Pioglitazone in Combination with Insulin—An Overview of Results from PROactive

Bernard Charbonnel, MD

Professor of Endocrinology and Metabolic Diseases, University of Nantes
and Department of Internal Medicine, Endocrinology and Diabetes, Hôtel Dieu, University Hospital of Nantes

Abstract

Pioglitazone provides one of several add-on therapy options for patients with unsatisfactory glycemic control treated with insulin. Although pioglitazone has the beneficial feature of low hypoglycemia risk, it has an overlapping adverse event profile with insulin in terms of edema (with the potential to exacerbate heart failure) and weight gain, leading to possible concern over their use in combination. Fortunately, subgroup analyses from the Prospective pioglitazone clinical trial in macrovascular events (PROactive) have provided valuable insights into the efficacy and safety profile of pioglitazone in patients on established insulin therapy. Pioglitazone improved glycemic control and lipids, while enabling patients to reduce their insulin requirements. With the combination, edema and weight were predictable with no excess exacerbation of heart failure. Importantly, pioglitazone had a good macrovascular safety profile (with a trend toward benefit), consistent with the overall population. This article provides an overview of the results from the insulin-treated subgroup in PROactive and highlights some of the clinical implications for pioglitazone–insulin combination therapy.

Keyword

Type 2 diabetes, pioglitazone, insulin, glycemic control, tolerability, safety, edema, weight gain, heart failure, cardiovascular disease, outcomes

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Correspondence: Bernard Charbonnel, MD, Clinique d'Endocrinologie, Maladies Métaboliques et Nutrition, CHU de Nantes, Hôtel Dieu, 1 place Alexis Ricordeau, 44093 Nantes Cedex 1, France. E: bernard.charbonnel@univ-nantes.fr

Many patients with type 2 diabetes require insulin therapy during the course of their disease, either as monotherapy or as an addition to existing oral glucose-lowering therapy.[1–3] However, this might not always be sufficient to maintain adequate glycemic control, and additional therapies might therefore be required.[1–3] The oral glucose-lowering drug pioglitazone is one of several options available for add-on therapy in patients whose glycemic control remains unsatisfactory on insulin treatment regimens.[2–7] Randomized controlled trials (RCTs) have shown that pioglitazone provides significant improvements in glycemic control and lipid profile in insulin-treated patients with type 2 diabetes.[8–13] In one recent meta-analysis of four efficacy/safety RCTs, the addition of pioglitazone to insulin therapy provided a 1.22 % reduction in glycated hemoglobin (HbA_{1c}) from baseline, as well as a 1.63 mmol/l improvement in fasting plasma glucose, a 0.21 mmol/l improvement in high-density lipoprotein (HDL) cholesterol, and a 0.05 mmol/l improvement in triglycerides.[13] The main adverse events associated with pioglitazone in these insulin-treated patients included edema, weight gain, and hypoglycemia.[12,13] Edema and weight gain are well-characterised adverse events associated with pioglitazone use regardless of background therapy, whereas pioglitazone use *per se* is generally associated with a low risk of hypoglycemia.[14,15] Improved glycemic control provided by pioglitazone probably contributes to any increased risk of insulin-induced hypoglycemia and, at least to some extent, weight gain.[14,15]

The Prospective pioglitazone clinical trial in macrovascular events (PROactive) was a landmark cardiovascular (CV) outcomes study looking at the impact of pioglitazone on macrovascular endpoints in high-CV-risk patients with type 2 diabetes.[16,17] Since publication of the main results in 2005, PROactive has continued to provide a wealth of information on the CV safety/efficacy profile and metabolic effects of pioglitazone via a range of predefined and post-hoc analyses.[17–28] Recently, several analyses have looked specifically at the subgroup of patients entering the study on insulin therapy, thus adding considerably to the existing data set on pioglitazone–insulin combination therapy.[26–28]

This article provides an overview of the key metabolic effects, impact on CV outcomes, and safety/tolerability profile of pioglitazone among insulin-treated patients in PROactive and briefly discusses the clinical implications of these findings. Relevant publications were identified via PubMed searches using the terms 'pioglitazone AND insulin AND (combination OR addition OR concomitant OR proactive)'.

Table 1: Characteristics of Participants in PROactive According to Baseline Insulin Use

	Receiving Insulin at Baseline		Not Receiving Insulin at Baseline	
	Pioglitazone (n=864)	Placebo (n=896)	Pioglitazone (n=1,741)	Placebo (n=1,737)
Male (n)	503 (58.2 %)	547 (61.0 %)	1,232 (70.8 %)	1,181 (68.0 %)
Age (years)	61.7±7.5	61.2±7.5	62.0±7.6	61.8±7.9
Duration of diabetes (years)	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
HbA_{1c} (%)	8.4±1.4	8.5±1.4	7.9±1.5	7.9±1.4
Microvascular disease (n)	544 (63.0 %)	537 (59.9 %)	569 (32.7 %)	539 (31.0 %)

PROactive = Prospective pioglitazone clinical trial in macrovascular events. Data are mean ± standard deviation or n (%). HbA_{1C} = glycated hemoglobin. Source: adapted from Charbonnel B, et al., 2010.[27]

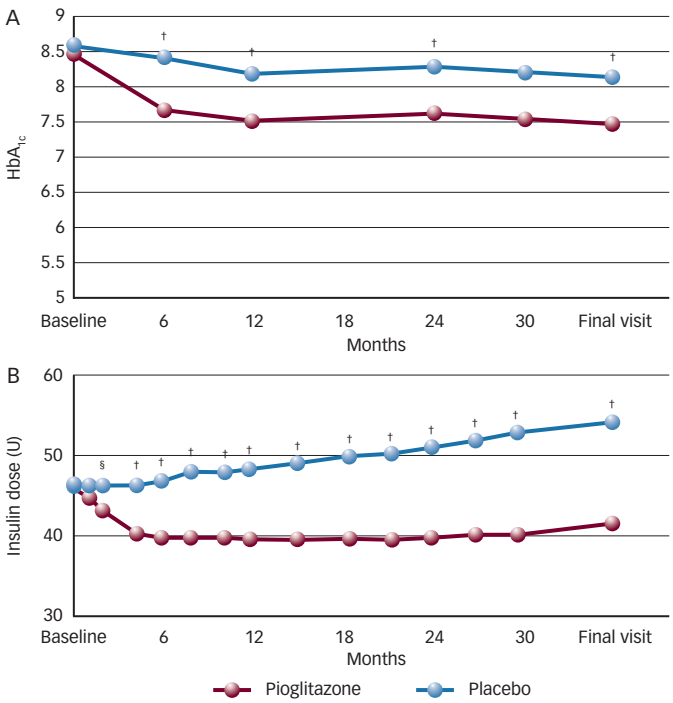
PROactive—Study Characteristics and Main Overall Findings

PROactive was a randomized, double-blind, multicenter, placebo-controlled, parallel-group study in 5,238 patients with type 2 diabetes and pre-existing macrovascular disease.[16] The study looked at the impact of a single glucose-lowering agent (pioglitazone) on macrovascular outcomes compared with placebo when added to background guideline-driven therapy (glucose-lowering and CV medications), thus providing a relatively unambiguous assessment of the CV and metabolic effects of pioglitazone. PROactive remains (at the time of writing) the only completed placebo-controlled outcomes study looking at the effects of a single glucose-lowering drug in type 2 diabetes, although many similar studies are now ongoing (see www.clinicaltrials.gov) in the light of recent regulatory guidelines on the CV safety of glucose-lowering drugs.[29,30] PROactive also remains the only completed outcomes study of glucose-lowering therapy exclusively in a high-risk population with established macrovascular disease.

PROactive was an event-driven study with an average observation period of 34.5 months. The primary endpoint was a complex composite of macrovascular events, including all-cause mortality, myocardial infarction (MI; including silent MI), stroke, acute coronary syndrome (ACS), endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle. In the final analysis for the overall population, there was a trend toward reduced risk in the pioglitazone group for this primary endpoint (hazard ratio [HR]=0.90, 95 % confidence interval [CI] [0.80, 1.02], p=0.095). However, there was a significant risk reduction for the predefined main secondary composite outcome of all-cause mortality, MI (excluding silent MI) and stroke (HR=0.84, 95 % CI [0.72, 0.98], p=0.27). Subsequent analyses also showed significant risk reductions for a host of other composite macrovascular endpoints, as well as significant reductions in recurrent MI and recurrent stroke.[18,20,22] Analyses of metabolic effects showed that pioglitazone provided a median -0.8 % improvement in HbA_{1C}, which was stable throughout the study and significantly greater than the 0.3 % reduction seen in the placebo group.[16] There were also significant improvements in HDL cholesterol, triglycerides, and the low-density lipoprotein (LDL):HDL ratio compared with placebo.[16]

When PROactive was designed, edema (not associated with other signs of heart failure) and heart failure were classified as adverse events of special interest. The incidence of edema was known to be increased among thiazolidinedione-treated patients and edema (rather than any direct effect on cardiac function) had been implicated as a potential driver of heart failure events reported in previous studies with this drug

Figure 1: Glycemic Control (A) and Insulin Dose (B) Over Time with Pioglitazone or Placebo in Patients Receiving Insulin at Baseline in PROactive

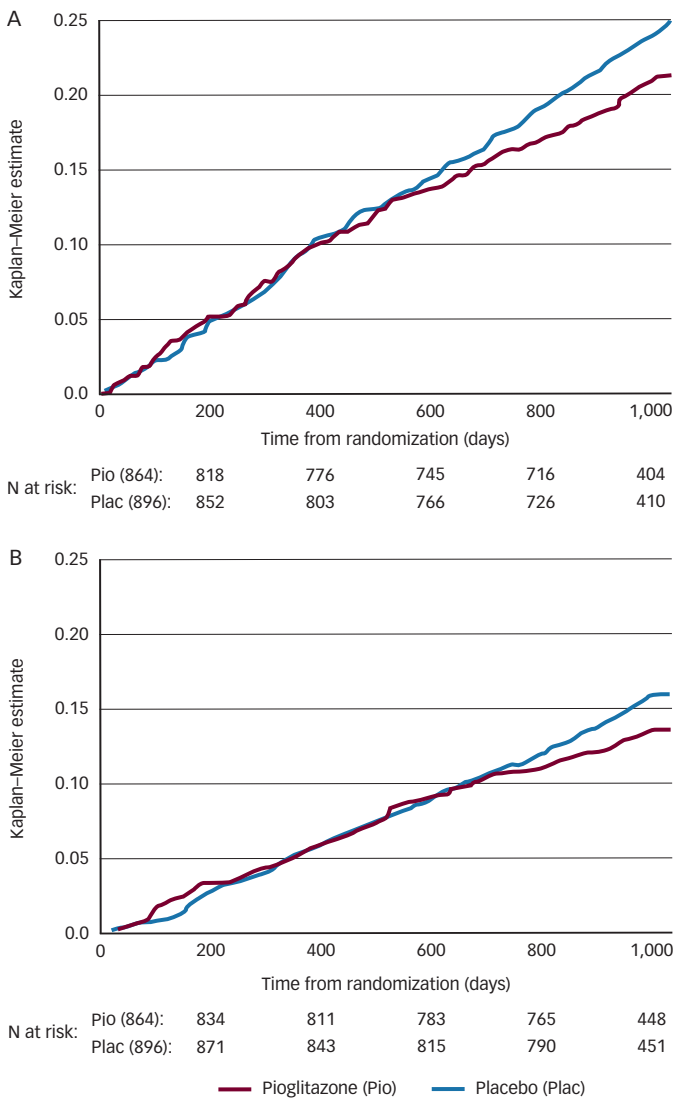


†p<0.0001 versus placebo; §p<0.0371 versus placebo. HbA_{1C} = glycated hemoglobin. Source: adapted from Charbonnel B, et al., 2010.[27]

class.[31,32] As expected, pioglitazone was associated with an increased rate of edema compared with placebo.[16] Overall, 26.4 % of patients in the pioglitazone group reported non-serious edema compared with 15.1 % in the placebo group, and this led to discontinuation in 2.7 versus 0.8 % of patients, respectively. There were only five cases of serious edema in the pioglitazone group and three in the placebo group.

In line with this finding, heart failure was reported in 10.8 % of pioglitazone-treated patients versus 7.5 % on placebo, whereas serious heart failure was reported in 5.7 versus 4.1 %, respectively (HR=1.41, 95 % CI [1.10, 1.80], p=0.007).[16,19] Reassuringly, however, mortality owing to heart failure was similar with pioglitazone and placebo (0.96 versus 0.84 %, p=0.639).[19] Furthermore, among those developing serious heart failure, overall mortality rates were also similar between the pioglitazone and placebo groups (26.8 versus 34.3 %, p=0.1338) and pioglitazone was associated with a significant reduction in the main secondary endpoint

Figure 2: Kaplan–Meier Curve of Time to the Primary Endpoint (A) and the Main Secondary Endpoint (B) in the Subgroup of Patients Treated with Insulin at Baseline in PROactive



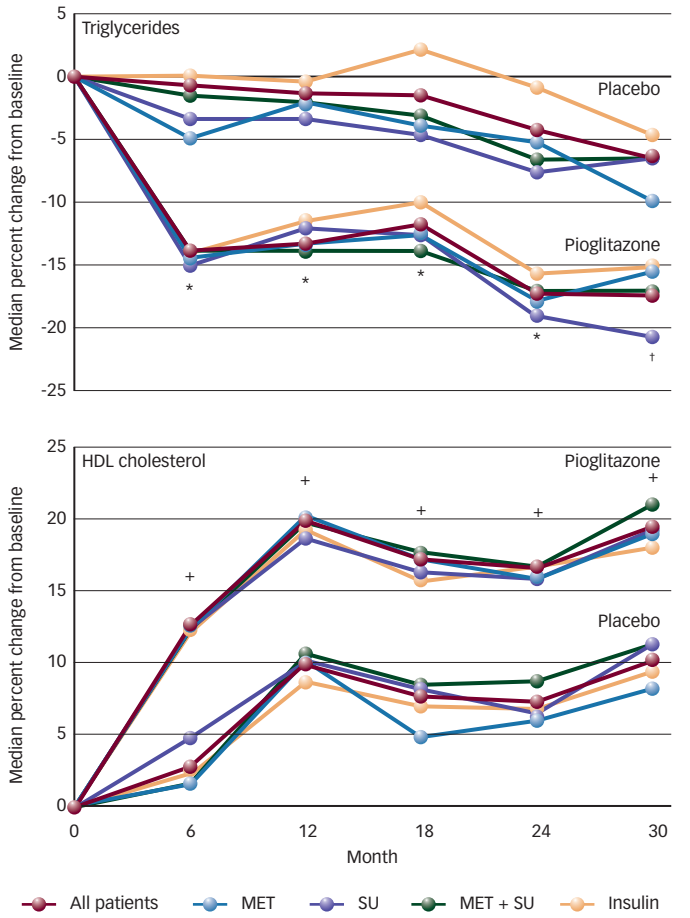
Primary endpoint: composite of all-cause mortality, myocardial infarction (MI) (including silent MI), stroke, acute coronary syndrome (ACS), endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle. Main secondary endpoint: composite of all-cause mortality, MI (excluding silent MI), and stroke. Source: adapted from Charbonnel B, et al., 2010.[27]

(34.9 versus 47.2 %; HR=0.64, 95 % CI [0.44, 0.95], p=0.025).[19] Thus, the heart failure associated with pioglitazone in PROactive appeared to follow a relatively benign course and did not negate the potential for pioglitazone to reduce macrovascular risk. Overall, the safety and tolerability of pioglitazone was predictable and manageable in line with previous efficacy/safety studies in lower-risk patients.[33]

Pioglitazone with Insulin in PROactive

Approximately one-third of patients in PROactive were receiving some form of insulin therapy at baseline (864 [33.2 %] in the pioglitazone group and 896 [34.0 %] on placebo).[27] Less than 1 % of these patients were on insulin alone, 53 % on insulin plus metformin, 24 % on insulin plus a sulfonylurea and 12 % on insulin plus both metformin and a sulfonylurea, with the remaining 10 % on insulin plus at least one other oral agent.[27] The mean daily insulin dose was 47 U/d and patients were receiving an average of 2.3 insulin injections per day (23 % one injection, 48 % two injections and 29 % ≥3 injections).[27] As expected, the characteristics of the insulin-treated population at baseline differed from the population not receiving insulin (see *Table 1*).[27] Patients on insulin had a longer duration of disease (by ~5 years on average), higher body mass index (by ~1.5kg/m^2) and worse glycemic control (~0.5 % higher HbA_{1c}). Furthermore, the incidence of microvascular disease was almost double than that seen in patients not receiving insulin. The patients on insulin thus represented a group with more advanced disease who were at particularly high CV risk. Within the insulin-treated subgroup, baseline characteristics were well balanced between the pioglitazone and placebo groups.

Figure 3: Triglyceride and HDL Cholesterol Changes Over Time According to Baseline Glucose-lowering Therapy in PROactive



*For treatment group comparisons (pioglitazone versus placebo): *p<0.01 for each cohort; †p<0.05 for each cohort; +p<0.0001 for each cohort. For the total population (red), p<0.0001 at all time points for triglycerides and high-density lipoprotein (HDL) cholesterol. MET = metformin; SU = sulfonylurea. Source: adapted from Spanheimer R, et al., 2009.[26]*

Metabolic Findings

Within the insulin-therapy subgroup, pioglitazone was associated with a significant improvement in HbA_{1c} compared with placebo (see *Figure 1A*).[27]

Table 2: Selected Key Outcomes in PROactive According to Insulin Use at Baseline

Endpoint	Insulin Use at Baseline	Pioglitazone Group Events, n/N (%)	Placebo Group Events, n/N (%)	Hazard Ratio (95% CI)	p
Primary endpoint (composite of all-cause mortality, MI [including silent MI], stroke, ACS, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle)	Overall	514/2,605 (19.7)	572/2,633 (21.7)	0.90 (0.80, 1.02)	0.0954
	Insulin	186/864 (21.5)	224/896 (25.0)	0.86 (0.70, 1.04)	0.1173
	No insulin	328/1,741 (18.8)	348/1,737 (20.0)	0.94 (0.80, 1.09)	0.3893
	p for interaction between subgroup and treatment = 0.4780				
Main secondary endpoint (composite of all-cause mortality, MI [excluding silent MI] and stroke)	Overall	301/2,605 (11.6)	358/2,633 (13.6)	0.84 (0.72, 0.98)	0.0277
	Insulin	120/864 (13.9)	147/896 (16.4)	0.85 (0.67, 1.08)	0.1783
	No insulin	181/1,741 (10.4)	211/1,737 (12.1)	0.84 (0.69, 1.03)	0.0915
	p for interaction between subgroup and treatment = 0.9723				
Composite of CV mortality, MI (excluding silent MI) and stroke	Overall	257/2,605 (9.9)	313/2,633 (11.9)	0.82 (0.70, 0.97)	0.0201
	Insulin	107/864 (12.4)	130/896 (14.5)	0.85 (0.66, 1.10)	0.2276
	No insulin	150/1,741 (8.6)	183/1,737 (10.5)	0.81 (0.65, 1.00)	0.0503
	p for interaction between subgroup and treatment = 0.7329				
Serious heart failure	Overall	149/2,605 (5.7)	108/2,633 (4.1)	1.41 (1.10, 1.80)	0.0071
	Insulin	54/864 (6.3)	47/896 (5.2)	1.21 (0.82, 1.79)	0.3430
	No insulin	95/1,741 (5.5)	61/1,737 (3.5)	1.56 (1.13, 2.15)	0.0067
	p for interaction between subgroup and treatment = 0.3216				
Edema (without heart failure)	Overall	563/2,605 (21.6)	341/2,633 (13.0)	1.82 (1.59, 2.08)	<0.0001
	Insulin	204/864 (23.6)	126/896 (14.1)	1.84 (1.48, 2.30)	<0.0001
	No insulin	359/1,741 (20.6)	215/1,737 (12.4)	1.81 (1.53, 2.14)	<0.0001
	p for interaction between subgroup and treatment = 0.8874				

ACS = acute coronary syndrome; CI = confidence interval; CV = cardiovascular; MI = myocardial infarction. Source: adapted from Erdmann E, et al., 2010.[28]

Mean HbA_{1c} levels decreased from 8.4 to 7.4 % (-0.93 %) at the final visit in the pioglitazone group and this was achieved alongside a significant reduction in insulin requirements from a mean of 46.5 U/d to 42.1 U/d (see *Figure 1B*).[27] This was a significantly greater improvement in HbA_{1c} than in the placebo group (8.5 to 8.1 %; -0.45 %). It should be noted that the small improvement in the placebo group required an increase in insulin use from 46.7 U/d to 54.9 U/d. Improvements were achieved after approximately six months, were maintained for the duration of the study and were independent of baseline insulin regimen. The magnitude of these effects was similar to that seen in the overall patient population (-0.8 % pioglitazone, -0.3 % placebo) or those on metformin and/or a sulfonylurea at baseline.[16,24,25] As well as decreasing daily insulin requirements, pioglitazone enabled patients to decrease the complexity of their insulin regimens significantly in terms of the number of injections per day compared with placebo.[27] Pioglitazone also enabled significantly more patients (8.6 %) to discontinue insulin therapy permanently compared with placebo (1.7 %, p<0.0001), as well as enabling more patients to discontinue concomitant oral agents.[27] In those not using insulin at baseline, significantly fewer patients on pioglitazone (11 %) progressed to permanent insulin use compared with placebo (22 %; HR=0.47, 95 % CI [0.39, 0.56], p<0.0001).[16]

An analysis compared the more insulin-resistant patients (defined as baseline insulin dose and HbA_{1c} both median or greater) with the less insulin-resistant ones (defined as baseline insulin dose and HbA_{1c} both less than median), the HbA_{1c} to insulin doses ratio at baseline was used as a potential index of insulin sensitivity.[27] The median insulin dose at baseline was 42 U/d and the median HbA_{1c} was 8.3 %. In the patients categorized as less insulin-resistant at baseline, the mean baseline HbA_{1c} was 7.3 % and insulin dose was 24 U/d, versus 9.6 % and 69 U/d in the more insulin-resistant patients (according to their insulin doses and HbA_{1c} both median or greater). The HbA_{1c} was more or less stable in the less insulin-resistant patients. In the more insulin-resistant patients, it decreased by 1.3 % from 9.6 to 8.3 % at final visit. In these patients with a baseline HbA_{1c} of 9.6 % or more, despite relatively high insulin doses of 69 U/d or more, the HbA_{1c} decrease shown in the placebo group was related to the intensification of insulin treatment (mean increase in insulin dose of 7 U/d from 69 to 76 U/d, associated with the intensification of the insulin regimen), whereas the greater HbA_{1c} decrease (-1.65 versus -0.92 %) on pioglitazone was obtained without any change in the insulin regimen and with lower doses of insulin (mean decrease in insulin units of 11 U/d from 68 to 57 U/d).

A separate analysis looked at how baseline glucose-lowering therapy affected lipid changes in PROactive.[26] In the subgroup of patients on insulin therapy, pioglitazone provided significant improvements in triglycerides and HDL cholesterol compared with placebo (see *Figure 3*). There were also significant improvements in the LDL:HDL cholesterol ratio. The lipid effects were consistent across all baseline glucose-lowering therapy subgroups, despite the higher baseline HbA_{1c} and longer duration of diabetes in insulin-treated patients (see *Figure 3*).[26,27]

Cardiovascular Outcomes

The main macrovascular outcomes in the subgroup of patients on insulin at baseline were consistent with the results reported for the overall population (see *Figures 2A* and *2B*).[16,27] For the primary composite endpoint, there was a non-significant trend toward benefit with pioglitazone compared with placebo (HR=0.86, 95 % CI [0.70, 1.02], p=0.1173). There was also a trend toward benefit for the main secondary composite endpoint (HR=0.85, 95 % CI [0.67, 1.08], p=0.1783).[27] Although a significant reduction was seen for this secondary endpoint in the overall population, there was less power to detect any differences in the smaller insulin-treated subgroup.

A separate analysis also investigated whether the impact of pioglitazone on CV risk differed between those on insulin and those not on insulin at baseline (see *Table 2*).[28] The impact on the primary and main secondary outcomes (as well as the composite of CV mortality, MI, and stroke) was similar regardless of baseline insulin use, and there were no significant interactions between the subgroup and randomized treatments. The main CV endpoint outcomes described above thus demonstrate that, as in the overall PROactive population, pioglitazone therapy is associated with a trend toward a macrovascular benefit compared with placebo when added to insulin therapy.

Safety and Tolerability

The CV outcomes results also demonstrate clearly that pioglitazone has a good macrovascular safety profile among insulin-treated patients, as seen in the overall PROactive population.[33] The adverse event profile of pioglitazone was similar to that of placebo, with the exceptions of edema and hypoglycemia, which were more frequent with pioglitazone, the latter being consistent with better glycemic control in the pioglitazone group.[27,28]

As both insulin and pioglitazone individually are associated with edema, and thus possible exacerbation of heart failure, these two aspects of safety and tolerability were of particular interest in the insulin-therapy subgroup in PROactive. Previous clinical studies suggested that the edema risk is greater when pioglitazone is added to insulin,[12,31] which might relate to the two therapies affecting fluid retention in different bodily compartments (mainly extracellular and extravascular with pioglitazone, but intravascular with insulin).[34] However, although pioglitazone increased edema in the insulin-treated subgroup in PROactive (~80 % relative increase in risk versus placebo), an almost identical increase in risk was seen in the non-insulin-treated subgroup (see *Table 2*).[27,28] Furthermore, in absolute terms, the risk of edema was only increased slightly in patients receiving insulin versus those not receiving insulin in either the pioglitazone (23.6 versus 20.6 %, respectively, for edema in the absence of heart failure) or the placebo groups (14.1 versus 12.4 %).[28] Notably, there were only four events of serious edema among insulin-treated patients in the pioglitazone group and two in the placebo group.[27] Thus, in the PROactive population, the increase in edema associated with pioglitazone therapy was predictable irrespective of baseline insulin therapy and insulin therapy itself had only a minor impact.

Overall rates of heart failure were significantly higher in insulin-treated (12.0 %) versus non-insulin-treated patients (7.7 %, p<0.0001), which suggests that, for whatever reasons (longer duration of the disease, poorer control, insulin itself, etc.), insulin-treated patients are at higher risk of heart failure. Within the insulin-treated group, heart failure events were reported more often with pioglitazone (13.5 versus 10.5 % for placebo, p<0.05).[27] Although the risk of serious heart failure with pioglitazone relative to placebo was consistent with the increased risk seen in the overall population, it did not appear to be enhanced among insulin-treated patients (HR=1.21, 95 % CI [0.82, 1.79], p=0.3430; see *Table 2*).[28] In absolute terms, rates of serious heart failure associated with pioglitazone were not significantly different in insulin-treated and non-insulin-treated patients (6.3 versus 5.5 %, respectively) and the placebo rate among insulin-treated patients (5.2 %).[27,28] Rates of fatal heart failure among insulin-treated patients were similar for pioglitazone and placebo (1.4 versus 1.1 %, respectively).[27]

Edema might also be one of the factors contributing to the weight gain typically associated with pioglitazone or insulin.[33] In the insulin-therapy subgroup, pioglitazone was associated with a 4.2 kg increase in body weight from baseline, which was marginally greater than the +3.6 kg seen in the overall population.[16,26] Weight gain correlated with the decline in HbA_{1C}, consistent with a calorie-sparing effect from better glycemic control.[15] Most of the weight gain occurred within the first year and stabilized within the second year.[16] The magnitude of this weight gain is consistent with previous long-term (2–3 year) studies of pioglitazone as either monotherapy or add-on therapy to other glucose-lowering agents, where increases of 2.5–5 kg have been reported.[35–37] In shorter-term studies (≤6 months) looking specifically at pioglitazone add-on to insulin, weight gain of approximately 4 kg has typically been reported.[8–12] By contrast, weight remained stable (-0.1 kg change) among insulin-treated patients in the placebo group (similar to the -0.4 kg change in the overall population), suggesting that any insulin-associated weight change had stabilized by the start of the study.

Insulin-treated patients would be expected to experience more hypoglycemic events than those not requiring insulin,[38] and this was confirmed in PROactive (all hypoglycemia, 35.5 versus 18.4 %, respectively; serious hypoglycemia, 1.3 versus 0.3 %).[27] Within the insulin subgroup, pioglitazone-treated patients also had a higher rate of hypoglycemia compared with placebo (all hypoglycemia, 42.1 versus 29.0 %, respectively; serious hypoglycemia, 1.9 versus 0.8 %) consistent with better glycemic control.[27] Baseline sulfonylurea use did not influence hypoglycemia rates.[27]

Conclusions

PROactive remains the only completed placebo-controlled CV outcomes study looking at the effects of a single glucose-lowering agent in type 2 diabetes and the only study exclusively in a high-CV-risk population with established macrovascular disease. From the results of PROactive alongside meta-analyses of efficacy/safety RCTs and large-scale surrogate CV endpoints studies (using carotid intima media thickness [cIMT] measurements and coronary vessel intravascular ultrasound), pioglitazone has one of the best characterized CV profiles of any glucose-lowering agent.[33,39–41] Overall, the evidence suggests that pioglitazone has good CV safety and could even provide some macrovascular benefit. The recent subgroup analyses from PROactive described here now extend these findings specifically to pioglitazone as an add-on therapy to insulin and suggest a similar good CV profile and trend toward macrovascular benefit in this patient population. This is particularly important in insulin-treated patients, as they tend to have more advanced disease and thus represent a more vulnerable population with higher CV risk.

From a metabolic perspective, pioglitazone provided improvements in glycemic control and lipids that were consistent irrespective of baseline glucose-lowering therapy. The improvements in HDL cholesterol provided by pioglitazone might be particularly relevant, as this appears to be the one of the main drivers of the anti-atherosclerotic effects of pioglitazone (based on analysis of the ability of pioglitazone to slow cIMT progression in the CHICAGO study).[42]

Clearly, pioglitazone might not be the most appropriate option in all patients on insulin therapy. However, the subgroup analyses from

PROactive suggest that some of the key pioglitazone-associated factors that warrant consideration (notably edema and weight gain) are predictable and have essentially the same impact, irrespective of whether a patient is on insulin therapy. Patients already with edema or excessive body weight might not be good candidates, as pioglitazone would be expected to exacerbate these factors irrespective of insulin therapy but, in the absence of these factors, pioglitazone might be a more viable option, especially in insulin-resistant patients with a poor glycemic control despite high doses of insulin. Clinicians can also be relatively confident that the risk of exacerbating heart failure with pioglitazone is no greater in insulin-treated patients, and it should also be remembered that any pioglitazone-associated heart failure that might occur appears to follow a relatively benign course, with no adverse impact on mortality or macrovascular outcomes. In patients with pre-existing heart failure, however, pioglitazone is contraindicated.[4,5] By contrast, pioglitazone might be a particularly appropriate option in some specific insulin-treated patient populations. For instance, pioglitazone is often used as an addition to insulin in lean Japanese patients, as metformin appears to be less effective in terms of glucose control in this population.[7]

One point that should be considered when interpreting these results from PROactive is that they relate to the addition of pioglitazone to insulin therapy, not to the addition of insulin to pioglitazone, which might occur in clinical practice as part of the standard stepwise approach to therapy.[2,3,43] The value of adding exogenous insulin to ongoing pioglitazone therapy still needs to be evaluated, as well as the potential benefit of initiating combined insulin and pioglitazone therapy early in the course of the disease. The impact on weight gain and risk of edema might be more significant in patients naive to both therapies.

Furthermore, the analyses from PROactive only relate to baseline insulin use and not to on-treatment insulin use. Nevertheless, the results demonstrate that the efficacy/tolerability profile of pioglitazone as an add-on to established insulin therapy is consistent with previous shorter-term RCTs.[8–13] Any increases in hypoglycemia would appear to be consistent with the improved glycemic control provided by pioglitazone.

In conclusion, subgroup analyses of insulin-treated patients from PROactive show that the addition of pioglitazone represents an effective, insulin-sparing, glucose-lowering therapy with a good CV safety profile. The predictability of potential tolerability issues of weight gain, edema, and exacerbation of heart failure seen in PROactive should be of benefit to clinicians when making decisions regarding the appropriateness of pioglitazone therapy for individual insulin-treated patients. ■

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