Pioglitazone Use and Heart Failure in Patients with Type 2 Diabetes and Preexisting Cardiovascular Disease: Data from the PROactive Study (PROactive 08)

Erland Erdmann, MD, FESC, FACC1; Bernard Charbonnel, MD2; Robert G Wilcox, MD3; Allan M Skene, PhD4; Massimo Massi-Benedetti, MD5; John Yates, MD6; Meng Tan, MD7; Robert Spanheimer, MD8; Eberhard Standl, MD9; John A Dormandy, FRCS, DSc10, on behalf of the PROactive investigators

1Medizinische Klinik III der Universität zu Köln, Köln, Germany; 2Clinique d’Endocrinologie, Hôtel Dieu, Nantes Cedex 1, France; 3Queen's Medical Centre, University Hospital, Nottingham, UK; 4Nottingham Clinical Research Limited, Nottingham, UK; 5University of Perugia, Medicine and Metabolic Diseases, Perugia, Italy; 6Medical Research and Development, Takeda Global Research and Development Center, Deerfield, IL, USA; 7Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, USA; 8Medical & Scientific Affairs, Takeda Pharmaceuticals North America, Inc., Deerfield, IL, USA; 9Munich Institute of Diabetes Research and Medical Department, Krankenhaus Munchen-Schwabing, Munich, Germany; 10St George’s Hospital, London, UK

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Corresponding author:
Prof. Dr. Erland Erdmann
Medizinische Klinik III der Universität zu Köln Kerpener Str. 62,
D-50937 Köln, Germany
Email: erland.erdmann@uni-koeln.de

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Abstract

OBJECTIVE—PROactive enrolled patients with type 2 diabetes and pre-existing cardiovascular disease. These patients were at high risk for heart failure (HF), so any therapeutic benefit could potentially be offset by risk of associated HF mortality. We analyzed the HF cases to assess the effects of treatment on morbidity and mortality following reports of serious HF (SHF).

RESEARCH DESIGN AND METHODS—PROactive was an outcome study in 5,238 patients randomized to pioglitazone or placebo. Patients with NYHA Class II–IV HF at screening were excluded. A SAE of HF was defined as HF that required hospitalization or prolonged a hospitalization stay, was fatal or life threatening, or resulted in persistent significant disability or incapacity. HF risk was evaluated by multivariate regression.

RESULTS—More pioglitazone (5.7%) than placebo patients (4.1%) had a SHF event during the study (P=0.007). However, mortality due to HF was similar (25/2605 [0.96%] for pioglitazone versus 22/2633 [0.84%] for placebo; P=0.639). Among patients with a SHF event, subsequent all-cause mortality was proportionately lower with pioglitazone (40/149 [26.8%]) versus 37/108 [34.3%] with placebo; P=0.1338). Proportionately fewer pioglitazone patients with SHF went on to have an event in the primary (47.7% with pioglitazone versus 57.4% with placebo; P=0.0593) or main secondary endpoint (34.9% with pioglitazone versus 47.2% with placebo; P=0.025).

CONCLUSIONS—Although the incidence of SHF was increased with pioglitazone versus placebo in the total PROactive population of patients with type 2 diabetes and macrovascular disease, subsequent mortality or morbidity was not increased in patients with SHF.
Thiazolidinediones (TZDs) are insulin-sensitizing agents that improve insulin resistance via peroxisome proliferator-activated receptors (PPAR)-γ. The specific PPAR-γ inhibition confers vasculoprotective effects, and pioglitazone in particular improves many cardiovascular risk factors and markers (e.g. diabetic dyslipidemia, hypertension, adiponectin, CRP, PAI-1, matrix metalloproteinases, and carotid intima-media thickness) through multiple mechanisms (1,2). However, concern has been expressed about the use of TZDs in patients with existing HF or at high-risk for HF (3,4). The American Heart Association (AHA) and the American Diabetes Association (ADA) issued joint guidelines for the use of TZDs in patients with type 2 diabetes and HF (5).

In PROactive, there was a non-significant trend towards fewer primary events among patients on pioglitazone than among patients randomized to placebo (Hazard Ratio [HR]=0.90; \( P=0.095 \), 6). Moreover, pioglitazone reduced risk for the main secondary endpoint, a composite of all-cause mortality, non-fatal MI, and stroke (HR=0.84; \( P=0.027 \)). Investigators reported serious HF (SHF) in 257 patients (4.9%) in the total study population in PROactive (5.7% in the pioglitazone group and 4.1% in the placebo group.

Here, we report a detailed analysis from PROactive, presenting more information on the investigator-reported HF rates to identify the risk factors for SHF and to assess the treatment effect on sequelae following SHF.

**RESEARCH DESIGN AND METHODS**— PROactive was a multicenter, double-blind, placebo-controlled, cardiovascular outcomes trial in 5,238 patients with type 2 diabetes and macrovascular disease. The PROactive inclusion and exclusion criteria are defined by Dormandy et al. (6). The major cardiovascular-related inclusion criterion was an established history of macrovascular disease defined as one or more of the following: MI, stroke, percutaneous coronary intervention, or coronary artery bypass graft ≥6 months before entry into the study; acute coronary syndrome ≥3 months before entry into the study; objective evidence of coronary artery disease; or symptomatic peripheral arterial obstructive disease. Patients with NYHA Class II–IV HF at screening were excluded. There was no collection of history of HF prior to enrolment in the study. Investigators were directed to optimize the glucose-lowering and cardiovascular therapy throughout the study according to International Diabetes Federation European Region 1999 guidelines.

**Serious adverse events**
A serious adverse event (SAE) was defined as that requiring hospitalization or prolongation of a hospitalization stay, was fatal or life threatening, or resulted in persistent significant disability or incapacity. Any SAE that was coded to one of the following preferred terms was considered to be SHF: acute left ventricular failure, cardiac asthma, cardiac failure, cardiac failure (acute or chronic), cardiac failure congestive, cardiopulmonary failure, congestive cardiomyopathy, left or right ventricular failure, low cardiac output syndrome, pulmonary edema, and ventricular dysfunction.

For all SAEs, the investigator was required to complete a separate event report booklet, which was used to record the course of each event, including diagnostic evaluations used and actions taken. The investigator reported the outcome of each such event, and if fatal, recorded a cause of
death. Each fatal event was adjudicated by an independent committee of experts to classify cause of death into one of the following categories: MI, other cardiac, other cardiovascular, cerebrovascular, or other (i.e. non-cardiovascular).

In addition, a post-hoc, blinded adjudication of all investigator-reported SHF events and pneumonia, as well as of all Endpoint Adjudication Committee classifications as “other cardiac” or “other cardiovascular” was performed by three independent cardiologists to validate the investigator-reported diagnoses and to achieve the best available evidence of potential downsides of pioglitazone treatment. Details of this have been reported elsewhere (7). In essence, investigator-reported diagnosis of SHF was confirmed.

Non-SAEs
At each visit (months 1, 2, 4, 6, 8, 10, 12, 15, 18, 21, 24, 27, 30, 33, 36, and 39), a case report form listing non-SAEs of special interest that included HF, edema, hypoglycemia, and any event leading to study medication discontinuation was completed. The following information was collected: nature of the event, duration, frequency, relationship to study drug (as judged by the investigator), action taken concerning study drug, and outcome. Thus, information regarding symptoms of non-serious edema and HF that had occurred since the last study visit was solicited specifically at each study visit and recorded on the case report form. However, there were no standardized, objective criteria used to diagnose or distinguish non-SHF from edema alone, and the investigator was not required to provide any detail beyond whether or not these events had occurred. Because new or worsening HF is considered a life-threatening event that typically necessitates inpatient management, non-SHF events were not the primary focus of the HF analysis.

Statistical analysis
Statistical methods used for the sample size calculation and endpoint analysis for the PROactive trial have been reported previously. The data presented here are from the full study population.

The incidence of serious heart failure was analysed by fitting a Cox-proportional hazards model for time to the first event. Simple descriptive statistics were otherwise used to compare the two treatment groups.

Multivariate regression analysis was used to identify factors predictive of serious heart failure; variable selection was carried out using a stepwise selection algorithm at a significance level of 0.05. This analysis considered 24 baseline characteristics identified in the statistical analysis plan (see Table 1), along with smoking status and study treatment.

RESULTS
SHF events
The overall incidence of SAEs (including HF) was comparable between groups (n=1204 [46.2%] for pioglitazone versus n=1275 [48.4%] for placebo; P=0.110) (6). After excluding events contributing to the primary composite endpoint, the incidence of SAEs was also similar: n=1079 [41.4%] for pioglitazone versus n=1150 [43.7%] for placebo (P=0.099) (6).

There were more patients with reports of SHF in the pioglitazone compared to the placebo group (149 patients [5.7%]) versus 108 patients [4.1%], respectively; HR=1.41; 95%CI=1.10, 1.80; P=0.007; Fig. 1). Twenty-five of the 149 (16.8%) patients in the pioglitazone group and 12 of the 108 (11.1%) placebo patients were no longer receiving study drug at the time of the event.

Predictors of SHF — multivariate analysis
Significant baseline predictors of SHF were creatinine ≥130 µmol/L, diuretic
use, LDL-cholesterol >3 mmol/L, previous MI, duration of diabetes ≥10 years, randomisation to pioglitazone, A1C ≥7.5%, age, and body mass index (BMI) (Table 1). These results are consistent with the differences in the baseline characteristics of those who subsequently developed SHF versus those who did not (data not shown). The only differences between the baseline characteristics of patients on pioglitazone versus placebo who developed HF were higher prevalence of previous TIA and previous PCI/CABG, and higher systolic blood pressure in the pioglitazone group (data not shown). There were also differences between the pioglitazone and placebo groups in some baseline medications: NSAIDs (12% versus 1%), insulin (36% versus 44%), and loop diuretics (40% versus 30%) (data not shown).

Even though insulin use at baseline was not a significant predictor of SHF in the multivariate analysis, we evaluated this subgroup in more detail due to the interest in concomitant use of TZDs and insulin. SHF occurred more frequently in patients who were insulin-treated compared to non-insulin-treated at baseline, irrespective of pioglitazone or placebo: 101/1760 (5.7%) versus 156/3478 (4.5%; P=0.045). Conversely, of the total of 257 patients who experienced a SHF event, 101/257 (39.3%) were on insulin at baseline versus 1659/4981 (33.3%) who did not experience SHF. However, of the 1760 patients who were receiving insulin at baseline (33.2% of the whole study pioglitazone group and 34.0% of the whole study placebo group), SHF was experienced by 54 (6.3%) patients in the pioglitazone group and 47 (5.2%) patients in the placebo group (P=0.343). One hundred and fifteen patients had received insulin prior to the onset of serious heart failure: 57 patients from the 149 in the pioglitazone group and 58 from 108 in the placebo group.

Mortality and SHF
Despite a significantly increased risk for SHF with pioglitazone, a similar number of patients in both treatment groups had a fatal SAE of HF (i.e. considered the primary cause of death), with fatal HF events occurring in 25 (0.96%) in the pioglitazone group and 22 (0.84%) in the placebo group (HR=1.15; 95%CI=0.65, 2.03; P=0.639). Of the patients who experienced SHF, proportionately fewer patients subsequently died from any cause in the pioglitazone group (40/149, 26.8%) compared with in the placebo group (37/108, 34.3%; HR=0.71; 95%CI=0.454, 1.111; P=0.1338; Fig. 2a).

Morbidity Following SHF
Among patients who developed SHF, proportionately fewer patients on pioglitazone experienced an event in the primary composite endpoint (71/149, 47.7% versus 62/108, 57.4% in the placebo group; HR=0.72; 95%CI=0.512, 1.013; P=0.0593). Likewise, proportionately fewer pioglitazone patients with SHF went on to have an event in the main secondary composite endpoint of all-cause mortality, non-fatal MI, and stroke (52/149, 34.9% in the pioglitazone group versus 51/108, 47.2% in the placebo group; ; HR=0.64; 95%CI=0.436, 0.946; P=0.025; Fig. 2b). After hospitalization for SHF, there was no significant difference between groups in the median number of days spent in hospital (11 days in both groups; P=0.682) and in the median number of days spent in intensive care/a high dependency unit (4 days in the pioglitazone group and 3 in the placebo group; P=0.584).

Reversibility of SHF
Only 34 patients (out of 149 [22.8%]) in the pioglitazone group and 17 (out of 108 [15.7%]) in the placebo group had a SHF event that resulted in permanent discontinuation of the study medication (P=0.1602). The number of patients
with SHF for whom the HF event resolved during follow-up was 116 (77.9%) for pioglitazone and 80 (74.1%) for placebo ($P=0.4822$).

**Non-SHF**

The proportion of patients who had a non-serious event of HF was higher in the pioglitazone group ($n=168$; 6.4%) than in the placebo group ($n=114$; 4.3%; $P=0.0007$). The absolute number of patients who progressed to SHF after a non-serious event was similar for both groups (21 pioglitazone-treated patients versus 20 placebo-treated patients). Six patients in each group who had a non-SHF event ultimately died of any cause.

**Edema**

There were 713 (27.4%) pioglitazone-treated patients and 419 (15.9%) placebo-treated patients who reported edema ($P<0.001$). Serious or non-serious edema without HF of any severity occurred in 563 (21.6%) patients in the pioglitazone group versus 341 (13.0%) in the placebo group ($P<0.0001$). Edema prior to SHF occurred in 51 out of 149 [34.2%] patients in the pioglitazone group and 26 out of 108 [24.1%] in the placebo group.

**CONCLUSIONS**— HF is a common comorbidity of type 2 diabetes (occurrence rates of 8–20%) and is associated with a poor outcome in this patient population (5,8,9). Age, diabetes duration, insulin use, ischemic heart disease, and elevated serum creatinine have been shown to be independent risk factors for HF in diabetes (9). Aggressive control of A1C confers a reduced risk for HF as demonstrated with UKPDS data that showed a 1% increase in A1C was associated with an approximately 10% increased risk of HF (10,11). However, this strategy is complicated by the fact that, over time, multiple agents are needed to achieve and maintain A1C targets and several glucose-reducing agents are themselves associated with a risk of HF (5,12,13).

In PROactive, there was a higher incidence of HF with pioglitazone versus placebo (6). While the overall rate of SHF was less than might be expected based on previous reports (5,14), the higher reporting rate with pioglitazone compared with placebo raises the question of whether the trend of benefit noted for reduction in cardiovascular events was diminished by increased HF (15–17). To address this question, we conducted several analyses, first to characterize the patients with SHF and then to look at outcome following SHF.

A post-hoc multivariate analysis indicated that several baseline parameters were associated with an increased risk of SHF. Age, duration of disease (type 2 diabetes), A1C $\geq 7.5\%$, creatinine $\geq 130$ µmol/L, prior MI, and diuretic use were associated with an increased risk of SHF, as were LDL-cholesterol $>4$ mmol/L (versus $<3$ mmol/L), and BMI. The multivariate analysis also showed that pioglitazone use was associated with an increased risk of HF. In this multivariate analysis, insulin use was not associated with an increased risk of HF. The finding may be open to debate as insulin use has long been associated with an increased risk of HF (5). It may be unique to this population of patients with long-standing type 2 diabetes and macrovascular disease and not applicable to a more general patient population. However, in the PROactive study population, the univariate analyses show, as expected, an increased absolute risk of SHF in insulin-treated patients; and the multivariate analysis data may therefore suggest that comorbidities more than insulin per se can explain this increased absolute risk. On the other hand, it must be emphasized that there was no increase of the relative risk of SHF between pioglitazone and placebo in this high-risk subgroup of insulin-
Despite a higher rate of SHF with pioglitazone in PROactive, several observations support the lack any associated increase in subsequent morbidity or mortality: 1) the overall incidence of SAEs (with or without endpoint events) in the total cohort was similar between treatment groups, and 2) the rate of a subsequent event of all-cause mortality, MI, or stroke in patients reported to have SHF was similar between treatment groups. These data are important for several reasons. First, that the overall rates of SAEs with pioglitazone remained similar to that observed for placebo suggest a similar overall safety profile for the two treatments, despite a higher rate of SHF with pioglitazone. Second, the most clinically important sequelae of HF in patients with type 2 diabetes are death, MI, or stroke. Therefore, the most serious outcomes of HF are already captured and accounted for in the composite endpoint of all-cause mortality, MI, and stroke. Because the rates for this composite endpoint subsequent to a report of SHF were similar between pioglitazone and placebo, the cardiovascular benefits observed in PROactive with pioglitazone were not diminished by the increased incidence of HF. Similarly, the clinical course of HF did not appear to differ between treatment groups with respect to time spent in hospital (including intensive care/high dependency units), necessity to discontinue study drug, or reversibility of the event.

Delea et al. (3) reviewed an insurance database of 5,441 patients treated with TZDs and found that TZD use was predictive of HF, with an adjusted incidence of HF (defined as requiring hospitalization or diagnosed at an outpatient visit) of 8.2% in the TZD group (n=5441) and 5.3% in the control group (other glucose-lowering agents; n= 8103) at 40 months. In contrast, an interim report of the 23,440 patients from the Kaiser Permanente Northern California Diabetes Registry failed to find evidence to support an association of short-term (10.2-month follow-up) pioglitazone use with an elevated risk of hospitalization for HF, with no significant differences between HF rates with pioglitazone versus sulfonylureas (18). In the recent Diabetes REduction Approaches with ramipril and rosiglitazone Medications (DREAM) study in 5,269 people with impaired glucose tolerance and/or impaired fasting glucose, there was a higher rate of HF in the rosiglitazone group (0.5%; n=14) than in the placebo group (0.1%, n=2; HR=7.03; 95%CI=1.60, 30.9; P=0.01) (19).

HF in type 2 diabetes is generally associated with a high death rate (e.g. 45% versus 24% of those with diabetes and no HF over 5 years) (20). As such, there has been much debate on TZDs’ potential exacerbation of HF in some patients versus their benefits on cardiovascular risk factors. Our data indicate that pioglitazone may increase signs of HF in susceptible patients. However, the occurrence of SHF did not translate to increased mortality or cardiovascular morbidity with pioglitazone compared with placebo treatment in the patients with SHF. Hence, PROactive provides no evidence that the CV benefits observed with pioglitazone were attenuated by the higher reported rates of SHF. Our findings are corroborated by a retrospective study of 16,417 Medicare claims in people with diabetes who were discharged after hospitalization for HF suggesting that mortality rates with TZDs were not increased compared with other oral glucose-lowering agents (1-year mortality rates were 30% with TZDs and 36% for glucose-lowering agents other than metformin or TZDs (21).
In PROactive, a major limitation was that HF was not included in the composite endpoint and therefore was not evaluated as an independently adjudicated event. Additionally, no diagnostic criteria were provided to the investigators to ensure a systemic consistent reporting of HF across sites during the study. Because of this, there was concern as to the accuracy of HF reports. To address this concern, an independent expert group of cardiologists (under the Chairmanship of Lars Rydén, Karolinska Institut, Sweden) reviewed all cases of SHF and pneumonia. After a review of all available documentation for each case of SHF, pneumonia, and cardiac- or cardiovascular-related death, this group concluded that the investigator-reported diagnoses were largely accurate and confirmed a higher reporting rate of SHF with pioglitazone compared to placebo. The committee’s findings validate the accuracy of the investigators’ diagnoses of serious or fatal HF: episodes of adjudicated SHF were more frequent in patients with advanced cardiovascular disease treated with pioglitazone than in patients given placebo (144 patients [5.5%] versus 111 patients [4.2%], respectively) and mortality due to HF was the same in each group (15 patients [0.6%]) (7).

The mechanisms of action behind the fluid retention with TZDs (e.g. cardiac cause or drug interaction with receptors on sodium channels) remain unclear, although it has been suggested that PPARγ may regulate sodium reabsorption in the cortical collecting ducts (segments of the nephron involved in regulation of sodium and water homeostasis) via stimulation of epithelial sodium channel activity (22). The long-term study of pioglitazone use and HF, funded by the ADA (18), argues against the possibility that TZDs cause HF. Another limitation is that the focus of PROactive was the evaluation of outcome in regard to major cardiovascular events. Since quality of life was not analyzed in this trial, we are not able to ascertain if there was a decrease in quality of life after a SHF episode.

In PROactive, pioglitazone was associated with an increased rate of SHF; subsequent death from any cause, was not increased among those with SHF. In addition, the subsequent event rate of a composite endpoint that included the most serious outcomes associated with heat failure, i.e. all-cause mortality, MI, and stroke, was proportionately lower in pioglitazone-treated patients with SHF.

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References


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Table 1—**Significant baseline predictors of HF risk by multivariate analysis**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine ≥ 130 µmol/L</td>
<td>2.70</td>
<td>(1.796, 4.061)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diuretic use</td>
<td>2.10</td>
<td>(1.620, 2.732)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LDL-cholesterol &gt;4 mmol/L (versus &lt;3 mmol/L)</td>
<td>1.74</td>
<td>(1.245, 2.442)</td>
<td>0.0012</td>
</tr>
<tr>
<td>Prior MI</td>
<td>1.70</td>
<td>(1.317, 2.205)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Duration ≥ 10 years (versus &lt;5 years)</td>
<td>1.53</td>
<td>(1.107, 2.115)</td>
<td>0.0100</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>1.53</td>
<td>(1.183, 1.979)</td>
<td>0.0012</td>
</tr>
<tr>
<td>HbA1c ≥ 7·5%</td>
<td>1.43</td>
<td>(1.078, 1.895)</td>
<td>0.0131</td>
</tr>
<tr>
<td>LDL-cholesterol 3–4 mmol/L (versus &lt;3 mmol/L)</td>
<td>1.17</td>
<td>(0.878, 1.569)</td>
<td>0.2805</td>
</tr>
<tr>
<td>Age (year)</td>
<td>1.07</td>
<td>(1.044, 1.087)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>1.03</td>
<td>(1.007, 1.061)</td>
<td>0.0145</td>
</tr>
<tr>
<td>Duration 5–10 years (versus &lt;5 years)</td>
<td>0.80</td>
<td>(0.530, 1.201)</td>
<td>0.2786</td>
</tr>
</tbody>
</table>

Baseline characteristics that were not significant: gender, stroke ≥6 months before entry into the study [yes/no], PCI or CABG ≥6 months before entry into the study [yes/no], acute coronary syndrome ≥3 months before entry into the study [yes/no], objective evidence of coronary artery disease [yes/no], peripheral arterial obstructive disease [yes/no], baseline Micral test strip results [+ve /-ve], metformin or sulfonylureas at baseline [both, including fixed combinations, metformin alone, sulfonylureas alone, neither], insulin as part of standard therapy at baseline [yes/no], serum triglycerides [low risk <1.7 mmol/L/at risk 1.7–2.2 mmol/L/high risk >2.2 mmol/L], serum HDL-cholesterol [low risk >1.2 mmol/L /at risk 1.0–1.2 mmol/L/high risk<1.0 mmol/L], combined blood pressure [low risk/high risk], the metabolic syndrome at baseline [present/absent], use of statins [Yes/No], use of ACE or ARB inhibitors [Yes/No], use of ß-blockers [Yes/No], smoking history [current/past/never], and prior photocoagulation therapy [Yes/No].
Figure 1—Kaplan Meier estimates of time to SHF.
**Figure 2**—Kaplan Meier estimates of time from SHF to (a) all-cause mortality and (b) the main secondary endpoint.