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

Long-term glycaemic control with metformin-sulphonylurea-pioglitazone triple therapy in PROactive (PROactive 17)

A. J. Scheen, M. H. Tan*[1], D. J. Betteridge†, K. Birkeland‡, O. Schmitz§ and B. Charbonnel¶ on behalf of the PROactive investigators

Division of Diabetes, Nutrition and Metabolic Disorders, Department of Medicine, University of Liège, Liège, Belgium, *Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN, USA, †Department of Medicine, University College Hospital, London, UK, ‡Department of Endocrinology, Aker University Hospital and Faculty Division, Aker University Hospital, University of Oslo, Oslo, Norway, §Department of Medicine M (Endocrinology and Diabetes), Århus Kommunehospitalet, Aarhus, Denmark and ¶Clinique d'Endocrinologie, Hotel Dieu, Nantes Cedex 1, France

Abstract

Aims We assessed the long-term glycaemic effects and the safety profile of triple therapy with the addition of pioglitazone vs. placebo in patients with Type 2 diabetes treated with combined metformin-sulphonylurea therapy in the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive).

Methods In a *post-hoc* analysis, we identified patients treated with metformin plus sulphonylurea combination therapy and not receiving insulin at baseline (n = 1314). In those patients, we compared the effects of pioglitazone (force-titrated to 45 mg/day, n = 654) vs. placebo (n = 660) on glycated haemoglobin (HbA_{1c}) reduction, 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).

Results Significantly greater reductions in HbA_{1c} and greater proportions of patients with HbA_{1c} at target were noted with pioglitazone vs, placebo, despite a decrease in the use of other oral glucose-lowering agents. There was an approximate twofold increase in progression to permanent insulin use in the placebo group vs. the pioglitazone group: 31.1 vs. 16.1 %, respectively, when added to combination therapy. The overall safety of the metformin-sulphonylurea-pioglitazone triple therapy was good.

Conclusions Intensifying an existing dual oral therapy regimen to a triple oral regimen by adding pioglitazone to the classical metformin-sulphonylurea combination resulted in sustained improvements in glycaemic control and reduced progression to insulin therapy. The advantages and disadvantages of adding pioglitazone instead of adding basal insulin should be assessed further.

Keywords : metformin ; pioglitazone ; sulphonylurea ; triple therapy ; type 2 diabetes

Abbreviations : ACCORD, Action to Control Cardiovascular Risk in Diabetes Study; ADA, American Diabetes Association; ADOPT, A Diabetes Outcome Progression Trial; CI, confidence interval; DCCT, Diabetes Control and Complications Trial; EASD, European Association for the Study of Diabetes; HbA_{1c}, glycated haemoglobin; IDF, International Diabetes Federation; PROactive, PROspective pioglitAzone Clinical Trial In macroVascular Events; UKPDS, UK Diabetes Prospective Study; VA-Diabetes, Veterans Affairs Diabetes Trial

Introduction

Combination of glucose-lowering agents that target the three main metabolic abnormalities of Type 2 diabetes simultaneously (for example, sulphonylureas that promote insulin secretion, metformin that inhibits hepatic glucose overproduction and thiazolidinediones that have insulin-sensitizing properties) is increasingly used to manage more advanced Type 2 diabetes [1-4]. In two recent randomized controlled trials, the Action to Control

[1] The present address of M. H. Tan is the Division of Metabolism, Endocrinology and Diabetes, University of Michigan, Ann Arbor, MI, USA

The PROactive study is registered as an International Standard Randomized Controlled Trial (ISRCTN NCT00174993)

Cardiovascular Risk in Diabetes Study [5] and the Veterans Affairs Diabetes Trial [6], intensifying diabetes therapy implied the use of combined oral therapies, including thiazolidinediones, together with insulin in most cases. In the recently updated consensus algorithm for the medical management of hyperglycaemia in Type 2 diabetes, metformin is considered as the initial option and the addition of a sulphonylurea is recommended as first choice for combined therapy. Pioglitazone is considered either in combination with lifestyle and metformin (in patients at risk of hypoglycaemia) or possibly in triple therapy combined with metformin and a sulphonylurea [3]. The consensus group members, however, placed pioglitazone among so-called less well validated therapies.

The PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) looked at the impact of pioglitazone treatment, in addition to existing glucose-lowering and cardiovascular medications, on the incidence of macrovascular co-morbidity and total mortality in over 5000 high-risk patients with Type 2 diabetes [7,8]. In the total population of patients entered into PROactive, there were statistically significant differences in favour of pioglitazone vs. placebo add-on to existing glucose-lowering therapies on glycated haemoglobin (HbA_{1c}) (-0.8% vs. -0.3%, respectively; $P < 0.0001$) [7].

The combination of metformin plus sulphonylurea remains the most popular combined therapy in the management of Type 2 diabetes [1,2,4]. Patients treated with combined metformin-sulphonylurea therapy represent almost one quarter of the whole PROactive cohort and the most important well-defined subgroup on oral treatment. This paper reports the glycaemic control, together with concomitant changes in medication, and initiation of permanent insulin in the 1314 patients treated with combined metformin plus sulphonylurea (and not receiving insulin) at baseline from the PROactive cohort. This analysis will provide valuable information on both long-term efficacy and safety of a metformin-sulphonylurea-pioglitazone triple therapy in Type 2 diabetic patients at high cardiovascular risk.

Patients and methods

Study design

The study design has been reported in detail elsewhere [7]. PROactive was a randomized, double-blind, multi-centre study in 5328 patients aged 35-75 years with Type 2 diabetes [HbA_{1c} above the local equivalent of 6.5% for a Diabetes Control and Complications Trial (DCCT) traceable assay] and a history of macrovascular disease. It was conducted in compliance with the Declaration of Helsinki and the requirements of Good Clinical Practice of the European Community. In addition to existing therapy, patients were randomized to pioglitazone (15 mg titrated to 45 mg, if tolerated) or placebo for a mean of 34.5 months. At least 93% of patients continuing on pioglitazone received 45 mg.

Study population

Specific details of the entry criteria of established history of macrovascular disease and details of the other inclusion and exclusion criteria are reported by Dormandy *et al.* [7]. Patients treated with insulin plus oral glucose-lowering agents ($n = 1760$), with oral monotherapy only ($n = 1608$) or with various oral therapies ($n = 342$) were eligible for entry into PROactive, but were not taken into account for the present analysis, which only deals with patients receiving combined metformin-sulphonylurea therapy at baseline ($n = 1314$).

Efficacy endpoints

The main objective of PROactive was to assess pioglitazone's ability to reduce total mortality and macrovascular morbidity and the primary endpoint was the time to the first occurrence of cardiovascular events or death [7].

This paper reports the glycaemic control data (pre-specified as an additional measure of interest in the statistical analysis plan [9]). Changes in HbA_{1c} from baseline were used as efficacy criteria. The proportion of patients reaching the HbA_{1c} targets defined by the American Diabetes Association (ADA) (< 7.0%) [10] and by the International Diabetes Federation (IDF) (< 6.5%) [11] at the end of the study was calculated to determine the clinical impact of the glucose-lowering therapy given to the patients. As physicians were instructed to adjust glucose-lowering treatment when necessary in order to reach target HbA_{1c} (< 6.5%) and to reduce cardiovascular risk factors, we also analysed concomitant changes in medication. A central laboratory (ICON Laboratories, Dublin, Ireland) conducted the analysis of all blood samples. 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. The normal reference range was 4.7-6.4% HbA_{1c}, assay sensitivity was 3.56% HbA_{1c} and intra- and interassay variability was < 1.0%. HbA_{1c} was measured at baseline and every 6 months.

In addition, we report the time to the start of permanent insulin use in these patients not receiving insulin therapy at baseline (a pre-specified analysis [7]). Permanent insulin use was defined as daily insulin use for a period of ≥ 90 days or ongoing use at death/final visit.

Safety endpoints

Investigators classified each adverse event into one of three categories: (i) serious adverse events, which included potential endpoint events as well as other serious adverse events; (ii) non-serious adverse events of special interest, i.e. hypoglycaemia, cardiac failure (new or worsening), oedema (in the absence of other signs of heart failure) and other non-serious events that led to permanent cessation of study medication; or (iii) other non-serious adverse events, i.e. those that were neither serious nor of special interest (data not reported in this manuscript). Serious adverse events were defined as resulting in death, life-threatening, needing or prolonging inpatient admission, resulting in persistent or significant disability or needing intervention to prevent any of the above. 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 [7]. The data presented here are from the intention-to-treat population of patients on metformin plus sulphonylurea (without insulin) 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

Baseline demographics and characteristics (Table 1)

Selected subjects were Type 2 diabetic patients on dual metformin-sulphonylurea therapy with a mean age of 65 years, a mean duration of diabetes around 10 years, a mean body mass index (BMI) of 30.5 kg/m^2 and a mean HbA_{1c} of 8.1-8.2%. Because of inclusion criteria of PROactive, all patients had macrovascular disease. About 40% of the metformin-sulphonylurea-treated patients also had microvascular complications.

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

	Metformin + sulphonylurea	
	Pioglitazone (*n* = 654)	Placebo (*n* = 660)
Male, *n* (%)	472 (72)	434 (66)
Caucasian, *n* (%)	639 (98)	651 (99)
Age (years), mean ± SD	61.7 ± 7.5	61.7 ± 7.7
Duration of diabetes (years), mean ± SD	9.5 ± 6.3	9.5 ± 6.4
Body mass index (kg/m), mean ± SD	30.4 ± 4.8	30.7 ± 4.8
History of hypertension, *n* (%)	495 (76)	509 (77)
Treated dyslipidaemia, *n* (%)	355 (54)	339 (51)
Macrovascular disease*, *n* (%)	649 (99)	648 (98)
MI, *n* (%)	306 (47)	280 (42)
Stroke, *n* (%)	118 (18)	139 (21)
Microvascular disease†, *n* (%)	258 (39)	259 (39)
HbA_{1c} (%), mean ± SD	8.2 ± 1.4	8.1 ± 1.4

* 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 symptomatic peripheral arterial obstructive disease [7].
† Investigator-diagnosed retinopathy, nephropathy, neuropathy. There were no significant differences between pioglitazone and placebo.
HbA_{1c}, glycated haemoglobin; MI, myocardial infarction; PROactive, PROspective pioglitAzone Clinical Trial In macroVascular Events; SD, standard deviation.

Glycaemic control results (Fig. 1, Table 2)

Pioglitazone add-on therapy resulted in better glycaemic control compared with the respective placebo group. At final visit, the decrease in HbA_{1c} for pioglitazone relative to placebo was 0.6% ($P < 0.01$) in the metformin plus sulphonylurea cohort. The differences between treatment groups were sustained and significantly different throughout the duration of the study (Fig. 1). The proportion of patients achieving both ADA and IDF HbA_{1c} targets in the pioglitazone group was significantly higher than that in the placebo group (Table 2).

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 the sulphonylurea plus metformin cohort from the PROactive study (*P < 0.0001).*

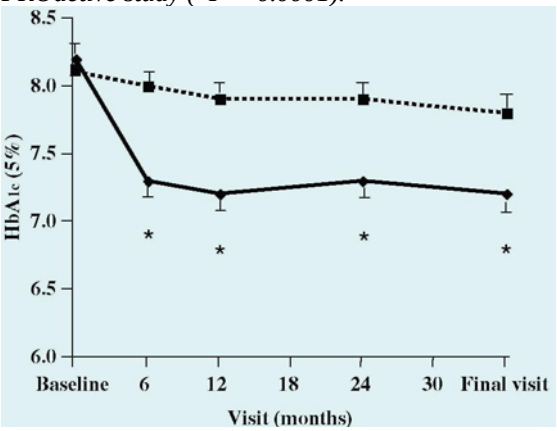


Table 2 *Mean changes in HbA_{1c}, proportion of patients reaching the ADA and IDF targets of HbA_{1c} and HbA_{1c} thresholds associated with a change in treatment regimen*

	Metformin + sulphonylurea	
	Pioglitazone (*n* = 654)	Placebo (*n* = 660)
Mean ± SD change in HbA_{1c} (%) (from baseline to final visit)	-0.9 ± 1.3	-0.3 ± 1.4†
Number and % of patients achieving HbA_{1c} < 7.0% (ADA)*	269 (46.4%)	152 (26.5%)†
Number and % of patients achieving HbA_{1c} < 6.5% (IDF)*	146 (25.2%)	65 (11.3%)†
Number and % of permanent insulin use at final visit	95 (15.5%)	190 (31.1%)†
Mean ± SD HbA_{1c} (%) at time of insulin initiation in patients who progressed to insulin use (*n*)	8.7 ± 1.6 (113)	8.9 ± 1.6 (204)

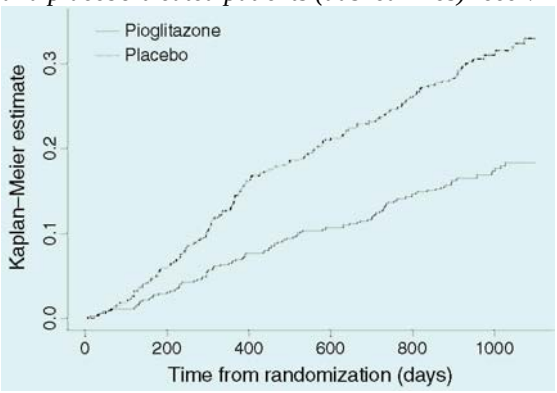
* The denominators used for the percentages are the numbers of patients with an HbA_{1c} measurement at final visit.
† $P < 0.001$ between-group difference. ADA, American Diabetes Association; HbA_{1c}, glycated haemoglobin; IDF, International Diabetes Federation; SD, standard deviation.

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

In this cohort of patients on dual metformin-sulphonylurea at baseline, pioglitazone significantly prolonged the time during which patients could be managed without the permanent addition of insulin to their treatment regimen. When pioglitazone was added to metformin-sulphonylurea combination therapy, the Kaplan-Meier rate

for insulin use was 16.1% (n = 134) compared with 31.1% (n = 257) when placebo was added [hazard ratio (HR) = 0.46; 95% CI = 0.38, 0.57; $P < 0.0001$; Fig. 2]. The mean HbA_{1c} above which insulin was started was 8.7% in the pioglitazone group and 8.9% in the placebo group (Table 2).

FIGURE 2 *Kaplan-Meier rates for time to permanent insulin use in pioglitazone-treated patients (solid lines) and placebo-treated patients (dashed lines) receiving metformin-sulphonylurea combination therapy at baseline.*



Changes from baseline in glucose-lowering medication (Table 3)

In the metformin plus sulphonylurea cohort, 16% of pioglitazone-treated patients had either metformin or sulphonylurea removed from their regimen and fewer patients (16%) had insulin added compared with 8 and 31%, respectively, in the placebo group.

Changes in the dose of oral glucose-lowering medication were more marked in the add-on pioglitazone group than in the addon placebo group, with significantly lower daily dosages of metformin and/or sulphonylurea after the addition of pioglitazone (Table 3). The mean daily insulin dose was lower with pioglitazone than with placebo in the metformin-sulphonylurea group (Table 3).

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

	Metformin + sulphonylurea	
	Pioglitazone (n = 613)	Placebo (n = 610)
Metformin only, n (%)	55 (9)	26 (4)
Sulphonylurea only, n (%)	37 (6)	22 (4)
Other oral monotherapies, n (%)	2 (0.3)	0 (0)
Metformin + sulphonylurea, n (%)	391 (64)	350 (57)
Other oral combinations, n (%)	17 (3)	18 (3)
No data available, n (%)	16 (3)	4 (1)
Mean daily insulin dose, U ± SD	35.9 ± 25.5	46.0 ± 29.5†
Mean metformin dose, mg/day ± SD (n)	1694 ± 617 (514)	1874 ± 646 (519)
Mean glibenclamide dose, mg/day ± SD (n)	10.3 ± 8.2 (116)	11.3 ± 5.0 (103)
Mean gliclazide dose, mg/day ± SD (n)	151.8 ± 97.7 (186)	154.2 ± 94.4 (173)
Mean glimepiride dose, mg/day ± SD (n)	3.4 ± 1.8 (122)	4.1 ± 1.5 (122)‡

† $P < 0.01$ between-group difference. ‡ $P < 0.001$ between-group difference. SD, standard deviation.

Safety and tolerability (Table 4)

A similar number of pioglitazone- and placebo-treated patients had serious adverse events. As HbA_{1c} was lower, more patients in the pioglitazone group had hypoglycaemia. However, the incidence of serious hypoglycaemia

was not higher in the pioglitazone group than in the placebo group (Table 4).

There were weight increases in the pioglitazone groups of 4.1 kg when added to metformin plus sulphonylurea dual therapy (vs. a decrease of 0.7 kg in the placebo group; $P < 0.001$ between-group difference). Oedema was reported more frequently in the pioglitazone group (Table 4). The rates of serious heart failure were slightly higher in the pioglitazone group than the placebo group. Fatal heart failure rates were low and similar between treatment groups.

The incidence of bone fractures was slightly higher when adding pioglitazone than when adding placebo to the baseline dual oral therapy [12 (1.8%) vs. 5 (0.8%)]. However, no serious fractures were noted in this metformin-sulphonylurea subgroup. There were no other between-group differences in adverse events.

Table 4 *Safety data*

	Metformin + sulphonylurea	
	Pioglitazone (*n* = 654)	Placebo (*n* = 660)
Any SAE, *n* (%)	298 (46)	318 (48)
Death, *n* (%)	38 (6)	45 (7)
Hypoglycaemia, *n* (%)	179 (27)	131 (20)†
Serious hypoglycaemia, *n* (%)	2 (0.3)	4 (0.6)
Oedema, *n* (%)	187 (29)	109 (17)‡
Serious heart failure, *n* (%)	40 (6)	33 (5)
Fatal heart failure, *n* (%)	5 (0.8)	5 (0.8)

† $P < 0.01$ between-group difference. ‡ $P < 0.001$ between-group difference. SAE, serious adverse event.

Discussion

Our *post-hoc* analysis of the effects of pioglitazone on gly-caemic control in patients on dual metformin-sulphonylurea therapy at baseline found that the glucose-lowering effects of pioglitazone were significantly better than placebo at final visit and were sustained across the 3 -year study period. Consequently, the percentages of patients reaching the target HbA_{1c} of < 7.0 or < 6.5% were higher, up to 50 and 100%, respectively, in the pioglitazone arm compared with the placebo arm at the final visit.

The IDF guidelines [11] (that the Investigators in PROactive were encouraged to use) recommend that insulin should be started when HbA_{1c} has deteriorated to > 7.5% after maximum attention to dietary control and oral glucose-lowering therapy. The ADA/European Association for the Study of Diabetes (EASD) consensus recommends initiation at HbA_{1c} > 7.0% [3], However, many patients are reluctant to consider insulin therapy because of side effects and worry about self-injections, safety and adherence issues [12]. In PROactive, the mean HbA_{1c} of patients on dual metformin-sulphonylurea therapy averaged 8.1-8.2% and, despite this poor glycaemic control, this important cohort of 1314 patients were not receiving insulin at baseline. We have shown here that intensifying a dual oral therapy regimen to a triple regimen by adding pioglitazone improves and sustains glycaemic control. In addition, intensifying the oral glucose-lowering combination regimens by adding pioglitazone resulted in an approximate 50% reduction in the initiation of permanent insulin therapy. It should be pointed out that, in the patients already on combined therapies, the HbA_{1c} threshold for switching to insulin therapy was high (8.7-8.9%) in PROactive, thus again well above the thresholds recommended in the various international guidelines [3,10,11,13]. These observations are in agreement with what is commonly observed in clinical practice and so-called 'therapeutic inertia' [14]. One might also hypothesize that some physicians were somewhat reluctant to shift to insulin in a trial using pioglitazone, as the combination of insulin plus a thiazolidinedione was not yet recognized in Europe.

Both treatment groups (pioglitazone and placebo) improved glycaemic control (as measured by HbA_{1c}), indicating that investigators were more aggressively treating to target HbA_{1c} during PROactive. The sustained HbA_{1c}-lowering effect of adding pioglitazone in PROactive is an encouraging finding as most studies, especially the UK Diabetes Prospective Study (UKPDS) [15] and ADOPT [16] showed a gradual deterioration of glucose control over time. Pioglitazone monotherapy has shown sustained glycaemic improvement over 2 years compared with gliclazide monotherapy [17]. Furthermore, the addition of pioglitazone to failing metformin

monotherapy provided sustained glycaemic control over 2 years, whereas control with gliclazide add-on to metformin deteriorated, suggesting that, when a patient is failing on metformin monotherapy, there may be an advantage to adding pioglitazone rather than a sulphonylurea [18]. Almost similar results were reported in an interim analysis at 18 months of the randomized open-label Rosiglitazone Evaluated for CardiacOutcomes and Regulation of glycaemia in Diabetes (RECORD) study providing a head-to-head assessment of rosiglitazone added to either a sulphonylurea or metformin as compared with the classical sulphonylurea-metformin combination [19]. The durability of glycaemic effect observed with pioglitazone in the high-cardiovascular-risk patient population in PROactive, both in the overall population [7] and in the present metformin-sulphonylurea subgroup, is supported by 4-year data from the ADOPT study, where rosiglitazone monotherapy slowed the progression of hyperglycaemia compared with metformin or glibenclamide in a lower cardiovascular-risk population as compared with the PROactive cohort [16].

Our results support the findings of a series of studies assessing triple oral glucose-lowering therapy in Type 2 diabetes [20-25]. It should be noted that these studies were open-label, of short duration, retrospective, were in a small patient number and the baseline HbA_{1c} was considerably higher than the 7.8% in PROactive. PROactive provides unique evidence of the beneficial effect of triple oral therapy, including a thiazolidinedione, in a large number of patients (654 patients were receiving triple therapy with pioglitazone, metformin and a sulphonylurea) followed in a double-blind fashion for a prolonged period of time (2.8 years).

The design of PROactive does not allow the comparison between adding pioglitazone to metformin-sulphonylurea combined therapy and adding basal insulin to oral agents, which was considered to be a better-validated therapy in the recent ADA-EASD consensus [3]. To date, there has been only one large-scale (n = 217), open-label randomized study of triple oral agent therapy vs. insulin add-on to metformin-sulphonylurea combination in Type 2 diabetes [26]. After 24 weeks, low-dose insulin glargine combined with a sulphonylurea and metformin resulted in similar HbA_{1c} improvements, except for greater reductions when baseline HbA_{1c} was > 9.5%, compared with add-on maximum-dose rosiglitazone. One smaller trial compared pioglitazone (uptitrated to 45 mg/day; n = 17) vs. glargine (n = 19) added to dual oral therapy (metformin plus sulphonylurea/meglitinide) [27]. After 16 weeks, the reduction in HbA_{1c} was slightly greater in the insulin glargine group than in the pioglitazone group (P = 0.05). The mechanisms of the glucose-lowering effect of basal insulin and thiazolidinedione are presumably different, although conflicting results about the respective effects on pancreatic B-cell function have been reported [27,28]. Further studies specifically designed to compare triple oral therapy with a basal insulin-based regimen would be helpful to compare the underlying mechanisms of action and to provide evidence-based recommendations in clinical practice.

Overall tolerability in the pioglitazone group (triple therapy regimen) was good, with only increases in oedema and weight, as seen in other trials with pioglitazone [17,18,29] and rosiglitazone [19,20]. A slightly higher incidence of non-serious bone fractures was observed in the pioglitazone arm of patients receiving metformin-sulphonylurea combined therapy, in agreement with previous data observed with rosiglitazone in the ADOPT trial [30]. The recent ADA-EASD consensus recognized that, specifically when hypoglycaemia is particularly undesirable, the addition of pioglitazone may be considered [3]. Very rare serious hypoglycaemia occurred on pioglitazone-metformin-sulphonylurea triple therapy and should most likely be attributed to the presence of a drug that stimulates insulin secretion such as a sulphonylurea [4]. The replacement of the sulphonylurea by a gliptin (dipeptidylpeptidase-4 antagonist), in order to reduce the risk of hypoglycaemia, deserves further assessment in future clinical trials on triple therapy [3,10]. Finally, there were small differences between groups with respect to serious heart failure (requiring hospital admission), but no clear patterns emerged. Fatal heart failure rates were low and similar between treatment groups [31].

In three recent clinical trials, Action to Control Cardiovascular Risk in Diabetes Study (ACCORD) [5], Veterans Affairs Diabetes Trial (VA-Diabetes) [6] and ADVANCE [32], which aimed at studying the effects of reducing HbA_{1c} to < 6.5% or 7.0% on cardiovascular events, the intensification of therapy combined several oral glucose-lowering agents and insulin in most patients [5,6]. None of these trials was able to separate the effects (positive or negative) related to insulin therapy per se or oral agents, including thiazolidinediones that were used in a large majority of patients (generally rosiglitazone in combination with insulin), especially in ACCORD and VA-Diabetes [5,6]. Ofnote, no reduction in cardiovascular events was observed in the intensifying groups as compared with the control groups receiving standard therapies in ADVANCE [32], ACCORD [5] and VA-Diabetes [6], despite HbA_{1c} differences of 0.6, 0.9 and 1.5% between the intensive vs. standard groups, respectively. In contrast, the 0.5% reduction observed when adding pioglitazone 45 mg in PROactive was accompanied by a non-significant 10% difference between the pioglitazone and placebo groups in the primary composite endpoint of disease- and procedure-related endpoints and a 16% difference for a secondary composite endpoint of all-cause mortality, non-fatal myocardial infarction or stroke (P = 0.027) [7,8].

The present *post-hoc* analysis demonstrates that the effect of pioglitazone on glycaemic control was better than placebo in the subgroup on dual metformin-sulphonylurea at baseline, despite a decrease in the use of these classical glucose-lowering agents. Many more patients reached HbA_{1c} targets after the addition of pioglitazone. In those patients not receiving insulin at baseline, the progression to permanent insulin use was reduced by 50% at 3 years with pioglitazone compared with placebo and better glycaemic control was seen with pioglitazone, despite a lower daily insulin dose. The overall safety profile of the triple therapy was good, even in this high-risk population. These findings support the use of pioglitazone in addition to dual metformin-sulphonylurea therapy to improve glucose control in patients with Type 2 diabetes. Whether the strategy of adding pioglitazone to previous oral agents is inferior to the addition of basal insulin, as recommended in the recent ADA-EASD consensus, remains to be determined.

Competing interests

AS, DJB, KB and OS are National Principal Investigators of the PROactive study. MHT and BC are on the PROactive Executive Committee. MHT worked for Lilly at the time the PROactive Study was conducted. DJB and BC have served as consultants to Takeda and received travel expenses and payments from Takeda for speaking at meetings.

References

1 Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus. Progressive requirement for multiple therapies (UKPDS 49). The UK Prospective Diabetes Study (UKPDS) Group, *J Am Med Assoc* 1999; 281: 2005-2012.

2 Scheen AJ, Lefèbvre PJ. Oral antidiabetic agents: a guide to selection. *Drugs* 1998; 55: 225-236.

3 Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zinman B; American Diabetes Association; European Association for the Study of Diabetes. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2009; 32: 193-203.

4 Krentz AJ, Bailey CJ. Oral antidiabetic agents. Current role in type 2 diabetes mellitus. *Drugs* 2005; 65: 385-411.

5 The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; 358: 2545-2559.

6 Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD *et al.* Glucose control and vascular complications in Veterans with type 2 diabetes. *N Engl J Med* 2009; 360: 129-139.

7 Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK *et al.* Secondary prevention of macro-vascular events in patients with type 2 diabetes: a randomized trial of pioglitazone. The PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events). *Lancet* 2005; 366: 1279-1289.

8 Betteridge DJ, DeFronzo RA, Chilton RJ. PROactive : time for a critical appraisal. *Eur Heart J* 2008; 29: 969-983.

9 PROactive. *Statistical Analysis Plan.* Available at http://www. proactive-results.com Last accessed 22 December 2008.

10 American Diabetes Association. Standards of medical care in diabetes—2009. *Diabetes Care* 2009; 32: S13-S61.

11 International Diabetes Federation (European Region), Brussels. A Desktop Guide to Type 2 Diabetes. *Diabet Med* 1999; 16: 716-730.

12 Peyrot M, Rubin RR, Lauritzen T, Skovlund SE, Snoek FJ, Matthews DR *et al.* Resistance to insulin therapy among patients and providers: results of the cross-national Diabetes Attitudes, Wishes, and Needs (DAWN) study. *Diabetes Care* 2005; 28: 2673-2679.

13 The American Association of Clinical Endocrinologists. *Medical Guidelines for the Management of Diabetes Mellitus: The AACE System of Intensive Diabetes Self-Management—2002 Update.* Available at http://www.aace.com/pub/pdf/guidelines/diabetes_ 2002.pdf Last accessed 22 December 2008.

14 Shah BR, Hux JE, Laupacis A, Zinman B, van Walraven C. Clinical inertia in response to inadequate glycemic control: do specialists differ from primary care physicians? *Diabetes Care* 2005; 28: 600-606.

15 UK Prospective Diabetes Study Group. UKPDS 28: a randomized trial of efficacy of early addition of metformin in sulfonylurea-treated type 2 diabetes. *Diabetes Care* 1998; 21: 87-92.

16 Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP *et al.* Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *New Engl J Med* 2006; 355: 2427-2443.

17 Tan MH, Baksi A, Krahulec B, Kubalski P, Stankiewicz A, Urquhart R *et al.* Comparison of pioglitazone and gliclazide in sustaining glycemic control over 2 years in patients with type 2 diabetes. *Diabetes Care* 2005; 28: 544-550.

18 Charbonnel B, Schernthaner G, Brunetti P, Matthews DR, Urquhart R, Tan MH, Hanefeld M. Long-term efficacy and tolerability of add-on pioglitazone therapy to failing monotherapy compared with addition of gliclazide or metformin in patients with type 2 diabetes. *Diabetologia* 2005; 48: 1093-1104.

19 Home PD, Jones NP, Pocock SJ, Beck-Nielsen H, Gomis R, Hanefeld M *et al.* Rosiglitazone RECORD study: glucose control outcomes at 18 months. *Diabet Med* 2007; 24: 626-634.

20 Bell DS, Ovalle F. Long-term glycaemic efficacy and weight changes associated with thiazolidinediones when added at an advanced stage of type 2 diabetes. *Diabetes Obes Metab* 2006; 8: 110-115.

21 Byrne J, Garg S, Vaidya A, Rajbhandari SM, Wallis SC. Efficacy of triple combination oral hypoglycaemic therapy using rosiglitazone, metformin and sulphonylurea in lowering HbA_{1c}. *Pract Diab Int* 2003; 20: 58-60.

22 Dailey GE III, Noor MA, Park JS, Bruce S, Fiedorek FT. Glycemic control with glyburide/metformin tablets in combination with rosiglitazone in patients with type 2 diabetes: a randomized, double-blind trial. *Am J Med* 2004; 116: 223-229.

23 Tran M, Davidson MB, Navar MD. Comparison of the glycemic effects of rosiglitazone and pioglitazone in triple oral therapy in type 2 diabetes. *Diabetes Care* 2006; 29: 1395-1396.

24 Orbay E, Sargin M, Sargin H, Gozu H, Bayramicli OU, Yayla A. Addition of rosiglitazone to glimepiride and metformin combination therapy in type 2 diabetes. *Endocr J* 2004; 51: *521-527.*

25 Roberts VL, Stewart J, Issa M, Lake B, Melis R. Triple therapy with glimepiride in patients with type 2 diabetes mellitus inadequately controlled by metformin and a thiazolidinedione: results of a 30-week, randomized, double-blind, placebo-controlled, parallel-group study. *Clin Ther* 2005; 27: 1535-1547.

26 Rosenstock J, Sugimoto D, Strange P, Stewart JA, Soltes-Rak E, Dailey G. Triple therapy in type 2 diabetes: insulin glargine or rosiglitazone added to combination therapy of sulfonylurea plus metformin in insulin-naïve patients. *Diabetes Care* 2006; 29: 554-*559.*

27 Dorkhan M, Frid A, Groop L. Differences in effects of insulin glargine or pioglitazone added to oral anti-diabetic therapy in patients with type 2 diabetes. What to add insulin glargine or pioglitazone? *Diabetes Res Clin Pract* 2008; 82: 340-345.

28 Ovalle F, Bell DSH. Effect of rosiglitazone versus insulin on the pancreatic beta-cell function of subjects with type 2 diabetes. *Diabetes Care* 2004; 27: 2585-2589.

29 Waugh J, Keating GM, Plosker GL, Easthope S, Robinson DM. Pioglitazone: a review of its use in type 2 diabetes mellitus. *Drugs* 2006; 66: 85-109.

30 Kahn SE, Zinman B, Lachin JM, Haffner SM, Herman WH, Holman RR *et al.* Rosiglitazone-associated fractures in type 2 diabetes: an analysis from A Diabetes Outcome Progression Trial (ADOPT). *Diabetes Care* 2008; 31: 845-851.

31 Erdmann E, Charbonnel B, Wilcox RG, Skene AM, Massi-Benedetti M, Yates J *et al.* Pioglitazone use and heart failure in patients with type 2 diabetes and preexisting cardiovascular disease: data from the PROactive Study (PROactive 08). *Diabetes Care* 2007; 30: 2773-2778.

32 The ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008; 358: 2560-2572.