Pioglitazone and the risk of cardiovascular events in patients with Type 2 diabetes receiving concomitant treatment with nitrates, renin–angiotensin system blockers, or insulin: results from the PROActive study (PROactive 20)

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Introduction

Patients with Type 2 diabetes mellitus (T2DM) are commonly treated with multiple glucose-lowering and cardiovascular (CV) agents.1,2 This use of polypharmacy is likely to escalate with increasing duration and severity of disease, heightening the possibility of treatment interactions. Therefore, an established safety...
profile of potential drug combinations is an important consideration for prescribing physicians.

There has been considerable debate recently over a potential association between rosiglitazone therapy and increased cardiovascular risk. This has been prompted primarily by several independent meta-analyses of adverse event data from randomized clinical trials involving rosiglitazone, some of which suggest a signal for increased risk of myocardial ischemic events or CV mortality, depending on the methodology used. In contrast, meta-analyses of studies involving pioglitazone do not appear to show any increased risk; rather, they show a trend towards reduced macrovascular risk, consistent with the findings of the large-scale prospective outcomes study, PROspective pioglitAzone Clinical Trial In macro-Vascular Events (PROactive). Meta-analyses of rosiglitazone studies have also provided further hypothesis-generating insights based on analysis of individual subgroups of patients. In particular, they have raised concerns over an apparent increased myocardial ischemic risk among patients who receive rosiglitazone while on therapy with either nitrates, renin–angiotensin system (RAS) blockers, or insulin, which may drive the overall effect on risk. Consequently, at present rosiglitazone is not recommended in combination with insulin or in patients receiving nitrates, and these safety concerns have led to a marked decrease in the use of rosiglitazone in the US, whereas pioglitazone use has remained relatively stable. Further analyses from CV outcomes studies with rosiglitazone, such as RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes), and other completed non-CV outcome studies, such as DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) and ADOPT (A Diabetes Outcome Progression Trial), are awaited, which may provide insights on these potential interactions (although no patients were receiving insulin at baseline in any of these studies).

Although an analogous interaction has not been suggested for pioglitazone, PROactive provides a rich dataset in which to investigate the CV safety profile of pioglitazone in patients on concomitant medications. In the present post hoc analysis of the PROactive data, we examined the effect of pioglitazone on macrovascular composite endpoints in the subgroups of patients using nitrates, angiotensin-converting enzyme inhibitors (ACEI) and/or angiotensin receptor blockers (ARBs), or insulin at baseline. Owing to the well-characterized association between thiazolidinedione therapy and fluid retention and the subsequent potential to precipitate heart failure, we also investigated the risk of edema and serious heart failure in these medication subgroups.

Methods

The PROactive study was a randomized double-blind placebo-controlled parallel-group multicenter study that evaluated the impact of pioglitazone on CV outcomes in 5238 patients with T2DM and a history of macrovascular disease. The study was conducted at 321 sites in 19 European countries, with recruitment taking place from May 2001 to April 2002. Details of the PROactive study design, measurements, and endpoints, as well as a complete list of exclusion criteria, have been published previously. Patients eligible for inclusion in PROactive were aged 35–75 years, had T2DM with HbA1c levels > 6.5%, and evidence of macrovascular disease. Patients with New York Heart Association (NYHA) Class II heart failure or above were excluded from the study. The study protocol was approved by local and national ethics committees and the study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines and all patients provided written informed consent.

In addition to their existing glucose-lowering and CV disease risk-management strategies, patients received pioglitazone 15 mg once daily (qd) titrated to 45 mg qd. Investigators were encouraged to optimize other therapies (for treatment of diabetes, dyslipidemia, and hypertension) according to the 1999 International Diabetes Federation (Europe) guidelines.

Patients were assessed regularly for at least 30 months (mean follow-up 34.5 months).

The primary outcome was a composite endpoint consisting of all-cause mortality, myocardial infarction (MI; including silent MI), stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle. A secondary outcome measure of the composite of all-cause mortality, MI, and stroke was also evaluated. Also included in this analysis was the secondary composite endpoint of CV mortality, MI (excluding silent MI), and stroke. As part of the safety analysis, edema (not associated with other signs of heart failure) and heart failure were classified as adverse events of special interest.

Statistical analysis

Statistical methods used for sample size calculation and endpoint analysis for the PROactive trial have been reported previously. The present report is based
primarily on a post hoc analysis from the PROactive database comparing the pioglitazone and placebo treatment groups according to the use of nitrates, ACEI/ARBs (grouped together), or insulin at baseline. Insulin and ACEI/ARBs were two prespecified subgroups for the primary endpoint; all other analyses (i.e. those involving the nitrate subgroup and endpoints other than the primary endpoint) were post hoc. The data presented here are for the full study population and include data from all randomized patients who subsequently took at least one dose of study medication.

Treatment groups according to the use of ACEI/ARBs (grouped together), nitrates, or insulin at baseline were compared using simple descriptive statistics. Event rates and time-to-event analyses, to calculate hazard ratios (HR) and associated 95% confidence intervals (CIs), were conducted as described previously.20 Analysis of endpoint events by subgroups were summarized graphically by displaying 95% CI estimates of the HR for each subgroup to allow visual comparison of treatment differences across subgroups.

Results

Patient demographic and baseline characteristics for the overall population in PROactive have been described in detail previously.20 Within each of the nitrate, ACEI/ARBs, and insulin baseline medication subgroups, patient characteristics were well balanced between those receiving pioglitazone or placebo (Table 1). Patient characteristics were also well balanced between the three baseline medication subgroups, except that patients on insulin had a longer duration of diabetes (by approximately 3 years) and had slightly worse glycemic control at baseline.

Just over one-third of patients were on nitrates, just over two-thirds were on ACEI/ARBs, one-third were on a diuretic (thiazide, loop, or potassium sparing), and approximately one-third of patients were on insulin at baseline, with similar proportions in the pioglitazone and placebo groups (Table 2). From baseline to final visit (overall mean follow-up 34.5 months), there was a slight decrease (<5%) in the use of nitrates and a slight increase (<7%) in the use of ACEI/ARBs in both the pioglitazone and placebo groups. There was a 9.5% and 7.0% increase in diuretic use in the pioglitazone and placebo groups, respectively. The proportion of patients using insulin remained relatively stable in the pioglitazone group (+2.7% absolute change), whereas it increased by 12.7% in the placebo group. Of the patients not using insulin at baseline, only half as many on pioglitazone ($n = 183; 11\%$) progressed to

### Table 1 Baseline characteristics of background therapy subgroups

<table>
<thead>
<tr>
<th></th>
<th>Nitrates</th>
<th>Placebo</th>
<th>ACEI/ARBs</th>
<th>Placebo</th>
<th>Insulin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pioglitazone</td>
<td>Placebo</td>
<td>Pioglitazone</td>
<td>Placebo</td>
<td>Pioglitazone</td>
<td>Placebo</td>
</tr>
<tr>
<td>$n$</td>
<td>1018</td>
<td>1045</td>
<td>1782</td>
<td>1821</td>
<td>864</td>
<td>896</td>
</tr>
<tr>
<td>Male (%)</td>
<td>62.7</td>
<td>61.9</td>
<td>65.0</td>
<td>63.5</td>
<td>58.2</td>
<td>61.0</td>
</tr>
<tr>
<td>BMI ($kg/m^2$)</td>
<td>31.0 ± 4.6</td>
<td>31.4 ± 4.8</td>
<td>31.1 ± 4.7</td>
<td>31.4 ± 4.7</td>
<td>31.6 ± 4.7</td>
<td>31.9 ± 4.7</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62.2 ± 7.6</td>
<td>62.7 ± 7.5</td>
<td>61.9 ± 7.5</td>
<td>61.5 ± 7.7</td>
<td>61.7 ± 7.5</td>
<td>61.2 ± 7.5</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>9.8 ± 7.1</td>
<td>10.0 ± 7.2</td>
<td>9.7 ± 7.0</td>
<td>9.9 ± 7.2</td>
<td>12.8 ± 7.0</td>
<td>13.1 ± 7.1</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.1 ± 1.5</td>
<td>8.1 ± 1.4</td>
<td>8.1 ± 1.4</td>
<td>8.2 ± 1.4</td>
<td>8.4 ± 1.4</td>
<td>8.5 ± 1.4</td>
</tr>
</tbody>
</table>

Unless indicated otherwise, data are given as the mean ± SD.
ACEI, angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blockers.

### Table 2 Change in background medication use from baseline to final visit

<table>
<thead>
<tr>
<th>Baseline medication</th>
<th>Baseline</th>
<th>Final visit</th>
<th>% Change from baseline to final visit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pioglitazone</td>
<td>Placebo</td>
<td>Pioglitazone</td>
</tr>
<tr>
<td>Nitrates ($n = 2605$)</td>
<td>1018 (39.1)</td>
<td>1045 (39.7)</td>
<td>864 (35.8)</td>
</tr>
<tr>
<td>ACEI/ARBs ($n = 2633$)</td>
<td>1782 (68.4)</td>
<td>1821 (69.2)</td>
<td>1762 (73.0)</td>
</tr>
<tr>
<td>Diuretics ($n = 2415$)</td>
<td>813 (31.2)</td>
<td>863 (32.8)</td>
<td>982 (40.7)</td>
</tr>
<tr>
<td>Insulin ($n = 2425$)</td>
<td>864 (33.2)</td>
<td>896 (34.0)</td>
<td>866 (35.9)</td>
</tr>
</tbody>
</table>

Unless indicated otherwise, data show the number of patients in each group, with percentages given in parentheses.
ACEI, angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blockers.
permanent insulin use (defined as insulin use for 90 days or more, or ongoing use at death/final visit) during the study compared with placebo (n = 362 (22%); HR = 0.47, 95% CI 0.39–0.56; P < 0.0001).

Macrovascular outcomes in baseline medication subgroups

For all the macrovascular composite endpoints investigated in this analysis, across all three baseline medication subgroups and in both the pioglitazone and placebo intervention groups, the event rates were higher for patients receiving nitrates, ACEI/ARBs, or insulin at baseline compared with those not receiving these medications at baseline (Figs 1 and 2).

In the overall trial population, as reported previously, treatment with pioglitazone was associated with a significant 16% reduction in proportional risk in the main secondary endpoint (composite of all-cause mortality, MI, and stroke) relative to placebo. As seen in Fig. 1a, this result was consistent across the subgroups of patients receiving or not receiving nitrates, ACEI/ARBs, or insulin at baseline, with proportional reductions in risk ranging from 13% to 19%. In most instances, the effects did not achieve statistical significance due to the reduced power, with the exception of the subgroup receiving ACEI/ARBs at baseline. There was no evidence of heterogeneity based on tests of interaction between subgroup and treatment. Similar results were seen for the frequently used composite of CV mortality, MI, and stroke, with risk reductions ranging from 11% to 25% (Fig. 1b). For this composite, the risk reduction achieved statistical significance in the subgroup receiving nitrates at baseline.

In the overall trial population, a trend towards reduced risk with pioglitazone was reported based on the complex primary composite endpoint. This trend was also evident in all subgroups receiving or not receiving nitrates, ACEI/ARBs, or insulin at baseline, with reductions in risk ranging from 3% to 17% (Fig. 2). The risk reduction achieved statistical significance in the subgroup receiving nitrates at baseline. Again, there was no evidence of heterogeneity based on tests of interaction between subgroup and treatment.

Edema and serious heart failure in baseline medication subgroups

In all subgroups receiving or not receiving nitrates, ACEI/ARBs, or insulin at baseline, pioglitazone therapy was associated with an almost doubling of the risk of patients experiencing edema relative to placebo. This appeared to be relatively consistent across the baseline medication subgroups, with no evidence of any significant interaction (Fig. 3a). The incidence of edema was only marginally higher among patients who were treated with insulin at baseline in both intervention groups compared with those not on insulin at baseline (23.6% vs 20.6%, respectively, in the pioglitazone group and 14.1% vs 12.4%, respectively, in the placebo group).

In the overall trial population, as reported previously, more patients receiving pioglitazone had an event of serious heart failure. This increased risk appeared to be relatively consistent across the baseline medication subgroups, with no evidence of any significant interaction (Fig. 3b). The event rates were higher for patients receiving nitrates, ACEI/ARBs or insulin at baseline in both intervention groups compared with those not receiving these medications at baseline. Notably, in the pioglitazone group, insulin therapy at baseline was associated with only an absolute 0.8% greater incidence of serious heart failure events compared with no insulin therapy at baseline. In the placebo group, baseline insulin therapy was associated with a 1.7% greater incidence of serious heart failure events compared with no baseline insulin.

Discussion

The results of the present post hoc analysis from the PROactive study did not reveal any increased risk of macrovascular events in patients receiving nitrates, ACEI/ARBs, or insulin at baseline in the pioglitazone-treated group relative to placebo. On the contrary, patients both receiving and not receiving these baseline medications realized the same trend to benefit with pioglitazone as reported in the overall analysis from PROactive, based on several different composite macrovascular endpoints. Because PROactive involved a high macrovascular risk population with advanced diabetes, there was extensive use of nitrates, ACEI/ARBs, and insulin at baseline. Those patients receiving these medications had higher macrovascular event rates within both intervention groups and thus represented particularly high-risk patients within this overall high-risk population.

As noted above, the use of these three groups of medications has been implicated as a potential driver of increased risk of ischemic myocardial events in patients receiving rosiglitazone, although this has not been investigated thoroughly in a robust CV outcomes dataset. The present analysis provides reassuring evidence that, at least in the high CV risk population investigated in the PROactive study, there is no signal
Figure 1 Baseline medication subgroup analyses for (a) the main secondary composite endpoint and (b) the composite of cardiovascular (CV) mortality, myocardial infarction (MI), and stroke in the PROactive study. The dotted line represents the result obtained for the respective outcome in the overall population, as reported previously.²⁰,²⁶ ACEI, angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blockers; CI, confidence interval.
for increased macrovascular risk with pioglitazone in patients on nitrates, ACEI/ARBs, or insulin.

The increased incidence of edema in patients receiving either rosiglitazone or pioglitazone is well established and data from clinical efficacy/safety studies suggest that the rate is increased when thiazolidinediones are used in combination with insulin. In the present analysis, the increased risk of edema associated with pioglitazone did not vary according to the use of nitrates, ACEI/ARBs, or insulin at baseline, suggesting that this adverse event is predictable in patients receiving these medications. Interestingly, there was only a slightly higher incidence of edema among patients using insulin at baseline compared with non-users in both the pioglitazone and placebo groups. This suggests that any additional impact of insulin (including use in combination with pioglitazone) on edema is relatively minor in this high-risk, highly medicated population.

An increased risk of edema has been implicated as the potential driver of the increase in heart failure events reported with thiazolidinedione therapy in PROactive and other studies. Data from clinical efficacy safety studies suggest that this risk may be increased when thiazolidinediones are used in combination with insulin. In the present analysis, patients on nitrates, ACEI/ARBs, or insulin at baseline who received pioglitazone had similar levels of risk for serious heart failure that were consistent with the overall group of pioglitazone-treated patients. Patients receiving these baseline medications had a higher incidence of serious heart failure event rates within both the pioglitazone and placebo groups. Notably, for patients in the pioglitazone group, baseline insulin use was associated with a relatively small (<1%) absolute increase in serious heart failure compared with non-insulin users, suggesting little propensity for excess risk of heart failure with the pioglitazone–insulin combination. As with edema, the risk of heart failure associated with pioglitazone would therefore appear to be predictable in patients on nitrates, ACEI/ARBs, or insulin.

The increased risk of serious heart failure associated with pioglitazone needs to be considered in the light of previous analyses of heart failure events from PROactive. Although more pioglitazone-treated patients had a serious heart failure event compared with placebo, absolute mortality rates due to heart failure were similar for pioglitazone and placebo, and proportionally fewer patients with heart failure on pioglitazone went on to have macrovascular events based on either

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**Figure 2** Baseline medication subgroup analyses for the primary composite endpoint (all-cause mortality, myocardial infarction (MI; including silent MI), stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle) in the PROactive study. The dotted line represents the result obtained for the respective outcome in the overall population, as reported previously. ACEI, angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blockers; CI, confidence interval.
The primary or secondary endpoints. As such, the excess risk of serious heart failure associated with pioglitazone in PROactive appeared to have a relatively benign presentation.

It should be acknowledged that the present analysis does have some limitations. Most notably, it was a post hoc analysis for the majority of composite outcome/subgroup interactions investigated (the exceptions...
being insulin and RAS blockers for the primary outcome). Nevertheless, PROactive provides one of the richest datasets available on CV outcomes in T2DM, especially in the secondary prevention setting, and therefore provides a valuable resource for such analyses. Second, the analysis was based solely on baseline medication use and on-treatment use was not investigated. Although the rates of nitrate and ACEI/ARB use were relatively stable during the study and similar in the pioglitazone and placebo groups, insulin use was a more dynamic component of the guideline-driven glycomic control strategy and insulin use increased considerably more in the placebo group. The impact of newly initiated nitrates, ACEI/ARBs, or, in particular, insulin during the study remains unknown and may be of particular relevance to heart failure events because patients with NYHA Class II–IV heart failure were excluded. Therefore, the results are more relevant to patients initiating pioglitazone while on pre-existing nitrates, ACEI/ARBs, or insulin therapy.

In conclusion, the present analysis from PROactive suggests that, in high-risk patients with diabetes and established macrovascular disease, the potential macrovascular benefit of pioglitazone does not appear to be influenced by the use of nitrates, ACEI/ARBs, or insulin, and certainly there is no evidence of any increased risk in patients receiving these medications. Similarly, the analysis suggests that these baseline medications do not appear to influence the risk of edema or the apparently benign excess risk of serious heart failure associated with pioglitazone. The CV effects of pioglitazone in patients on nitrates, ACEI/ARBs, or insulin would therefore appear to be predictable and consistent with effects observed in the overall high-risk population studied in PROactive.

Acknowledgments

The authors thank all the investigators who took part in PROactive (see Dormandy et al.). A preliminary report of this analysis was presented at the American Diabetes Association 68th Scientific Sessions, 6–10 June 2008, San Francisco, CA, USA.

Disclosures

E. Erdmann and B. Charbonnel were members of the PROactive Executive Committee and have served as consultants to Takeda and received travel expenses and payments from Takeda for speaking at meetings. R. Spanheimer is an employee of Takeda Pharmaceuticals North America Limited.

References

Baseline medication and CV events in PROactive


