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# Safety and Tolerability of Pioglitazone in High-Risk Patients with Type 2 Diabetes

## An Overview of Data from PROactive

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## Abstract

People with type 2 diabetes mellitus have an excess risk of macrovascular disease and a poorer prognosis. PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events) was a landmark study of secondary cardiovascular disease (CVD) prevention in type 2 diabetes that suggested a beneficial effect of pioglitazone therapy on macrovascular outcomes. Previous studies have already shown that pioglitazone has a good safety and tolerability profile in people with type 2 diabetes, but PROactive provided an opportunity to assess tolerability and safety associated with long-term exposure in a vulnerable subpopulation at very high cardiovascular risk. This review discusses all the key safety and tolerability characteristics associated with pioglitazone therapy in PROactive.

As in previous studies, pioglitazone was associated with typical, but manageable, increases in oedema (26.4% vs 15.1% for placebo) and weight gain (mean change of +3.8 kg vs –0.6 kg for placebo). Increased hypoglycaemia

with pioglitazone was consistent with improved glycaemic control. Despite more reports of serious heart failure in the pioglitazone group (5.7% vs 4.1% for placebo), there was a proportional improvement in macrovascular outcomes among patients developing heart failure, and absolute rates of macrovascular events and mortality were similar to those in the placebo group. Liver function tests confirmed the hepatic safety of pioglitazone with long-term use and revealed a tendency to improved hepatic function, which may reflect reductions in liver fat. The comparative incidence of malignancies was similar; however, more cases of bladder neoplasm (14 vs 5) and fewer cases of breast cancer (3 vs 11) were observed in the pioglitazone versus placebo arms of the study. A higher rate of bone fractures observed among pioglitazone-treated female patients (5.1% vs 2.5%) warrants further investigation. Overall, safety and tolerability was predictable, and adverse events were not treatment limiting. These results suggest that any beneficial effects of pioglitazone on macrovascular outcomes are accompanied by good long-term tolerability in this population of very high-risk patients with type 2 diabetes and established CVD.

People with type 2 diabetes mellitus have an excess risk of macrovascular disease[1-4] and those with pre-existing cardiovascular disease (CVD) have a particularly poor prognosis compared with non-diabetic individuals.[2,5,6] Consequently, type 2 diabetes is associated with excess mortality, chiefly due to this combination of excess CVD alongside poorer outcomes.[7]

PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events) was a large-scale, controlled study that investigated the impact of a glucose-lowering agent (pioglitazone) on macrovascular outcomes in patients with type 2 diabetes and pre-existing CVD.[8] The combination of type 2 diabetes and established CVD imparts a very high risk of recurrent macrovascular events in this population. In PROactive, pioglitazone therapy was associated with a clear trend towards a reduced risk of macrovascular events compared with placebo (hazard ratio [HR] = 0.90; 95% CI 0.80, 1.02; p = 0.095) based on the primary endpoint (the composite of all-cause mortality, nonfatal myocardial infarction [MI; including silent MI], stroke, major leg amputation, acute coronary syndrome [ACS], cardiac intervention [bypass graft or percutaneous coronary intervention] or leg revascularization).[8] Among the individual components within the primary composite endpoint, the only event that occurred more frequently in the pioglitazone group was leg revascularization (HR = 1.25; 95% CI 0.90, 1.73; p = 0.19) [table I]. For the predefined main secondary endpoint (the composite of all-cause mortality, nonfatal MI or stroke), pioglitazone therapy was associated with significant reduction in risk (HR = 0.84; 95% CI 0.72, 0.98; p = 0.027).

There were also significant reductions in risk with pioglitazone based on other prespecified secondary macrovascular endpoints, including fatal/nonfatal MI (excluding silent MI) [HR = 0.77; 95% CI 0.60, 1.00; p = 0.046] and the composite of cardiovascular (CV) death, MI (excluding silent MI) or stroke (HR = 0.82; 95% CI 0.70, 0.97; p = 0.020), as well as a range of other *post hoc* major adverse CV event endpoints.[9,10] Furthermore, in the subgroup of patients with previous MI, pioglitazone significantly reduced the risk of recurrent MI (fatal or nonfatal) [HR = 0.72; 95% CI 0.52, 0.99; p = 0.045],[11] and in patients with previous stroke, pioglitazone significantly reduced the risk of recurrent stroke (HR = 47% vs placebo; p = 0.008).[12] In terms of mortality, the proportion of patients who died of any cause was comparable between groups (6.8% for pioglitazone vs 7.1% for placebo; HR = 0.96; 95% CI 0.78, 1.18; p = 0.68), and there were similar findings for CV

**Table I.** Total number of events for each component within the primary composite endpoint

| Event | No. of first events contributing to the primary endpoint | | No. of first events (of a particular type) | | Total no. of events | |
|---|---|---|---|---|---|---|
| | pioglitazone (n = 2605) | placebo (n = 2633) | pioglitazone (n = 2605) | placebo (n = 2633) | pioglitazone (n = 2605) | placebo (n = 2633) |
| Any event | 514 | 572 | NA | NA | 803 | 900 |
| Death | 110 | 122 | 177 | 186 | 177 | 186 |
| Nonfatal MI (excluding silent) | 85 | 95 | 96 | 119 | 107 | 130 |
| Silent MI | 20 | 23 | 24 | 27 | 24 | 27 |
| Stroke | 76[a] | 96[a] | 86[b] | 107[b] | 92[b] | 119[b] |
| Acute coronary syndrome | 42 | 63 | 56 | 72 | 65 | 78 |
| Cardiac intervention | 101 | 101 | 169 | 193 | 195 | 240 |
| Major leg amputation | 9 | 15 | 26 | 26 | 28 | 28 |
| Leg revascularization | 71 | 57 | 80 | 65 | 115 | 92 |

a Nonfatal stroke.

b Fatal/nonfatal stroke.

**MI** = myocardial infarction; **NA** = not applicable.

death (4.9% vs 5.2%; HR = 0.94; 95% CI 0.74, 1.20; p = 0.62).[9,10]

Relative to placebo, there were significantly greater improvements in glycosylated haemoglobin [$HbA_{1c}$] (–0.5%), triglycerides (–13.2%), high-density lipoprotein (HDL) cholesterol (+8.9%), low-density lipoprotein (LDL)/HDL cholesterol ratio (–5.3%) and systolic blood pressure (–3 mmHg) with pioglitazone. There was also a 50% reduction in the rate of progression to permanent insulin use in the pioglitazone group compared with the placebo group; in other words, the 10% probability of needing permanent insulin therapy was delayed by nearly 2 years in the pioglitazone group.[13]

A well-established favourable safety profile is an important consideration when determining the value of any intervention that might improve CV outcomes in a vulnerable population, such as that represented in PROactive. The current review discusses all the key safety and tolerability characteristics associated with pioglitazone therapy in PROactive.

## 1. Study Design

PROactive was a randomized, double-blind, placebo-controlled CV outcomes study in high-risk patients with type 2 diabetes (aged 35–75 years).[8,14] Patients received pioglitazone (titrated from 15 mg to 45 mg; n = 2605) or matched placebo (n = 2633), as an addition to standard contemporary therapy (glucose-lowering agents [with/without insulin], lipid-lowering therapy, antihypertensive therapy and antiplatelet drugs). During the study, investigators were encouraged to strive for a target $HbA_{1c}$ <6.5% and to provide optimum lipid-altering, antiplatelet and antihypertensive therapy in line with contemporary (International Diabetes Federation) guidelines for people with type 2 diabetes. The minimum duration of follow-up was 30 months.

The adverse event reporting process focused on the collection of serious events, as well as those for which the relationship to study medication required further investigation. Adverse events were classified as 'serious adverse events', which included potential macrovascular or fatal endpoint events (see below); 'non-serious adverse events of special interest', which included hypoglycaemia, cardiac failure (new or worsening), oedema (in the absence of other signs of heart failure) and non-serious events that led to permanent cessation of study medication; and 'other' non-serious adverse events (i.e. those that were neither serious nor of special interest) for which only an event term, but no other information, was collected. Serious adverse events were defined as those that resulted in death, were life-threatening, needed or prolonged inpatient

hospitalization, resulted in persistent or significant disability or needed significant medical intervention to prevent any of the above.

In the study analysis, a set of serious adverse events was predefined as being of special interest if they were related to any of the following individual events or class of events: cardiac ischaemia, carotid disorders, cerebrovascular disorders, transient ischaemic attack, oedema, heart failure, hypertension, hypoglycaemia or liver disorder. The list of preferred terms that were included in each category of special interest was developed from a blinded review of the database. In addition, malignancy was defined as a serious adverse event of special interest in the statistical analysis plan, which was approved prior to database lock and unblinding.

In contrast to the aggregate categories used to define serious adverse events of special interest, non-serious events of hypoglycaemia, oedema and heart failure were prespecified in the Case Report Form at each visit and, as such, were largely coded to a single Medical Dictionary of Regulatory Activities (MedDRA) preferred term, with the exception of those non-serious events leading to permanent discontinuation of study medication.

### 1.1 Patient Characteristics

A total of 5238 subjects (mean age 61.8 years; mean duration of diabetes 9.5 years; 3463 male) were randomized and 4373 subjects were still receiving study medication at final visit. All patients had a history of pre-existing CVD (MI, stroke, percutaneous coronary intervention or coronary artery bypass surgery ≥6 months before study entry, acute coronary syndrome ≥3 months before study entry, or objective evidence of coronary artery disease or obstructive arterial disease in the leg), with almost half of all patients having a history of more than two macrovascular events.

The mean duration of exposure to study medication for patients in the pioglitazone group was approximately 30.3 months for each treatment. Approximately 90% of the patients in the pioglitazone group had the dose titrated to 45 mg at month 2 of the study (as scheduled). From that visit onward, over 90% of the patients who remained on study medication received the 45 mg dose. At month 30, there were 1943 (94.5%) patients who received pioglitazone 45 mg and 2040 (97.7%) who received placebo. A total of 427 subjects in the pioglitazone group and 438 in the placebo group discontinued study medication prematurely, mainly because of adverse events (235 and 202 in pioglitazone and placebo groups, respectively). One-third (33.6%) of patients were receiving insulin therapy and 25.1% were receiving metformin/sulfonylurea combination therapy at baseline.

## 2. General Safety Profile

The proportion of patients who had any adverse event while participating in PROactive was similar for both treatment groups: 81.7% for the pioglitazone group and 80.6% for the placebo group (table II). The overall incidence of serious adverse events was also similar between groups, if somewhat lower in the pioglitazone group (46.2% for pioglitazone vs 48.4% for placebo) [table II]. Even after events contributing to the primary composite endpoint were excluded, there were similar event rates in both groups, although again somewhat lower in the pioglitazone group (41.4% for pioglitazone vs 43.7% for placebo). The proportion of patients who permanently ceased study medication because of a serious adverse event was approximately 4% in both groups.

The incidences of individual events by MedDRA preferred term are summarized in table III, and serious adverse events are summarized in table IV (MedDRA preferred terminology) and table V (categories of special interest). As is also evident in table II, there was an overall increase in non-serious adverse events of special interest in the pioglitazone group. This related to an expected increase in the predefined events of hypoglycaemia, oedema and heart failure (table III). Each is discussed in more detail below.

This long-term outcome study provides a useful opportunity to evaluate the type of serious adverse events experienced by a chronically ill population with long-standing diabetes and

**Table II.** Overview of adverse events in the study[a]

| Event category | Pioglitazone (n = 2605) [no. (%)] | Placebo (n = 2633) [no. (%)] |
|---|---|---|
| Total no. of patients with any adverse event | 2127 (81.7) | 2121 (80.6) |
| No. of patients with a non-serious adverse event of special interest | 1230 (47.2) | 886 (33.6) |
| related[b] | 1005 (38.6) | 627 (23.8) |
| not related | 542 (20.8) | 454 (17.2) |
| mild | 928 (35.6) | 622 (23.6) |
| moderate | 596 (22.9) | 426 (16.2) |
| severe | 104 (4.0) | 76 (2.9) |
| led to permanent cessation of study medication | 136 (5.2) | 94 (3.6) |
| No. of patients with other non-serious adverse events | 1538 (59.0) | 1566 (59.5) |
| No. of patients with a serious adverse event | 1204 (46.2) | 1275 (48.4) |
| related[b] | 103 (4.0) | 74 (2.8) |
| not related | 1172 (45.0) | 1256 (47.7) |
| led to permanent cessation of study medication | 110 (4.2) | 109 (4.1) |
| fatal | 177 (6.8) | 186 (7.1) |

a Adverse events that occurred between the date of the first dose and the end of the study, whether or not the patient was still receiving study medication, were considered to have occurred 'whilst in the study'.

b Events attributed by investigator as definitely, probably or possibly related to study drug.

macrovascular disease that is receiving contemporary multidrug therapy over a period of at least 3 years (tables IV and V). Patients experienced high rates of CV events. In the placebo group, 400 patients (15.2%) had a cardiac ischaemic event (including 126 patients [4.8%] with MI), 182 (6.9%) experienced a cerebrovascular event and 108 (4.1%) had serious heart failure (table V). In the pioglitazone group, the corresponding rates were 328 patients (12.6%) with a cardiac ischaemic event, 144 (5.5%) with a cerebrovascular event and 149 (5.7%) with serious heart failure. Furthermore, nearly half of all patients required hospitalization at some point during the study, with lower frequency in the pioglitazone group than in the placebo group (43.7% vs 45.8%). As the results in table IV demonstrate, there were comparable rates of other serious adverse events commonly associated with diabetes (eye disorders, metabolism and nutritional disorders, vascular disorders, nervous system disorders, and infections and infestations) in the two arms of the study, confirming the tolerability of pioglitazone when added to existing glucose-lowering therapies in a high-risk and elderly population.

There were four fatal serious adverse events that the investigators considered possibly, probably or definitely related to study medication (two in each group). The two patients in the pioglitazone group died of cardiac failure, while one patient in the placebo group died of cardiac failure and the other of cerebral haemorrhage. All four were on study medication at the onset of the fatal event.

## 3. Specific Macrovascular Events

The efficacy results from PROactive demonstrated a clear trend towards a reduced incidence of macrovascular events with pioglitazone compared with placebo. However, as is the normal process with endpoint trials, the investigators' assessments of serious adverse events that were (potential) endpoint events were not reconciled with the assessments made through the adjudication process, which were completed for the purposes of the efficacy analysis (table I). Nevertheless, the adverse event reporting confirmed the efficacy analysis of fewer macrovascular events with pioglitazone (tables III and IV). MI was reported as a serious adverse event in

3.0% of pioglitazone-treated patients compared with 3.9% on placebo, and rates of ACS were 0.7% and 1.1%, respectively. There were also lower rates of unstable angina and atrial fibrillation reported in the pioglitazone group.

Similarly, cardiac interventions were lower in the pioglitazone group: coronary artery surgery (1.4% vs 1.8%) and coronary angioplasty (0.7% vs 1.0%) were reported less frequently as serious adverse events in the pioglitazone group, and coronary arterial stent insertion was reported in 1.1% of patients in the pioglitazone group and 1.3% in the placebo group. Cerebrovascular accident (1.8% vs 2.2%) and transient ischaemic attack (1.2% vs 1.4%) were also reported less frequently with pioglitazone. Similar lower adverse event rates were seen when events were classified according to categories of special interest (table V).

**Table III.** Treatment-emergent adverse events reported in ≥3% of patients in either treatment group.[a] Non-serious events of hypoglycaemia, oedema and heart failure were each coded to a single Medical Dictionary of Regulatory Activities (MedDRA) preferred term. In contrast, the aggregate categories were used to define serious adverse events of special interest

| Preferred term | Pioglitazone (n = 2605) [no. (%)] | Placebo (n = 2633) [no. (%)] |
|---|---|---|
| Hypoglycaemia | 709 (27.2) | 494 (18.8) |
| Oedema | 689 (26.4) | 397 (15.1) |
| Cardiac failure | 204 (7.8) | 159 (6.0) |
| Angina pectoris | 133 (5.1) | 195 (7.4) |
| Nasopharyngitis | 151 (5.8) | 185 (7.0) |
| Pain in the extremity | 166 (6.4) | 150 (5.7) |
| Arthralgia | 142 (5.5) | 150 (5.7) |
| Back pain | 144 (5.5) | 134 (5.1) |
| Chest pain | 133 (5.1) | 129 (4.9) |
| Accident | 114 (4.4) | 84 (3.2) |
| Unstable angina | 99 (3.8) | 106 (4.0) |
| Hypertension | 94 (3.6) | 104 (3.9) |
| Myocardial infarction[b] | 79 (3.0) | 103 (3.9) |
| Dizziness | 99 (3.8) | 92 (3.5) |
| Headache | 82 (3.1) | 101 (3.8) |
| Influenza | 97 (3.7) | 92 (3.5) |
| Diarrhoea | 92 (3.5) | 94 (3.6) |
| Weight increased | 95 (3.6) | 35 (1.3) |
| Bronchitis | 90 (3.5) | 82 (3.1) |
| Cough | 78 (3.0) | 88 (3.3) |
| Dyspnoea | 85 (3.3) | 56 (2.1) |
| Fatigue | 74 (2.8) | 84 (3.2) |
| Diabetes mellitus management | 44 (1.7) | 84 (3.2) |

a Events that occurred between the dates of a patient's first and last dose were considered to have taken place while on study medication (i.e. 'treatment-emergent').

b Excluding silent myocardial infarction.

In line with the increase in leg revascularization seen in the efficacy analysis (3.1% vs 2.5% with placebo), there were slightly more serious adverse events related to peripheral vascular disease in the pioglitazone group. In the pioglitazone group, 13 (0.5%) patients had femoral arterial stenosis and 17 (0.7%) had intermittent claudication reported as a serious adverse event, whereas these events were reported for 4 (0.2%) and 12 (0.5%) patients, respectively, in the placebo group. The incidence of serious adverse events of peripheral occlusive disease and peripheral vascular disorder, on the other hand, was similar in the two groups: 11 (0.4%) and 20 (0.8%) patients, respectively, in the pioglitazone group and 12 (0.5%) and 20 (0.8%), respectively, in the placebo group. Furthermore, leg amputation was reported as a serious adverse event in only 3 (0.1%) pioglitazone-treated patients compared with 7 (0.3%) placebo recipients.

Thus, with the exception of heart failure (see section 5), CV serious adverse events were, for the most part, reported less frequently with pioglitazone than with placebo.

## 4. Oedema

Oedema is a well-documented adverse effect associated with thiazolidinedione use, and others have described an increased incidence of oedema when thiazolidinediones are given in combination with insulin therapy.[15-19] A recent meta-analysis suggests that thiazolidinediones are associated with a 2-fold increase in the risk of oedema compared with placebo, other oral glucose-lowering agents or insulin in people with type 2 diabetes, although the risk may be greater with rosiglitazone compared with pioglitazone.[15]

In PROactive, 689 (26.4%) pioglitazone-treated patients and 397 (15.1%) placebo-treated patients experienced at least one treatment-emergent case

**Table IV.** Serious adverse events occurring in >1% of subjects (including endpoints) according to Medical Dictionary of Regulatory Activities (MedDRA) terminology; treatment-emergent events[a]

| System organ class preferred term | Pioglitazone (n = 2605) [no. (%)] | Placebo (n = 2633) [no. (%)] |
|---|---|---|
| Cardiac disorders | 424 (16.3) | 457 (17.4) |
| angina pectoris | 77 (3.0) | 110 (4.2) |
| angina unstable | 90 (3.5) | 103 (3.9) |
| myocardial infarction | 79 (3.0) | 103 (3.9) |
| cardiac failure | 71 (2.7) | 49 (1.9) |
| atrial fibrillation | 33 (1.3) | 62 (2.4) |
| cardiac failure congestive | 35 (1.3) | 26 (1.0) |
| acute coronary syndrome | 18 (0.7) | 30 (1.1) |
| Surgical and medical procedures | 271 (10.4) | 327 (12.4) |
| diabetes mellitus management | 44 (1.7) | 84 (3.2) |
| coronary artery surgery | 36 (1.4) | 47 (1.8) |
| coronary arterial stent insertion | 28 (1.1) | 35 (1.3) |
| coronary angioplasty | 19 (0.7) | 27 (1.0) |
| Infections and infestations | 159 (6.1) | 169 (6.4) |
| pneumonia | 43 (1.7) | 30 (1.1) |
| Nervous system disorders | 161 (6.2) | 188 (7.1) |
| cerebrovascular accident | 48 (1.8) | 58 (2.2) |
| transient ischaemic attack | 30 (1.2) | 36 (1.4) |
| Vascular disorders | 129 (5.0) | 130 (4.9) |
| Injury, poisoning and procedural complications | 87 (3.3) | 89 (3.4) |
| accident | 47 (1.8) | 39 (1.5) |
| Musculoskeletal and connective tissue disorders | 68 (2.6) | 72 (2.7) |
| Investigations | 71 (2.7) | 67 (2.5) |
| General disorders and administration site conditions | 50 (1.9) | 50 (1.9) |
| Metabolism and nutrition disorders | 32 (1.2) | 45 (1.7) |
| Eye disorders | 28 (1.1) | 39 (1.5) |

a Events that occurred between the dates of a patient's first and last dose were considered to have taken place while on study medication (i.e. 'treatment-emergent').

of non-serious oedema. Non-serious oedema led to cessation of study medication for 70 (2.7%) patients in the pioglitazone group and 22 (0.8%) in the placebo group. Serious adverse events of oedema were reported for five pioglitazone- and three placebo-treated patients.

As expected, the incidence of oedema was higher among patients receiving insulin at baseline (24.4% vs 20.2% in non-insulin-treated patients). A total of 30.8% of patients receiving insulin in the pioglitazone group and 18.2% receiving insulin in the placebo group reported oedema.[20] Serious oedema was seen in only 6 (0.7%) of these patients (four in the pioglitazone group and two in the placebo group).

## 5. Heart Failure

It is well established that people with diabetes are much more likely to develop heart failure (i.e. symptomatic cardiac dysfunction) than people without diabetes, with an estimated incidence of >30% over a 6-year period.[21] This increased risk may be partly attributable to diabetes-specific cardiomyopathy or may be a secondary consequence of coronary artery disease or other risk factors (e.g. hypertension) associated with type 2 diabetes.[22,23]

Notably, about one-third of patients with type 2 diabetes have evidence of subclinical left ventricular (LV) cardiac dysfunction even in the absence

**Table V.** Serious adverse events occurring in >1% of subjects (including endpoints) according to categories of special interest while in the study[a]

| Special interest category preferred term | Pioglitazone (n = 2605) [no. (%)] | Placebo (n = 2633) [no. (%)] |
|---|---|---|
| Cardiac ischaemic | 328 (12.6) | 400 (15.2) |
| myocardial infarction[b] | 94 (3.6) | 126 (4.8) |
| angina pectoris | 89 (3.4) | 122 (4.6) |
| angina unstable | 97 (3.8) | 108 (4.1) |
| acute coronary syndrome | 23 (0.9) | 38 (1.4) |
| coronary artery stenosis | 22 (0.8) | 29 (1.1) |
| Cerebrovascular disorders | 144 (5.5) | 182 (6.9) |
| cerebrovascular accident | 63 (2.4) | 75 (2.8) |
| transient ischaemic attack | 34 (1.3) | 39 (1.5) |
| Heart failure | 149 (5.7) | 108 (4.1) |
| cardiac failure | 91 (3.5) | 74 (2.8) |
| cardiac failure congestive | 45 (1.7) | 30 (1.1) |
| Malignancy | 97 (3.7) | 99 (3.8) |
| Hypertension | 29 (1.1) | 45 (1.7) |
| Carotid disorders | 24 (0.9) | 27 (1.0) |

a Adverse events that occurred between the date of the first dose and the end of the study, whether or not the patient was still receiving study medication, were considered to have occurred 'whilst in the study'.

b Excluding silent myocardial infarction.

of coronary artery disease and LV hypertrophy[24,25] and may therefore be susceptible to developing symptomatic heart failure when put under stress (e.g. in the presence of peripheral fluid retention). Such a mechanism may underlie the increase in heart failure seen with thiazolidinediones,[26,27] as clinical studies provide good evidence that these drugs do not have any detrimental effect on cardiac function.[19,28] Certainly, pioglitazone-induced heart failure cannot be attributable to worsening cardiac ischaemia given the suggested macrovascular benefit seen in PROactive and the recent observation that pioglitazone can slow the progression of coronary atherosclerosis.[29] Thus, pioglitazone-associated heart failure probably represents a reversible and treatable condition arising from its well-defined effects on peripheral fluid retention and should not impart the poor prognosis typically associated with this condition.

In PROactive, patients with overt heart failure (New York Heart Association [NYHA] class II or above) at entry were excluded. It should be noted that history of heart failure was not collected prior to enrolment in the study. Heart failure was reported in 10.8% of patients in the pioglitazone group compared with 7.5% in the placebo group. Furthermore, 5.7% (n = 149) of pioglitazone-treated patients were reported with serious heart failure (i.e. leading to hospitalization, or meeting one of the other seriousness criteria outlined earlier) compared with 4.1% (n = 108) of placebo-treated patients (HR = 1.41; 95% CI 1.10; p = 0.007) [figure 1].[30] As heart failure was not an endpoint *per se* in this study, these events were not adjudicated. For this reason, a subsequent external and blinded review of the data was obtained, which overall confirmed the investigator-reported diagnoses of heart failure.[31]

Despite the increased incidence of heart failure with pioglitazone reported in PROactive, rates of mortality due to heart failure were similar to those in the placebo group (0.96% vs 0.84% for pioglitazone vs placebo). Similarly, among those with serious heart failure, the proportion of patients who subsequently died of any cause (regardless of whether or not death was temporally associated with the event of heart failure) was slightly higher in the placebo group than in the pioglitazone group (26.8% [n = 40] pioglitazone vs 34.3% [n = 37] for placebo; p = 0.13). A *post hoc* time-to-event analysis showed that, among patients with serious heart failure, the risk of

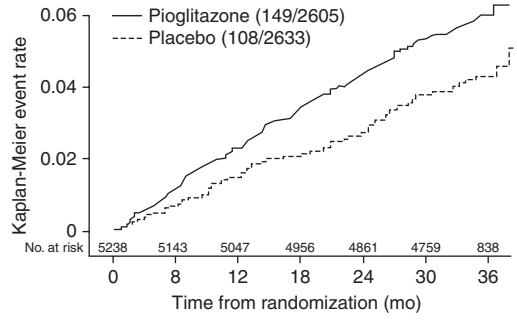


**Fig. 1.** Kaplan-Meier estimates of time to serious heart failure (reproduced from Erdmann et al.,[30] with permission from the American Diabetes Association. Copyright © 2007 American Diabetes Association).

subsequent death, MI or stroke (i.e. the main secondary endpoint) was 36% lower in the pioglitazone group compared with placebo (34.9% [n = 52] vs 47.2% [n = 51]; p = 0.025).[30] Importantly, only 34 pioglitazone- and 17 placebo-treated patients permanently ceased study medication because of serious heart failure; 20 pioglitazone- and 14 placebo-treated patients temporarily ceased study medication. Thus, nearly 80% of patients with an event of heart failure achieved successful recompensation under ongoing medication or could resume medication after the event without deleterious effects. For this reason, any heart failure developing while on pioglitazone therapy would appear to be manageable and not suggestive of progressive cardiomyopathy.

These results from PROactive are consistent with a recent study in patients with type 2 diabetes and systolic dysfunction (NYHA class II/III), which showed no increase in CV mortality after 6 months of treatment with pioglitazone compared with glyburide, despite an earlier time to heart failure onset and a higher rate of heart failure progression.[32] One important consideration, however, is whether the results from PROactive are generalizable to a real-world population that would tend to have greater comorbidity (notably pre-existing heart failure, which was an exclusion in PROactive) and would be likely to have poorer levels of overall care. Some observational studies involving real-world populations (based on claims databases) appear to be reassuring in this regard, and suggest that there is no detrimental effect of thiazolidinedione therapy on mortality among patients with established heart failure.[33,34] However, PROactive remains the only source of evidence available regarding macrovascular and mortality outcomes among patients who develop thiazolidinedione-associated heart failure.

Patients with type 2 diabetes requiring insulin are generally those with a more severe disease state and longer disease duration than those not requiring insulin, and these patients tend to be older. This observation was also true for the patients enrolled in PROactive. In this study, there was an increased incidence of serious heart failure among the one-third of patients who were receiving insulin treatment at baseline and this was seen irrespective of the treatment group. In the pioglitazone group, the rate of serious heart failure was 5.5% in those not receiving insulin at baseline and 6.3% in those receiving insulin (i.e. an absolute increase of 0.8%), whereas in the placebo group the rates were 3.5% and 5.2%, respectively (i.e. an absolute increase of 1.7%). Thus, based on baseline insulin use, there appears to be no absolute increase in the risk of heart failure associated with the combined use of pioglitazone and insulin as part of a glucose control regimen compared with the combination of other glucose-lowering therapies and insulin. Unfortunately, an accurate assessment of the relationship between on-treatment insulin therapy and heart failure is hampered by the evolution of insulin use during the study (in line with glycaemic control guidelines), and insulin use increased much more in the placebo group (12.4% absolute increase vs 2.7% with pioglitazone). Overall, 115 out of 257 patients were receiving insulin prior to the onset of serious heart failure (57/149 in the pioglitazone group and 58/108 in the placebo group).

## 6. Fractures

Recent publications of clinical trial and epidemiological data have raised a concern that thiazolidinediones may increase the risk of fractures in women.[35-37] Several plausible mechanisms for such an association exist, with some *in vitro* evidence suggesting that peroxisome proliferator-activated receptor (PPAR)-γ activation promotes adipogenesis at the expense of osteoblastogenesis, thus providing the potential to inhibit bone formation and induce bone loss.[38] A review of clinical trials involving 8100 patients treated with pioglitazone and 7400 comparator patients showed more reports of fractures in female patients taking pioglitazone, but no increase in rate of fracture for men.[39] The majority of fractures were in the distal upper limb (forearm, hand and wrist) or distal lower limb (foot, ankle, fibula and tibia). The fracture

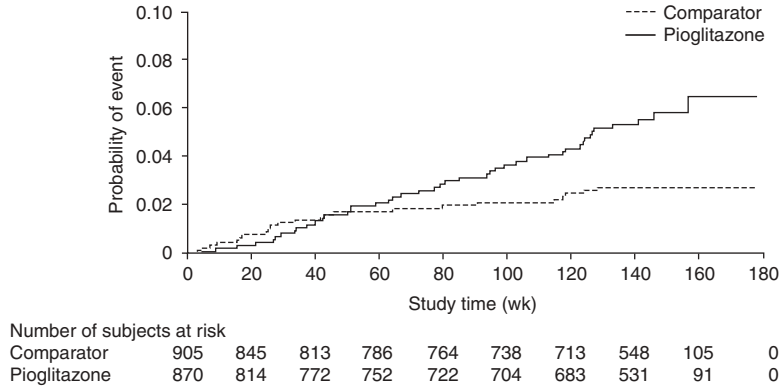


**Fig. 2.** Kaplan-Meier estimates of event rate for fracture in women enrolled in PROactive. Unpublished data from the PROactive trial.

incidence was calculated to be 1.9 fractures per 100 patient-years in pioglitazone-treated women and 1.1 per 100 patient-years for comparator groups.

The data for fractures from PROactive were very similar to the entire clinical trials data presented above: 44/870 (5.1%; 1.0 fractures per 100 patient-years) of pioglitazone-treated female patients experienced fractures compared with 23/905 (2.5%; 0.5 per 100 patient-years) of women treated with placebo (figure 2). The majority of events were seen in women older than 55 years, and no increase in fracture rates was observed in men treated with pioglitazone (1.7%) versus placebo (2.1%). The observed excess risk of fractures for women on pioglitazone in this study is therefore 0.5 fractures per 100 patient-years of use and was seen beyond the first year of exposure (figure 2). In PROactive, as in previous analyses, limb fractures (n = 36) were the most common type seen among women in the pioglitazone group, including 22 distal limb fractures (vs 11 with placebo), 7 proximal limb fractures (vs 1 with placebo) and 7 where the location in the limb was undefined (vs 4 with placebo). Notably, only two of these fractures were located in the hip. The remaining factures were spinal (6 vs 0, for pioglitazone vs placebo) and osteoporotic/pathological (2 in each group). This association will be investigated further to ascertain any relationship with specific patient characteristics or risk factors.

## 7. Liver Function

In PROactive, there was a trend toward normalization of markers of liver function (ALT and AST) in the pioglitazone group compared with no change or an increase in these enzyme levels in the placebo group ($p < 0.001$).[40] These results are consistent with previous clinical studies with pioglitazone in patients with type 2 diabetes, or those with non-alcoholic steatohepatitis.[41-43]

Elevated ALT is closely related to liver fat accumulation and may be a consequence of impaired hepatic insulin signalling.[44] Changes in ALT with pioglitazone may reflect improved hepatic insulin sensitivity and a reduction in liver fat.[45,46] Pioglitazone has been shown to cause a shift in fat distribution from visceral to subcutaneous adipose depots that is associated with improvements in hepatic and peripheral insulin sensitivity[47] and, more specifically, to cause a decrease in hepatic fat content.[48] It should be noted that the patients with the most impaired hepatic function (ALT >2.5 times the upper limit of normal) were excluded from PROactive; these may be the patients who had the greatest hepatic fat content and potentially could have responded best to pioglitazone.

The incidence of serious liver disorders was low and balanced between the treatment groups in PROactive (4 for pioglitazone and 5 for placebo), which is consistent with real-world observational analyses.[49]

## 8. Malignancy

The overall incidence of cancer in PROactive was equivalent in the pioglitazone and placebo groups (table VI). There was a total of 196 patients with at least one malignancy: 97 (3.7%) in the pioglitazone group and 99 (3.8%) in the placebo group. A similar number of patients in each treatment group died of a malignancy: 35 (1.3%) in the pioglitazone group and 31 (1.2%) in the placebo group. The most frequently reported malignancy, colorectal cancer, occurred with a similar incidence in both groups: 16 patients (0.6%) in the pioglitazone group and 15 (0.6%) in the placebo group.

Nevertheless, there were some imbalances regarding the incidence of specific malignancies reported in the two treatment groups. There were 14 (0.5%) cases of bladder neoplasm in the pioglitazone group and 6 (0.2%) in the placebo group. On the other hand, breast cancer was reported for only 3 (0.1%) pioglitazone-treated patients, but 11 (0.4%) placebo recipients. Nine cases of prostate malignancy were observed in the pioglitazone group (0.3%) and 5 (0.2%) in the placebo group, whereas renal malignancies were reported in 3 patients (0.1%) in the pioglitazone group versus 7 (0.3%) in the placebo group.

Owing to previous nonclinical observations of benign and/or malignant transitional cell neoplasms in the bladder of male rats (but not male or female mice or female rats) after 2 years of treatment with pioglitazone,[50] the Data and Safety Monitoring Committee (DSMC) decided to evaluate further the 20 cases of bladder neoplasms reported in PROactive. A urological oncologist and a specialist in environmental carcinogens performed a blinded review of the 20 cases. Independent of each other, they both eliminated 11 cases that were reported within 1 year of randomization because of lack of pharmacological plausibility for any association with study medication. That left six cases in the pioglitazone group and three in the placebo group with bladder neoplasm diagnosed in the second year of exposure (although one of the three cases in the placebo arm had a benign histology). Of the eight patients with malignant histology, five had known risk factors for bladder cancer (all had a history of chronic smoking, two had a history of chronic bladder irritation, one had a history of potential carcinogen exposure and one had a previous vesical tumour), thus leaving only three cases (two in the pioglitazone group and one in the placebo group) without other more likely causative factors. On the basis of

**Table VI.** Incidence of malignant neoplasms

| Event | Pioglitazone (n = 2605) [no. (%)] | Placebo (n = 2633) [no. (%)] |
|---|---|---|
| No. of patients with any malignant neoplasm | 97 (3.7) | 99 (3.8) |
| colorectal | 16 (0.6) | 15 (0.6) |
| lung | 15 (0.6) | 12 (0.5) |
| bladder | 14 (0.5) | 6 (0.2) |
| haematological | 6 (0.2) | 10 (0.4) |
| breast | 3 (0.1) | 11 (0.4) |
| prostate | 9 (0.3) | 5 (0.2) |
| pancreas | 8 (0.3) | 6 (0.2) |
| gastric | 5 (0.2) | 6 (0.2) |
| renal | 3 (0.1) | 7 (0.3) |
| skin | 6 (0.2) | 4 (0.2) |
| metastases | 5 (0.2) | 5 (0.2) |
| ovarian/uterine | 4 (0.2) | 5 (0.2) |
| other | 7 (0.3) | 10 (0.4) |

these independent reviews, the DSMC concluded that bladder cancer was not likely to be a safety issue with pioglitazone in the PROactive study.

This conclusion is supported by findings from other studies. During prospective evaluation of urinary cytology involving more than 1800 patients receiving pioglitazone in clinical trials up to 1 year in duration, no new cases of bladder tumours were identified, and abnormal urinary cytology results were observed both in patients treated with pioglitazone (0.72%) and patients treated with placebo (0.88%).[50] In fact, *in vitro* studies suggest that pioglitazone may actually inhibit the growth of some neoplastic human urothelial cell lines.[51]

## 9. Other Adverse Events

### 9.1 Hypoglycaemia

There were 709 (27.2%) pioglitazone- and 494 (18.8%) placebo-treated patients who experienced a treatment-emergent episode of hypoglycaemia. The incidence of non-serious hypoglycaemia was highest in the first 6 months of the study, when 479 (18.4%) patients in the pioglitazone group and 266 (10.1%) in the placebo group experienced an event. This period coincides with the initial uptitration of the pioglitazone dose and onset of insulin-sensitizing effects. After 6 months in the trial, 467 (17.9%) pioglitazone- and 386 (14.7%) placebo-treated patients reported an event.

Rates of hypoglycaemia were particularly low in patients receiving metformin monotherapy at baseline (8% for pioglitazone and 13% for placebo).[52] Among patients on sulfonylurea monotherapy at baseline, rates were 21% for the pioglitazone group and 13% for the placebo group. As expected, the incidence of hypoglycaemia was higher in patients using insulin at baseline: 42.2% in the pioglitazone group and 29.1% in the placebo group.[20] Rates of hypoglycaemia among patients on metformin/sulfonylurea combination therapy at baseline (i.e. those on triple oral agent therapy that included pioglitazone) were similar to those of the overall population (27.4% for pioglitazone and 19.8% for placebo).[53] The observation of increased hypoglycaemic events when pioglitazone was combined with either insulin secretagogues (such as sulfonylureas) or insulin itself is consistent with the insulin-sensitizing pharmacological activity of pioglitazone and could be related to the improved glycaemic control seen in PROactive. However, this rarely developed into serious hypoglycaemia requiring medical intervention.

The incidence of serious adverse events related to hypoglycaemia was low in both treatment groups: 20 (0.8%) pioglitazone- and 12 (0.5%) placebo-treated patients; none of these events was fatal. One patient in each group experienced a hypoglycaemic coma. Thus, any hypoglycaemia associated with pioglitazone therapy was predictable (based on improved glycaemia), manageable and not treatment limiting.

### 9.2 Weight Gain

Average weight gain from baseline with pioglitazone was 3.8 kg (after 30 months or at the final visit) compared with –0.6 kg for placebo, and most of this increase occurred during the first 15 months. However, this led to permanent discontinuation of study medication in only 0.8% of patients in the pioglitazone group (compared with 0.2% in the placebo group). Weight gain with thiazolidinediones is a consistent finding and, while its mechanism is not fully understood, fluid retention appears to account for the greater part (~75%) of the effect, at least in the short term.[54,55] Although there may also be some contribution from increased body fat, any possible detrimental effect of this increase may be offset by potentially beneficial qualitative effects of pioglitazone on fat topography, with a shift of fat away from the more metabolically active visceral depots to less active subcutaneous depots.[47,54] It is also possible that improved glycaemia contributed to the greater weight gain seen with pioglitazone in PROactive; a 0.5% difference in $HbA_{1c}$ might explain 1 kg of weight gain difference due to the calorie-sparing effect of reduced glucosuria.[56]

### 9.3 Hypertension

The incidence of serious adverse events of hypertension was lower in the pioglitazone group

(29 patients [1.1%]) than in the placebo group (45 patients [1.7%]). This may reflect the previously reported significant beneficial effects on blood pressure of thiazolidinedione addition to sulfonylurea therapy in patients with type 2 diabetes and the metabolic syndrome.[57] Overall in the PROactive study, there was a mean decrease of blood pressure of 2 mmHg in the pioglitazone group, while no such effect was observed in the placebo group.

### 9.4 Other Adverse Events

Other adverse events (MedDRA preferred terms) occurring in ≥3% of patients included nasopharyngitis, pain in the extremity, arthralgia, back pain, chest pain, accident, dizziness, influenza, diarrhoea, bronchitis, cough, dyspnoea, fatigue and diabetes management. The only events for which there was a >1% difference between groups were nasopharyngitis (5.8% vs 7.0%), where the incidence was lower with pioglitazone, and accident (4.4% vs 3.2%) and dyspnoea (3.3% vs 2.1%), where the incidence was higher with pioglitazone (table II). There was also a slightly higher incidence of anaemia reported for pioglitazone (44 patients [1.7%]) compared with placebo (20 patients [0.8%]). Although there was a slightly higher incidence of pneumonia among pioglitazone-treated patients (1.7% vs 1.1%), the incidence of infections and infestations overall was comparable to that with placebo (6.1% vs 6.4%). Among other serious adverse events (preferred terms) occurring in >1% of patients, differences between groups were small (≤0.5%) [table IV].

## 10. Discussion

PROactive was a landmark study of secondary CVD prevention in type 2 diabetes. The mechanisms underlying the suggested macrovascular outcomes benefits of pioglitazone remain unclear, although pioglitazone has multiple pleiotropic actions that may play a role.[58-64] The clinical utility of such a therapy would be severely hampered without an appropriate level of safety and tolerability in a highly vulnerable population, such as that studied in PROactive. Previous studies have demonstrated good safety and tolerability for pioglitazone in typical representative populations of people with type 2 diabetes.[42] The results from PROactive confirm that, even in this very high CV risk patient subpopulation, the safety profile of pioglitazone is predictable and consistent with previous studies in lower-risk populations.

Oedema was increased with pioglitazone, which is consistent with previous studies.[15-19] Despite more reports of heart failure in the pioglitazone group, overall macrovascular outcomes were improved, and heart failure events were not treatment limiting. Furthermore, absolute mortality due to heart failure was similar to that with placebo, despite the higher incidence of heart failure events observed with pioglitazone. It is important to note that the most severe sequelae of heart failure – death, MI and stroke – are the same events that comprise the main secondary composite endpoint of PROactive. Thus, any effect of heart failure is already accounted for in the analysis of major macrovascular events. In other words, events of serious heart failure do not diminish the positive CV protective effect extended to patients on pioglitazone in the PROactive study. More recently, a meta-analysis of clinical trials has supported the suggestion that the higher incidence of heart failure is probably not associated with worse outcome.[27]

It has been suggested recently that rosiglitazone treatment may be associated with an increased risk of MI and CV mortality, albeit based on meta-analyses with considerable methodological limitations.[65-67] Based on the results from PROactive, there is no evidence to suggest that this is an issue with pioglitazone, where, on the contrary, adverse event reporting confirmed the efficacy findings of improved macrovascular outcomes, including MI. This is supported by another meta-analysis by the Nissen group.[68] This meta-analysis of pioglitazone trials (which had a different endpoint and included fewer studies than the rosiglitazone trial, but a similar total number of patients) showed no increased risk of the composite of death, MI or stroke with

pioglitazone. This finding persisted when looking at MI in isolation and also when the PROactive study was excluded from the analysis. Recent observational studies also suggest that outcomes may be better with pioglitazone compared with rosiglitazone, but this remains to be established in a prospective head-to-head trial.[69,70]

The incidence of hypoglycaemia was greater with pioglitazone, which is consistent with improved glycaemic control, and was highly dependent upon the use of other glucose-lowering therapies, especially insulin. However, pioglitazone therapy allowed patients to reduce their insulin requirements while improving glycaemic control,[20] which could help to minimize the typical pioglitazone-associated adverse effects of oedema and weight gain that may be increased with the combination. It remains unclear whether the reduced insulin requirements would translate into less hypoglycaemia for similar levels of glycaemic control. The greater weight gain seen with pioglitazone in PROactive is consistent with increased oedema and improved glycaemic control,[54-56] and any increases in body fat may be offset by beneficial effects on fat topography depots.[47,54] Liver function tests revealed a tendency toward improved hepatic function, which is consistent with previous studies and may reflect reductions in liver fat and improved hepatic insulin sensitivity.[41,46] The hepatic safety of pioglitazone with long-term use observed in this study is consistent with the data that have been observed in another recently completed 3-year study.[71]

## 11. Conclusion

The results of PROactive demonstrate that the suggested beneficial effects of pioglitazone on macrovascular outcomes do not appear to be associated with compromised safety and tolerability in this particularly vulnerable population of very high-risk patients with type 2 diabetes and established CVD. The safety and tolerability profile is predictable and manageable, in line with previous experience in lower-risk populations.

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