

Pioglitazone Use in Combination with Insulin in the Prospective Pioglitazone Clinical Trial in Macrovascular Events Study (PROactive19)

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Objective: In this *post hoc* analysis, we examined insulin requirements and regimens, glycemic control, cardiovascular outcomes, and safety in the patients treated with insulin at baseline in the Prospective Pioglitazone Clinical Trial in Macrovascular Events study.

Design: The Prospective Pioglitazone Clinical Trial in Macrovascular Events study was a double-blind, placebo-controlled outcome study (mean follow-up 34.5 months) in 5238 high-risk patients with type 2 diabetes randomized to pioglitazone (force titrated to 45 mg) or placebo. One third of the total population (pioglitazone 864; placebo 896) were receiving insulin at baseline.

Results: A rapid and sustained decrease in insulin dose was observed with pioglitazone vs. a progressive increase with placebo. By study end, the mean insulin dose was lower with pioglitazone (42 vs. 55 U/d with placebo; $P < 0.0001$). The insulin regimen (number on insulin, need for multiple injections, and reduction in oral agents) had been simplified vs. placebo; nevertheless, a greater glycosylated hemoglobin reduction was observed with pioglitazone (-0.93%) vs. placebo (-0.45% ; $P < 0.0001$). At the final visit, insulin had been discontinued in 9% of pioglitazone vs. 2% of placebo patients ($P < 0.0001$). More insulin-resistant patients (defined as poorly controlled type 2 diabetes despite high doses of insulin) in the pioglitazone plus insulin group showed the greatest glycosylated hemoglobin decline. There were nonsignificant reductions with pioglitazone relative to placebo in the cardiovascular primary (hazard ratio 0.86; 95% confidence interval 0.71, 1.04; $P = 0.1198$) and main secondary (hazard ratio 0.85; 95% confidence interval 0.67, 1.08; $P = 0.1831$) end points in insulin-treated patients. The rates of overall heart failure, edema, and hypoglycemia were higher with pioglitazone [13.5 vs 10.5% ($P = 0.0489$); 30.8 vs. 18.2% ($P < 0.0001$); and 42.1 vs 29.0% ($P < 0.0001$), respectively], but there were no significant differences in serious events.

Conclusions: Pioglitazone use in combination with insulin resulted in a sustained improved glycemic control and allowed the treatment regimens to be simplified and the insulin doses reduced. (*J Clin Endocrinol Metab* 95: 0000–0000, 2010)

Type 2 diabetes is a progressive disease characterized by insulin resistance and diminished insulin secretion (1). Neither sulfonylureas nor metformin has a long-term effect to preserve β -cell function, and many patients with type 2 diabetes fail to reach target [glycosylated hemoglobin (HbA_{1c}) $<7.0\%$], despite combined metformin/sulfonylurea therapy (2–5). Hence, many patients with type 2 diabetes will eventually require insulin therapy.

Insulin therapy is commonly initiated as a once-daily basal insulin injection, with the addition of rapid-acting insulin with dose and number of injections based on the height of postprandial glucose excursions (6). A step-wise insulin optimization strategy frequently includes appropriate combination with oral agents to improve glycemic control and reduce the dose of insulin (7). Thiazolidinediones are oral glucose-lowering agents that reduce insulin resistance in liver and muscle (8). A number of studies have shown the benefits of a thiazolidinedione and insulin in combination (9–16).

Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) evaluated the effects of long-term treatment with pioglitazone on cardiovascular events in a population of 5238 patients with type 2 diabetes at high risk for macrovascular events (17). The primary measure of efficacy was time to analysis for a composite end point comprising seven cardiovascular-related events. Patients entered the study on their existing glucose-lowering therapies, which were continued. This paper reports an exploratory analysis evaluating long-term insulin requirements, insulin regimens, glycemic control, cardiovascular outcomes, and safety in the 1760 patients who entered PROactive on insulin therapy.

Subjects and Methods

Study design

PROactive was a randomized, double-blind, multicenter, placebo-controlled, parallel-group study in 5238 patients with type 2 diabetes and a history of macrovascular disease. Details of enrollment and trial conduct have been published (17). All participants provided written informed consent. A brief summary of the inclusion and exclusion criteria will be presented in the following paragraphs.

To be eligible for randomization, patients had to be adults (aged 35–75 yr, inclusive) with type 2 diabetes (defined as an HbA_{1c} level above the upper limit of normal, *i.e.* the local equivalent of 6.5% for a diabetes control and complications trial traceable assay) and an established history of macrovascular disease (17). Current use of pioglitazone or other thiazolidinediones, and insulin monotherapy for 2 wk or longer at any time in the previous 3 months excluded subjects from entry into the study. However, insulin-treated patients were eligible if insulin was combined with oral agents.

Patients were randomized to 45 mg pioglitazone or placebo in addition to the existing background glucose-lowering therapies (including diet and exercise). The dose of pioglitazone could be

increased or decreased within the range of 15–45 mg throughout the study: more than 90% of patients who remained on study medication received 45 mg pioglitazone. Treatment randomization was not stratified by existing glucose-lowering treatment, and all investigators were encouraged to adjust and/or add glucose-lowering agents to achieve and maintain 1999 International Diabetes Federation (IDF) targets ($HbA_{1c} <7.0\%$). Therefore, it was anticipated that background treatment would change over the course of the study. Patients also continued with existing therapy for hypertension, dyslipidemia, and thrombotic conditions to reduce cardiovascular risk (adjusted again using the 1999 IDF guidelines).

Efficacy end points

In the main PROactive study, the primary end point was the time to the first occurrence of cardiovascular events or death; these data have been published (17).

This manuscript reports *post hoc* data from the patients who were receiving insulin at baseline. The analyses performed were changes in the percentages of patients remaining on insulin therapy *vs.* switching to oral agents/discontinuing insulin; changes in the insulin regimens (*i.e.* in number of injections); changes in mean daily insulin dosage; glycemic control (HbA_{1c} over time), cardiovascular end points; and safety data in patients receiving insulin therapy at baseline. We also conducted an analysis of the glycemic control and insulin dose changes in patients categorized as more insulin-resistant (defined as baseline insulin dose and HbA_{1c} both median or greater) compared with less insulin-resistant patients (defined as baseline insulin dose and HbA_{1c} both less than median) as a potential index of insulin sensitivity. The median insulin dose at baseline was 42 U/d and the median HbA_{1c} was 8.3%.

Statistical methods

The main statistical and analytical methods have been described previously (17). The data presented here are from the intention-to-treat population of patients (defined as all randomized patients who subsequently took at least one dose of study medication) who were receiving insulin at the time of entry into the study.

Concomitant glucose-lowering medication was recorded at baseline and at each subsequent visit by class (insulin, metformin, sulfonylureas, others) and dose. Statistical methods for summarizing concomitant glucose-lowering medication considered the percentage of patients (in the pioglitazone and placebo treatment groups) receiving each type of medication. Mean dose by visit, change from baseline in percentage of patients with a medication dose increase or decrease, and percentage of patients newly starting, continuing, stopping, or decreasing medication were considered.

Changes from baseline to final visit in HbA_{1c} were calculated for each of two cohorts (patients receiving and patients not receiving insulin) and compared by treatment group. For HbA_{1c} , the differences between treatment groups and changes from baseline were examined by visit and compared using ANOVA. An area under the curve measure (linear interpolation and adjustment for duration of exposure) was used as an aggregate measure of HbA_{1c} . 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

At baseline, one third of the total study population [$n = 1760$ patients; 864 (33.2%) in the pioglitazone group and 896 (34.0%) in the placebo group] was receiving insulin. There were some differences in baseline data between those receiving and those not receiving insulin (Table 1).

Although there were differences in baseline characteristics between the patients with *vs.* without insulin, there were no important differences between patient characteristics and baseline laboratory data between the insulin-treated patients in the pioglitazone group and those in the placebo group. Similarly, there were no relevant differences between non-insulin-treated patients in the pioglitazone group *vs.* the placebo group (Table 1).

At baseline, the mean daily insulin dose was 46.6 U and the mean number of insulin injections per day was 2.3 (23.4% were receiving one injection; 47.6%, two injections; and 29.0%, three or more injections). There were no important differences in insulin doses or regimens between the pioglitazone and placebo groups (data not shown).

At baseline, concomitant medications in the insulin-treated groups were: metformin, 52.9%; sulfonylurea, 24.3%; metformin plus sulfonylurea, 12.0%; other oral agents as monotherapy or combination, 10.8%. These percentages were similar in the pioglitazone and placebo groups.

Glycemic control

Both treatment groups showed an improvement in glycemic control. Mean HbA_{1c} levels decreased from 8.4 to 7.4% in the pioglitazone group and from 8.5 to 8.1% in the placebo group ($P < 0.001$ *vs.* baseline for both groups; $P < 0.0001$ between groups at all time points; Fig. 1A). The improvement in HbA_{1c} with pioglitazone was independent of the baseline insulin regimen (*i.e.* the number of injections or daily dose of insulin). The HbA_{1c} decreases from baseline to the final visit with pioglitazone *vs.* placebo were 0.84 *vs.* 0.22% for patients receiving one; 1.02 *vs.* 0.44% for patients receiving two; and 0.82 *vs.* 0.56% for patients receiving three insulin injections at baseline. At end point, the proportion of patients achieving good glycemic control (mean HbA_{1c} $\leq 7.0\%$) was 41.7% ($n = 308$) with pioglitazone *vs.* 24.3% with placebo ($n = 188$).

Changes in doses of insulin

In the patients who were on insulin at baseline, the mean daily dose of insulin decreased in the pioglitazone

group, beginning at the first study visit and continued throughout the study (Fig. 1B). The mean daily insulin dose initially remained stable in the placebo group, but by month 6, the daily insulin dose steadily increased throughout the study. By final visit, the mean insulin dose had decreased from 46.5 U at baseline to 42.1 U/d in the pioglitazone group compared with an increase from 46.7 U to 54.9 U/d in the placebo group ($P < 0.0001$ between group difference). These differences in insulin dose between pioglitazone and placebo were shown for any insulin regimen.

Changes in treatment regimens

Background treatments for diabetes were not controlled for and investigators were encouraged to treat to 1999 European IDF glycemic goals. As expected, the background glucose-lowering treatments shifted throughout the course of the study. There were no major differences between groups for the use of oral agents combined with insulin over time (Table 2). Nevertheless, significantly more insulin-treated patients receiving pioglitazone discontinued concomitant oral agents (such as metformin or a sulfonylurea) than those receiving placebo. The percentage of patients who discontinued insulin therapy from baseline to the end of the study was greater in the pioglitazone group than the placebo group [8.6% ($n = 74$) *vs.* 1.7% ($n = 15$) $P < 0.0001$]. Moreover, the number of insulin injections per day increased significantly on placebo compared with pioglitazone. The number of insulin injections per day increased significantly in placebo patients treated with one, two, or three or more injections per day compared with the pioglitazone group (Table 3). Of note, the percentage of patients receiving two or three or more injections per day at final visit decreased significantly in the pioglitazone group ($P < 0.01$).

Changes in doses or regimen of insulin according to insulin sensitivity

In the patients categorized as less insulin resistant at baseline (according to their insulin doses and HbA_{1c} both less than median), the mean baseline HbA_{1c} was 7.3% and insulin dose was 24 U/d *vs.* 9.6% and 69 U/d in the more insulin-resistant patients (according to their insulin doses and HbA_{1c} both median or greater). These two groups appear to have different insulin needs and behave differently on pioglitazone.

In the less insulin-resistant patients, the insulin dose increased from 24 to 34 U in the placebo group, with no increase of insulin dose in the pioglitazone group. HbA_{1c} was more or less stable, with a slight 0.3% decline in the pioglitazone group, whereas it increased slightly in the placebo group by 0.2% ($P < 0.0001$). In the more insulin-resistant patients, HbA_{1c} decreased by 1.3% from 9.6 to 8.3% at final visit.

TABLE 1. Patient characteristics by treatment in those with type 2 diabetes and cardiovascular disease receiving insulin vs. those not receiving insulin at baseline in the PROactive study

	Receiving any combination of insulin		Not receiving insulin	
	Pioglitazone (n = 864)	Placebo (n = 896)	Pioglitazone (n = 1741)	Placebo (n = 1737)
Patient characteristics				
Male, n (%)	503 (58.2%)	547 (61.0%)	1232 (70.8%)	1181 (68.0%)
Caucasian, n (%)	854 (98.8%)	887 (99.0%)	1710 (98.2%)	1713 (98.6%)
Age (yr)	61.7 ± 7.5	61.2 ± 7.5	62.0 ± 7.6	61.8 ± 7.9
Duration of diabetes (yr)	12.8 ± 7.1	13.1 ± 7.1	7.8 ± 6.2	7.8 ± 6.4
Body mass index (kg/m ²)	31.6 ± 4.7	31.9 ± 4.7	30.3 ± 4.7	30.6 ± 4.8
History of hypertension, n (%)	658 (76.2%)	695 (77.6%)	1289 (74.0%)	1310 (75.4%)
Smoking				
Current, n (%)	93 (10.8%)	103 (11.5%)	247 (14.2%)	278 (16.0%)
Past, n (%)	381 (44.1%)	392 (43.8%)	818 (47.0%)	767 (44.2%)
Microvascular disease, n (%) ^a	544 (63.0%)	537 (59.9%)	569 (32.7%)	539 (31.0%)
Laboratory values				
HbA _{1c} (%)	8.4 ± 1.4	8.5 ± 1.4	7.9 ± 1.4	7.9 ± 1.4
Systolic blood pressure (mm Hg)	144 ± 17.6	144 ± 17.6	143 ± 17.8	143 ± 17.9
Diastolic blood pressure (mm Hg)	82 ± 9.8	82 ± 9.7	83 ± 10.0	84 ± 9.3
Triglycerides [mg/dl (mmol/liter)]	207 ± 212 (2.34 ± 2.4)	198 ± 159 (2.24 ± 1.8)	193 ± 142 (2.18 ± 1.6)	199 ± 159 (2.25 ± 1.8)
HDL cholesterol [mg/dl (mmol/liter)]	45.2 ± 11.6 (1.17 ± 0.3)	44.8 ± 11.6 (1.16 ± 0.3)	44.4 ± 11.6 (1.15 ± 0.3)	44.8 ± 11.6 (1.16 ± 0.3)
LDL cholesterol [mg/dl (mmol/liter)]	114 ± 38.6 (2.96 ± 1.0)	114 ± 38.6 (2.94 ± 1.0)	114 ± 34.7 (2.95 ± 0.9)	115 ± 38.6 (2.99 ± 1.0)
LDL cholesterol to HDL cholesterol ratio	2.68 ± 1.1	2.67 ± 1.1	2.68 ± 0.9	2.69 ± 1.0

Values represent the mean ± SD unless otherwise specified. HDL, High-density lipoprotein; LDL, low-density lipoprotein.

^a Investigator-diagnosed retinopathy, nephropathy, and neuropathy.

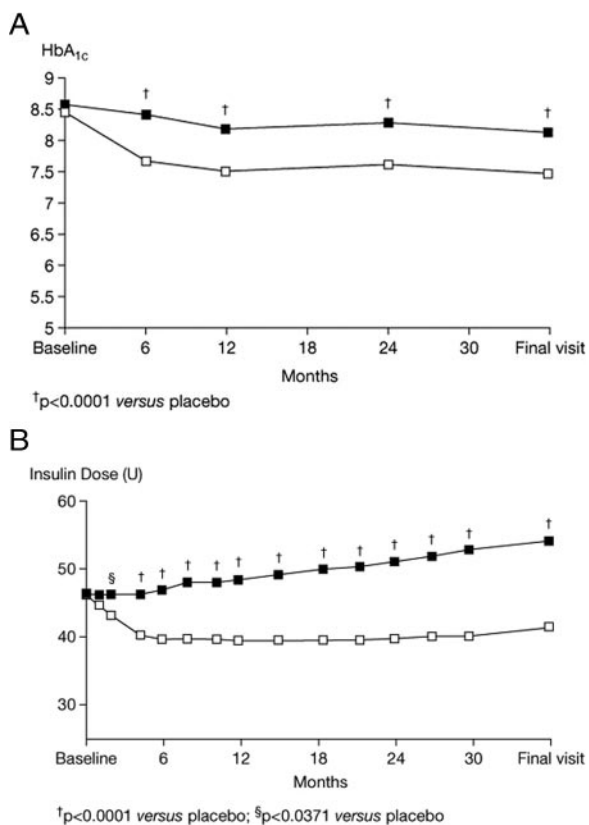


FIG. 1. Changes in glycemic control (A) and insulin dose (B) over time with pioglitazone or placebo in patients receiving insulin at baseline (open squares, pioglitazone; closed squares, placebo).

The decrease in HbA_{1c} in these patients was largely accounted for by an improvement in the pioglitazone-treated patients, with a mean decrease from 9.5 to 7.9%, despite a mean decrease in insulin units of 11 U/d from 68 to 57 U/d. In the placebo group, the decrease in HbA_{1c} was significantly less (from 9.6 to 8.6%), despite a mean increase in insulin dose of 7 U from 69 to 76 U/d (both $P < 0.001$ between treatment group difference), associated with the intensification of the insulin regimen.

Cardiovascular primary and main secondary end points

As in the total PROactive patient population (17), there was a consistent trend of benefit with pioglitazone in the insulin-treated patients with respect to the primary end

point (event rate of 20.7% with pioglitazone vs. 24.3% with placebo; hazard ratio 0.86; 95% CI 0.71, 1.04; $P = 0.1198$; Fig. 2A). There was a similar nonsignificant 15% risk reduction with pioglitazone in the main secondary end point, a composite of death, nonfatal myocardial infarction, and stroke (event rate of 13.5% with pioglitazone vs. 15.8% with placebo; hazard ratio 0.85; 95% CI 0.67, 1.08; $P = 0.1831$; Fig. 2B).

Safety and tolerability

There were more serious adverse events (both end point and non-end point events) in patients treated with insulin (52.2%) vs. those not receiving insulin (44.9%; $P < 0.0001$). Heart failure rates were significantly higher in insulin-treated (12.0%) than non-insulin-treated patients (7.7%; $P < 0.0001$). There were no significant differences in rates of serious heart failure (defined as requiring hospitalization or prolongation of a hospitalization stay, fatal or life threatening, or resulted in persistent significant disability or incapacity; 5.7% in the insulin group and 4.5% in the no insulin group) or of fatal heart failure (1.3% in the insulin group and 0.7% in the no insulin group). As expected, there were higher rates of all hypoglycemia (35.5 vs. 18.4%; $P < 0.0001$), serious hypoglycemia (1.3 vs. 0.3%; $P < 0.001$), and edema (24.4 vs. 20.2%; $P = 0.005$) in the insulin group than the no-insulin group.

The relative occurrence of adverse events in the pioglitazone group compared with the placebo group was similar in these insulin-treated patients as in the total PROactive population (17). Serious adverse events occurred in 434 patients (50.2%) in the pioglitazone group and 484 (54.0%) in the placebo group ($P = NS$). There were no differences in the safety profiles in the pioglitazone and placebo groups (with or without other treatments) in those receiving insulin at baseline, with the exception of edema and hypoglycemia (Table 4). The rates of hypoglycemia were the same, irrespective of baseline sulfonylurea use (Table 4).

There were no significant differences in the incidence of serious (*i.e.* requiring hospitalization) or fatal heart failure between the pioglitazone and placebo groups in the pa-

TABLE 2. Glucose-lowering regimens by treatment at baseline and final visit in those receiving insulin at baseline

	Pioglitazone		Placebo	
	Baseline (n = 864)	Final visit (n = 783)	Baseline (n = 896)	Final visit (n = 811)
Insulin only	5 (0.6%)	104 (13.3%)	8 (0.9%)	127 (15.7%)
Insulin + metformin	456 (52.8%)	357 (45.6%)	475 (53.0%)	405 (49.9%)
Insulin + sulfonylurea	209 (24.2%)	119 (15.2%)	219 (24.4%)	125 (15.4%)
Insulin + other oral therapy	55 (6.4%)	39 (5.0%)	48 (5.4%)	30 (3.7%)
Insulin + metformin + sulfonylurea	105 (12.2%)	72 (9.2%)	107 (11.9%)	81 (10.0%)
Insulin + other oral combinations	34 (3.9%)	18 (2.3%)	39 (4.4%)	28 (3.5%)

TABLE 3. Change in dose of insulin from baseline to final visit according to the number of injections per day at baseline

	Pioglitazone		Placebo		Between-group difference
	Baseline (n = 864)	Final visit (n = 783)	Baseline (n = 896)	Final visit (n = 811)	
One injection, daily dose (U)	20.4	26.3	19.6	34.1	$P = 0.002$
Tywo injections, daily dose (U)	48.2	41.6	47.4	53.2	$P < 0.0001$
Three or more injections, daily dose (U)	64.9	54.4	66.9	72.6	$P < 0.0001$

tients who were receiving any insulin combination at baseline (Table 4).

There was a 4.2-kg increase in body weight from baseline to final visit in insulin-treated patients in the pioglitazone group, whereas there was a decrease of 0.1 kg from baseline to final visit in the placebo group ($P < 0.0001$ between group difference). Most of the weight gain with pioglitazone occurred in the first year and weight plateaued by the end of the second year. The increase in body weight in insulin-treated patients receiving pioglitazone were correlated ($r = -0.12$, $P = 0.0012$) with the decline in HbA_{1c}.

Discussion

Insulin optimization strategy in type 2 diabetes includes insulin intensification with multiinjections, titration of insulin doses, and combination with oral drugs (6). Insulin sensitizers, such as thiazolidinediones, are a good option from the mechanistic point of view and have been proved to work in many short-term studies of insulin-requiring patients with type 2 diabetes, for troglitazone (9–12), rosiglitazone (13), and pioglitazone (14–16). However, large long-term studies are needed both for long-term efficacy and safety issues. This is why this exploratory analysis of the large cohort of 1760 patients entering PROactive on insulin therapy may be of interest.

This analysis showed an improved glycemic control in pioglitazone-treated compared with placebo-treated pa-

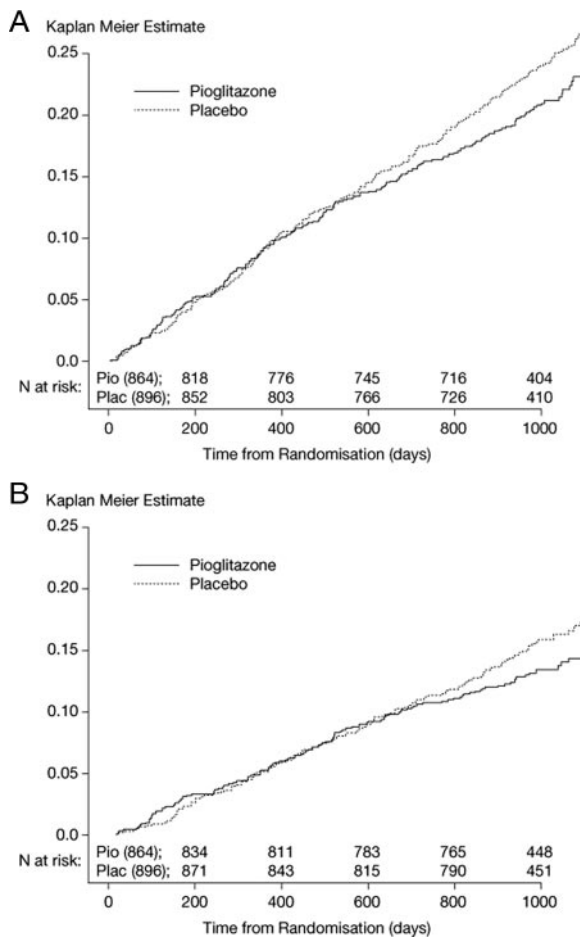


FIG. 2. Kaplan-Meier curve of time to the primary end point (A) and the main secondary end point (B) in the subgroup of patients treated with insulin at baseline.

TABLE 4. Adverse events occurring in insulin-treated patients

	Receiving any combination of insulin	
	Pioglitazone n (%)	Placebo n (%)
Serious adverse events	434 (50.2%)	484 (54.0%)
End point event	141 (16.3%)	172 (19.2%)
Non-end point event	395 (45.7%)	439 (49.0%)
Any report of heart failure	117 (13.5%) ^a	94 (10.5%)
Serious heart failure ^b	54 (6.3%)	47 (5.2%)
Fatal heart failure	12 (1.4%)	10 (1.1%)
Any report of hypoglycemia (all groups)	364 (42.1%) ^c	260 (29.0%)
Serious ^b	16 (1.9%)	7 (0.8%)
Nonserious	358 (41.4%) ^c	253 (28.2%)
Any report of hypoglycemia (baseline sulfonylurea group)	134 (40.6%) ^c	96 (27.7%)
Serious ^b	5 (1.5%)	3 (0.9%)
Nonserious	129 (39.1%) ^c	93 (26.9%)
Edema	266 (30.8%) ^c	163 (18.2%)
Serious ^b	4 (0.5%)	2 (0.2%)
Nonserious	265 (30.7%) ^c	163 (18.2%)
Serious pneumonia ^b	25 (2.9%)	21 (2.3%)

^a $P < 0.05$ vs. placebo.

^b Defined as requiring hospitalization or prolongation of a hospitalization stay, fatal or life-threatening, or resulted in persistent significant disability or incapacity.

^c $P < 0.001$ vs. placebo.

tients. Both treatment groups (pioglitazone and placebo) improved glycemic control in this subgroup of patients receiving insulin at baseline. However, pioglitazone provided sustained and significantly better glycemic control than placebo at all time points, irrespective of baseline insulin regimen. This benefit was sustained for the duration of the study (mean 34.5 months). Thus, the statistically significant and sustained benefit of pioglitazone *vs.* placebo on glycemic control that was observed in the total PROactive patient population persisted in this group of insulin-treated patients. A higher percentage of pioglitazone-treated patients discontinued insulin therapy, 8.6 *vs.* 1.7%. Whereas the insulin regimen intensified and the mean daily insulin dose increased in the placebo group, there was a decrease in mean daily insulin dose and a simplification of the glucose-lowering regimen in the pioglitazone group. There were minor changes in the number of insulin injections in the pioglitazone group along with a shift to a less intensified regimen with respect to the use of concomitant oral drugs in both groups, but this was more marked in the pioglitazone group. This suggests that there was no need for insulin intensification, whereas there was a major intensification of the insulin regimen in the placebo group, more patients on multiple injections, and higher doses of insulin (in line with protocol guidelines to achieve glycemic targets). This improvement in glycemic control for simpler insulin regimens and lower doses of insulin was shown with pioglitazone, despite an increase in body weight. Moreover, this increase in body weight in insulin-treated patients receiving pioglitazone was correlated with the decline in HbA_{1c}.

To achieve an HbA_{1c} less than 7.0%, most patients require high-dose (>60 U/d) insulin therapy (18, 19). However, many insulin-resistant patients remain poorly controlled, even when receiving high doses of insulin (19, 20). Of note, the improvement in glycemic control (HbA_{1c} <7.0%) with pioglitazone was observed despite a reduction in insulin dose. This supports the use of an insulin-sensitizing agent to optimize insulin action (8, 21) and reduce the daily insulin dose. It is interesting to note that patients with baseline insulin dose and HbA_{1c} both greater than median responded better to pioglitazone. In these patients with a high baseline HbA_{1c}, 9.6% or greater, despite relatively high insulin doses, 69 U/d or greater, the HbA_{1c} decrease shown in the placebo group was logically related to the intensification of insulin treatment, whereas the greater HbA_{1c} decrease (–1.65 *vs.* –0.92%) on pioglitazone was obtained without any change in the insulin regimen and with lower doses of insulin, which suggests that this improvement is related to the insulin-sensitizing action of the drug. Thus, poorly controlled, insulin-treated patients appear to respond well to the addition of piogli-

tazone. It could be argued that insulin doses mainly reflect the physician's approach more than insulin needs; thus, we used a combined way using both insulin doses and HbA_{1c} greater than the median to define these patients in whom adding pioglitazone to insulin was the most effective. The mechanism by which thiazolidinediones are effective involves reduced liver fat and enhanced hepatic insulin sensitivity, as recently shown in a small group of patients with a high HbA_{1c}, despite very high mean doses of insulin greater than 200 U/d (20).

However, aggressive insulin therapy in type 2 diabetes prompts safety concerns regarding the effects of supra-physiological doses of insulin, including hypoglycemia, weight gain, edema, and heart failure (22–24), as recently evidenced in the ACCORD study (25). We also found that there were more events of heart failure, all hypoglycemia, serious hypoglycemia, and edema in patients treated with insulin *vs.* those not receiving insulin, but there were no significant differences in rates of serious or of fatal heart failure. There were higher rates of edema and hypoglycemia and more weight gain in pioglitazone plus insulin group *vs.* the placebo plus insulin group. The rates of hypoglycemia were not affected by baseline sulfonylurea use. A key result of this exploratory analysis of PROactive is to show that the cardiovascular trend to benefit conferred by pioglitazone in the total PROactive population (17) persisted in the insulin-treated patients.

The lipid profile and the blood pressure profile improvements on pioglitazone compared with placebo were similar in these insulin-treated patients to those published for the whole PROactive study population (data not shown).

It should be noted that this analysis is limited by its *post hoc* nature.

The patients included in PROactive were at high risk of macrovascular disease. The patients included in this analysis appeared to be at even greater risk, including greater risk of heart failure, as evidenced by the number of end point events and as reflected by the baseline characteristics: patients who were on insulin at baseline had a higher HbA_{1c} and a longer duration of diabetes, and a greater percentage of patients had microvascular complications than those not receiving insulin. To the contrary, there was a tendency toward a reduction in recurrent cardiovascular events and deaths in patients in the insulin and pioglitazone group.

As expected, the rates of hypoglycemia, edema, and heart failure were higher in diabetic patients receiving insulin than in those not receiving insulin in our analysis of PROactive data. Serious heart failure occurred more frequently in patients who were insulin treated compared with non-insulin-treated patients, irrespective of piogli-

zone or placebo. This reflects the well-known observation that insulin-treated patients are at higher risk due to the longer duration of diabetes and more severe underlying cardiovascular disease. Importantly, the addition of pioglitazone in these insulin-treated patients did not show any difference compared with what was published for the whole PROactive study population (17): the rate of serious heart failure was numerically, but nonsignificantly, higher compared with the placebo group, whereas the relative increase of serious heart failure with pioglitazone compared with placebo was not significantly greater in these patients who were receiving any insulin combination at baseline (6.3% in the pioglitazone group and 5.2% in the placebo group) than in the total PROactive population (5.7% in the pioglitazone group and 4.1% in the placebo group). As with the total PROactive population, the rates of fatal heart failure were similar between groups.

In conclusion, in the insulin-treated patients in PROactive, pioglitazone use resulted in simplified insulin regimens, lower doses of insulin and better glycemic control over time, with a similar cardiovascular and safety profile as in the whole study population.

Acknowledgments

This study was designed by the International Steering Committee, who approved the protocol and amendments. The PROactive study is registered as an international standard randomized controlled trial (ISRCTN NCT00174993).

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