioglitazone (*n* = 508)	Placebo (*n* = 493)
Any SAE, *n* (%)	106 (42)	112 (43)	217 (43)	230 (47)
Death, *n* (%)	14 (6)	9 (3)	30 (6)	38 (8)
Hypoglycaemia, *n* (%)	20 (8)	33 (13)	108 (21)	65 (13) ‡
Serious hypoglycaemia, *n* (%)	1 (0.4)	0 (0)	0 (0)	1 (0.2)
Oedema, *n* (%)	68 (27)	39 (15) ‡	112 (22)	56 (11)‡
Serious heart failure, *n* (%)	11 (4)	5 (2)	24 (5)	14 (3)
Fatal heart failure, *n* (%)	3 (1.2)	1 (0.4)	1 (0.2)	4 (0.8)
Bone fracture, *n* (%)	4 (1.6)	4 (1.5)	7 (1.4)	3 (0.6)
Serious bone fracture, *n* (%)	1 (0.4)	1 (0.4)	0 (0)	0 (0)

‡ p<0.001 between-group difference
SAE, serious adverse event

Discussion

The primary endpoint in PROactive was the effect of pioglitazone on macrovascular disease in patients with Type 2 diabetes and cardiovascular disease [5,6]. This *post-hoc* analysis in patients on metformin or sulphonylurea monotherapy at baseline revealed that glycaemic control with pioglitazone was significantly better at final visit than that with placebo and was sustained across the study period of approximately 3 years, the longest and largest follow-up to date with dual therapies including pioglitazone studied in a randomized controlled trial. This was irrespective of oral baseline monotherapy treatment. Across the two subgroups, the percentages of patients reaching the target HbA_{1c} of <7.0% or <6.5% were consistently higher, up to 50% and 100%, respectively, in the pioglitazone arm compared with the placebo arm at final visit. The favourable effect of adding pioglitazone was as marked in patients on sulphonylurea therapy at baseline compared to patients on metformin monotherapy at baseline. We also showed that the rate of progression to permanent insulin use in patients not receiving insulin at baseline was halved in the pioglitazone group than in the placebo group. Again, this was irrespective of baseline oral glucose-lowering regimen. Our observations demonstrate that pioglitazone may be added to sulphonylurea therapy in as efficacious a manner as when added to metformin alone.

In the cohort of PROactive patients treated with oral monotherapy at baseline, only one third were receiving metformin and two thirds a sulphonylurea. This is in contrast to what is recommended in the recent consensus statement, which unanimously advocates metformin as first-line therapy in the management of Type 2 diabetes [4]. This discordance may be explained by the fact that diabetic patients included in PROactive were at high cardiovascular risk (around half with antecedents of myocardial infarction). Many physicians may be somewhat reluctant to prescribe a biguanide in such patients, because of the potential risk of lactic acidosis. However, metformin has been shown to exert various positive cardiovascular effects, both in animal models and in humans [11]. This has been confirmed in two clinical trials that reported a lower incidence of cardiovascular events in diabetic patients receiving metformin as compared to other glucose-lowering agents [12,13]. This was observed not only in obese patients with newly diagnosed Type 2 diabetes in the UKPDS [12], but also in diabetic patients

with recent myocardial infarction in the DIGAMI 2 trial [13]. PROactive was not designed to assess cardiovascular prognosis according to the various glucose-lowering therapies at baseline.

The median known duration of diabetes at baseline in the whole PROactive cohort was 8 years (around 5 years in the metformin monotherapy and 7 years in the sulphonylurea monotherapy groups). According to the observations of the UKPDS [1], one would expect many of the patients to have been receiving combination therapy on entrance into the study. In fact, almost one-third were receiving oral monotherapy, even though most of them were not within target HbA_{1c}. These data support the common observation that many patients with diabetes are not treated intensively enough in clinical practice, in agreement with so-called "therapeutic inertia" [14]. There is now an increased understanding of the need to treat hyperglycaemia more intensively. The recently published consensus statement of the ADA/EASD [4] suggest that an $HbA_{1c} \geq 7.0\%$ should serve as a call to action to initiate or change therapy, with the goal of achieving an HbA_{1c} level of <7.0%. Both pioglitazone and placebo improved glycaemic control irrespective of treatment regimen, suggesting that investigators were treating to target HbA_{1c} more aggressively during PROactive (as recommended in the IDF guidelines they were encouraged to use [9]) than they would do in routine clinical practice (where there is a certain degree of clinical inertia and less impetus to treat-totarget). At final visit, the decreases in HbA_{1c} with pioglitazone were 0.8% with metformin monotherapy and 0.9% with sulphonylurea vs. placebo decreases of 0.3 and 0.4% ($P < 0.001$ between-group differences in the two cohorts). Treatment appeared to be more efficient in the pioglitazone arm of the study, presumably in part because of insufficient adjustments in treatments regimens in the placebo arm, again an argument supporting the concept of therapeutic inertia in the management of Type 2 diabetes [14]. This occurs even within the frame of a clinical trial. However, it should be mentioned that PROactive was a cardiovascular outcome study [5], and that no strict treat-to-target recommendations were given to the investigators as far as HbA_{1c} levels were concerned. Nevertheless, the sustained decreases in HbA_{1c} in PROactive are encouraging as the majority of studies show gradual deteriorations in glycaemic control over time, especially when no adjustment of therapies was made during follow-up. The recent ADOPT study comparing different oral monotherapies in patients with newly diagnosed diabetes showed that the 4-year escape in glycaemic control was less pronounced with rosiglitazone, most impressive with glibenclamide and intermediate with metformin monotherapy [15]. In the UKPDS, there was an increase in HbA_{1c} over time in the sulphonylurea monotherapy group to the extent that at the 3-year time point the levels had increased beyond those at baseline [16]. The thiazolidinediones were not available when the UKPDS began, but over 2 years pioglitazone has shown sustained glycaemic improvement in monotherapy vs. gliclazide [17] and as add-on to failing metformin monotherapy vs. gliclazide add-on which deteriorated. This suggests that, when a patient is failing on metformin monotherapy, there may be an advantage to adding pioglitazone rather than a sulphonylurea [18]. For patients given pioglitazone add-on therapy to failing sulphonylurea monotherapy, maintenance of glycaemic control was comparable to metformin add-on [18]. Furthermore, recent observations showed that pioglitazone as an add-on to either failing metformin or sulphonylurea therapy improved post-load glucose excursions, without affecting insulin secretion [19]. These data suggest that pioglitazone reduces peripheral insulin resistance *via* mechanisms different from those of metformin [19]. In an interim analysis of the randomized open-label Rosiglitazone Evaluated for CardiacOutcomes and Regulation of glycaemia in Diabetes (RECORD) study in 1,122 patients with Type 2 diabetes, rosiglitazone in combination with metformin or sulphonylurea was demonstrated to be non-inferior to the standard combination of metformin plus a sulphonylurea in lowering HbA_{1c} over 18 months [20]. The IDF guidelines [9] recommend that insulin should be started when HbA_{1c} levels have deteriorated to >7.5% after maximum attention to dietary control and oral glucoselowering therapy and the ADA/EASD recommends initiation at $HbA_{1c} \geq 7.0\%$ [4]. However, many patients (and physicians) are reluctant to consider insulin therapy due to side effects, and worry about self-injections, safety and compliance issues [21]. Intensifying the oral glucose-lowering monotherapy by adding pioglitazone resulted in an approximate 50% reduction in the initiation of permanent insulin therapy. The HbA_{1c} threshold for switching to insulin therapy was high in PROactive. As observed in clinical practice, HbA_{1c} thresholds were well above the thresholds recommended in the various international guidelines [4,8,9,21]: 8.3–8.5% in the sulphonylurea monotherapy group and 9.0–9.3% in the metformin monotherapy group. It is also possible that some physicians were reluctant to switch to insulin therapy in a trial using pioglitazone, as the insulin plus thiazolidinedione combination was not recognized in Europe at the time of the study.

There was good general tolerability in the pioglitazone groups. As expected with thiazolidinediones [15,17,18,20,23], there were increases in oedema and body weight. Pioglitazone-associated weight change vs. placebo was not higher in the sulphonylureatreated group (average weight gain of 3.9 kg) than in the metformin-treated group (5.2 kg) after a mean follow-up of 2.8 years, despite the different body weight changes observed with each monotherapy (weight gain with rosiglitazone and with glibenclamide, slight weight decrease with metformin) in ADOPT [15]. Similar to data from ADOPT [23], there was a slightly higher incidence of non-serious bone fractures with pioglitazone plus sulphonylurea monotherapy. Despite the better glycaemic control, almost no serious hypoglycaemia occurred. The recent ADA-EASD consensus statement recognized that,

specifically when hypoglycaemia is particularly undesirable, the addition of pioglitazone may be considered [4]. No serious adverse effect appeared as a consequence of pioglitazone long-term treatment in the total PROactive cohort. There were small differences between treatment groups with respect to serious heart failure (requiring hospital admission), but no clear patterns emerged. Fatal heart failure rates were low and similar between cohorts and between treatment groups [25]. There were some imbalances in the incidence of individual tumours in the total PROactive cohort where there were more bladder tumours (14 vs. six) and fewer cases of breast cancer (three vs. 11) reported with pioglitazone vs, placebo [5]. There were no differences between pioglitzone and placebo in the incidence of individual cancers in the metformin monotherapy and sulphonylurea monotherapy groups. Intensifying an existing mono- to a dual oral therapy regimen by adding pioglitazone resulted in a sustained improvement in HbA_{1c} and a reduced initiation of insulin. However, it is noteworthy that the design of PROactive does not allow the comparison between adding pioglitazone to metformin monotherapy and adding basal insulin to metformin as considered as a better validated therapy in the recently updated ADAEASD consensus statement [4]. We have shown that the effect of pioglitazone on glycaemic control was better than placebo, irrespective of the initial existing baseline diabetes regimen and despite a decrease in the use of other glucose-lowering agents. A larger percentage of pioglitazone-treated patients reached HbA_{1c} targets than placebotreated patients. The progression to permanent insulin use was reduced by 50% at 3 years with pioglitazone compared with placebo in those patients not receiving insulin at baseline. In addition, there was better glycaemic control with pioglitazone, despite a lower daily insulin dose. These long-term findings support the use of pioglitazone in combination with a single oral glucose-lowering agent as well as in addition to a dual metformin-sulphonylurea therapy [10] to improve glycaemic control in patients with Type 2 diabetes.

Disclosure summary:

A Scheen, DJ Betteridge, K Birkeland and O Schmitz are National Principal Investigators of the PROactive study. MH Tan and B Charbonnel are on the PROactive Executive Committee. MH Tan worked for Lilly at the time the PROactive Study was conducted. DJ Betteridge and B Charbonnel have served as consultants to Takeda and received travel expenses and payments from Takeda for speaking at meetings.

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