Pioglitazone Use and Heart Failure in Patients With Type 2 Diabetes and Preexisting Cardiovascular Disease

Data from the PROactive Study (PROactive 08)

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OBJECTIVE — PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) enrolled patients with type 2 diabetes and preexisting cardiovascular disease. These patients were at high risk for heart failure, so any therapeutic benefit could potentially be offset by risk of associated heart failure mortality. We analyzed the heart failure cases to assess the effects of treatment on morbidity and mortality after reports of serious heart failure.

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

RESULTS — More pioglitazone (5.7%) than placebo patients (4.1%) had a serious heart failure event during the study ($P = 0.007$). However, mortality due to heart failure was similar (25 of 2,605 [0.96%] for pioglitazone vs. 22 of 2,633 [0.84%] for placebo; $P = 0.639$). Among patients with a serious heart failure event, subsequent all-cause mortality was proportionately lower with pioglitazone (40 of 149 [26.8%] vs. 37 of 108 [34.3%] with placebo; $P = 0.1338$). Proportionately fewer pioglitazone patients with serious heart failure went on to have an event in the primary (47.7% with pioglitazone vs. 57.4% with placebo; $P = 0.0593$) or main secondary end point (34.9% with pioglitazone vs. 47.2% with placebo; $P = 0.025$).

CONCLUSIONS — Although the incidence of serious heart failure 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 serious heart failure.

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Thiazolidinediones (TZDs) are insulin-sensitizing agents that improve insulin resistance via peroxisome proliferator–activated receptor-γ. The specific peroxisome proliferator–activated receptor-γ inhibition confers vasculoprotective effects, and pioglitazone in particular improves many cardiovascular risk factors and markers (e.g., diabetic dyslipidemia, hypertension, adiponectin, C-reactive protein, plasma activator inhibitor 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 heart failure or at high risk for heart failure (3,4). The American Heart Association and the American Diabetes Association issued joint guidelines for the use of TZDs in patients with type 2 diabetes and heart failure (5).

In PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive), there was a nonsignificant trend toward 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 end point, a composite of all-cause mortality, nonfatal myocardial infarction (MI), and stroke (HR 0.84; $P = 0.027$). Investigators reported serious heart failure 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 heart failure rates to identify the risk factors for serious heart failure and to assess the treatment effect on sequelae after serious heart failure.

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Abbreviations: MI, myocardial infarction; SAE, serious adverse event; TZD, thiazolidinedione.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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 New York Heart Association Class II–IV heart failure at screening were excluded. There was no collection of history of heart failure before enrollment 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 serious heart failure: 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., noncardiovascular).

In addition, a post hoc blinded adjudication of all investigator-reported serious heart failure 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 serious heart failure was confirmed.

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

	HR	95% CI	*P*
Creatinine ≥130 μmol/l	2.70	1.796–4.061	<0.0001
Diuretic use	2.10	1.620–2.732	<0.0001
LDL cholesterol >4 mmol/l (vs. <3 mmol/l)	1.74	1.245–2.442	0.0012
Prior MI	1.70	1.317–2.205	<0.0001
Duration ≥10 years (vs. <5 years)	1.53	1.107–2.115	0.0100
Pioglitazone	1.53	1.183–1.979	0.0012
A1C ≥7.5%	1.43	1.078–1.895	0.0131
LDL cholesterol 3–4 mmol/l (vs. <3 mmol/l)	1.17	0.878–1.569	0.2805
Age (years)	1.07	1.044–1.087	<0.0001
BMI (kg/m^2)	1.03	1.007–1.061	0.0145
Duration 5–10 years (vs. <5 years)	0.80	0.530–1.201	0.2786

n = 5,092. Baseline characteristics that were not significant: sex, stroke ≥6 months before entry into the study (yes/no), percutaneous coronary intervention or coronary artery bypass graft ≥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 angiotensin receptor blocker inhibitors (yes/no), use of β-blockers (yes/no), smoking history (current/past/never), and prior photocoagulation therapy (yes/no).

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 heart failure, 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 nonserious edema and heart failure 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 nonserious heart failure 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 heart failure is considered a life-threatening event that typically necessitates inpatient management, nonserious heart failure events were not the primary focus of the heart failure analysis.

Statistical analysis

Statistical methods used for the sample size calculation and end point 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 analyzed 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 (Table 1), along with smoking status and study treatment.

RESULTS

Serious heart failure events

The overall incidence of SAEs (including heart failure) was comparable between groups (*n* = 1,204 [46.2%] for pioglitazone vs. *n* = 1,275 [48.4%] for placebo; *P* = 0.110) (6). After excluding events contributing to the primary composite end point, the incidence of SAEs was also

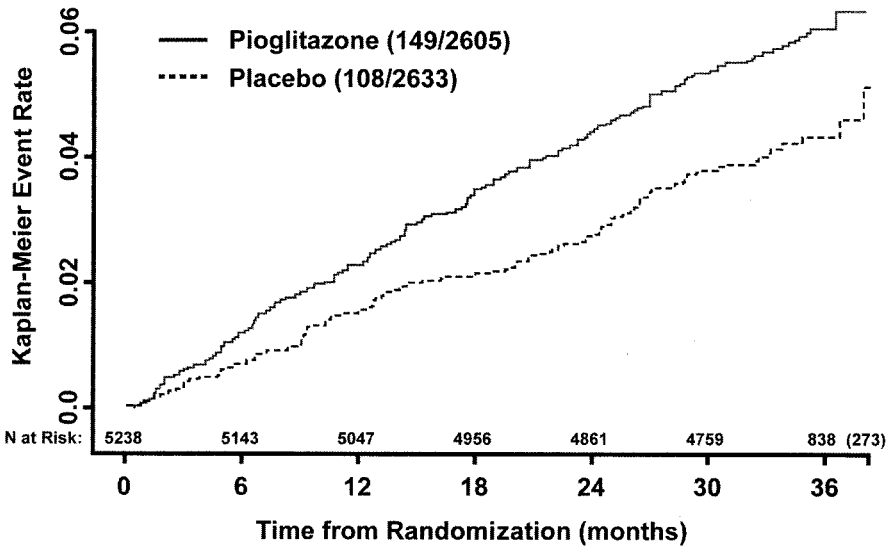

Figure 1—*Kaplan-Meier estimates of time to serious heart failure.*

similar (n = 1,079 [41.4%] for pioglitazone vs. n = 1,150 [43.7%] for placebo; P = 0.099) (6).

There were more patients with reports of serious heart failure in the pioglitazone group than in the placebo group (149 [5.7%] vs. 108 [4.1%] patients, respectively; HR 1.41 [95% CI 1.10–1.80]; P = 0.007) (Fig. 1). A total of 25 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 serious heart failure: multivariate analysis

Significant baseline predictors of serious heart failure were creatinine ≥130 μmol/l, diuretic use, LDL cholesterol >3 mmol/l, previous MI, duration of diabetes ≥10 years, randomization to pioglitazone, A1C ≥7.5%, age, and BMI (Table 1). These results are consistent with the differences in the baseline characteristics of those who subsequently developed serious heart failure versus those who did not (data not shown). The only differences between the baseline characteristics of patients on pioglitazone versus placebo who developed heart failure were higher prevalence of previous transient ischemic attack and previous percutaneous coronary intervention/coronary artery bypass graft 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: nonsteroidal anti-inflammatory drugs (12 vs. 1%), insulin (36 vs. 44%), and loop diuretics (40 vs. 30%) (data not shown).

Even though insulin use at baseline was not a significant predictor of serious heart failure in the multivariate analysis, we evaluated this subgroup in more detail because of the interest in concomitant use of TZDs and insulin. Serious heart failure occurred more frequently in patients who were insulin treated compared with non–insulin treated at baseline, irrespective of pioglitazone or placebo: 101 of 1,760 (5.7%) vs. 156 of 3,478 (4.5%) (P = 0.045). Conversely, of the total of 257 patients who experienced a serious heart failure event, 101 of 257 (39.3%) were on insulin at baseline versus 1,659 of 4,981 (33.3%) who did not experience serious heart failure. However, of the 1,760 patients who were receiving insulin at baseline (33.2% of the whole study pioglitazone group and 34.0% of the whole study placebo group), serious heart failure was experienced by 54 (6.3%) patients in the pioglitazone group and 47 (5.2%) patients in the placebo group (P = 0.343). A total of 115 patients had received insulin before the onset of serious heart failure: 57 of 149 patients in the pioglitazone group and 58 of 108 in the placebo group.

Mortality and serious heart failure

Despite a significantly increased risk for serious heart failure with pioglitazone, a similar number of patients in both treatment groups had a fatal SAE of heart failure (considered the primary cause of death), with fatal heart failure events occurring in 25 (0.96%) in the pioglitazone group and 22 (0.84%) in the placebo

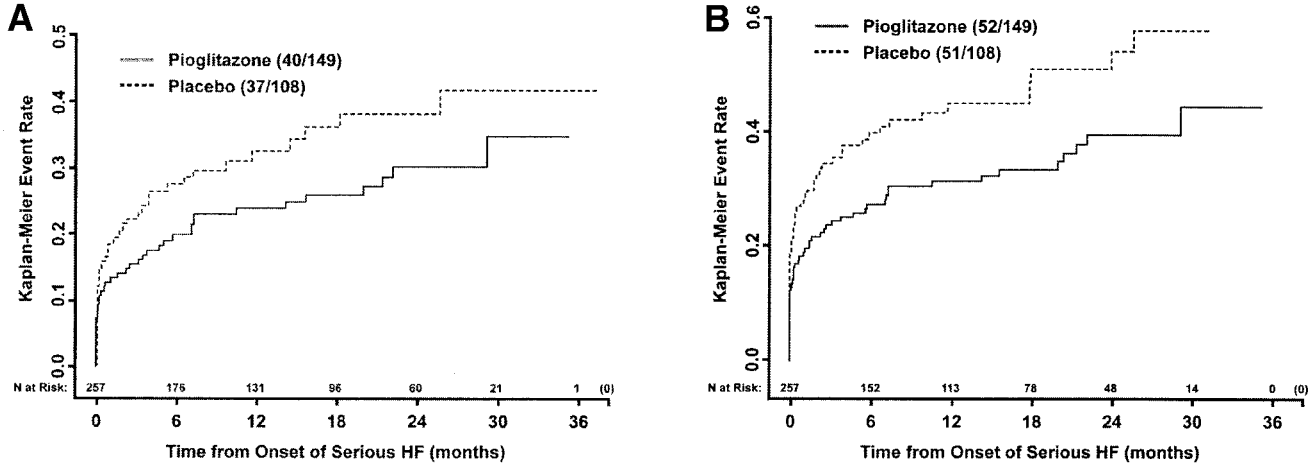

Figure 2—*Kaplan-Meier estimates of time from serious heart failure to all-cause mortality* (A) *and the main secondary end point* (B). *HF, heart failure.*

group (HR 1.15 [95% CI 0.65–2.03]; $P = 0.639$). Of the patients who experienced serious heart failure, proportionately fewer patients subsequently died from any cause in the pioglitazone group (40 of 149 [26.8%]) compared with those in the placebo group (37 of 108 [34.3%]; HR 0.71 [95% CI 0.454–1.111]; $P = 0.1338$) (Fig. 2*A*).

Morbidity after serious heart failure

Among patients who developed serious heart failure, proportionately fewer patients on pioglitazone experienced an event in the primary composite end point (71 of 149 [47.7%] vs. 62 of 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 serious heart failure went on to have an event in the main secondary composite end point of all-cause mortality, nonfatal MI, and stroke (52 of 149 [34.9%] in the pioglitazone group vs. 51 of 108 [47.2%] in the placebo group; HR 0.64 [95% CI 0.436–0.946]; $P = 0.025$) (Fig. 2*B*).

After hospitalization for serious heart failure, there was no significant difference between groups in the median number of days spent in the 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 serious heart failure

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 serious heart failure event that resulted in permanent discontinuation of the study medication ($P = 0.1602$). The number of patients with serious heart failure for whom the heart failure event resolved during follow-up was 116 (77.9%) for pioglitazone and 80 (74.1%) for placebo ($P = 0.4822$).

Nonserious heart failure

The proportion of patients who had a nonserious event of heart failure 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 serious heart failure after a nonserious event was similar for both groups (21 pioglitazone-treated patients vs. 20 placebo-treated patients). Six patients in each group who had a nonserious heart failure 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 nonserious edema without heart failure 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 before serious heart failure 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 — Heart failure 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 heart failure in diabetes (9). Aggressive control of A1C confers a reduced risk for heart failure, as demonstrated with UK Prospective Diabetes Study data that showed a 1% increase in A1C was associated with an ~10% increased risk of heart failure (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 heart failure (5,12,13).

In PROactive, there was a higher incidence of heart failure with pioglitazone versus placebo (6). While the overall rate of serious heart failure 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 heart failure (15–17). To address this question, we conducted several analyses, first to characterize the patients with serious heart failure and then to look at outcome after serious heart failure.

A post hoc multivariate analysis indicated that several baseline parameters were associated with an increased risk of serious heart failure. Age, duration of disease (type 2 diabetes), A1C ≥7.5%, creatinine ≥130 μmol/l, prior MI, and diuretic use were associated with an increased risk of serious heart failure, as were LDL cholesterol >4 mmol/l (vs. <3 mmol/l) and BMI. The multivariate analysis also showed that pioglitazone use was associated with an increased risk of heart failure. In this multivariate analysis, insulin use was not associated with an increased risk of heart failure. The finding may be open to debate, as insulin use has long been associated with an increased risk of heart failure (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 serious heart failure in insulin-treated patients; 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 serious heart failure between pioglitazone and placebo in this high-risk subgroup of insulin-treated patients.

Despite a higher rate of serious heart failure with pioglitazone in PROactive, several observations support the lack of any associated increase in subsequent morbidity or mortality: *1*) the overall incidence of SAEs (with or without end point 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 serious heart failure was similar between treatment groups. These data are important for several reasons. First, that the overall rates of SAEs with pioglitazone remained similar to those observed for placebo suggests a similar overall safety profile for the two treatments, despite a higher rate of serious heart failure with pioglitazone. Second, the most clinically important sequelae of heart failure in patients with type 2 diabetes are death, MI, or stroke. Therefore, the most serious outcomes of heart failure are already captured and accounted for in the composite end point of all-cause mortality, MI, and stroke. Because the rates for this composite end point subsequent to a report of serious heart failure were similar between pioglitazone and placebo, the cardiovascular benefits observed in PROactive with pioglitazone were not diminished by the increased incidence of heart failure. Similarly, the clinical course of heart failure did not appear to differ between treatment groups with respect to time spent in hospital (including inten-

sive 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 heart failure, with an adjusted incidence of heart failure (defined as requiring hospitalization or diagnosed at an outpatient visit) of 8.2% in the TZD group ($n = 5,441$) and 5.3% in the control group (other glucose-lowering agents; $n = 8,103$) 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 heart failure, with no significant differences between heart failure 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 heart failure 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).

Heart failure in type 2 diabetes is generally associated with a high death rate (45 vs. 24% of those with diabetes and no heart failure over 5 years) (20). As such, there has been much debate on TZDs' potential exacerbation of heart failure in some patients versus their benefits on cardiovascular risk factors. Our data indicate that pioglitazone may increase signs of heart failure in susceptible patients. However, the occurrence of serious heart failure did not translate to increased mortality or cardiovascular morbidity with pioglitazone compared with placebo treatment in the patients with serious heart failure. Hence, PROactive provides no evidence that the cardiovascular benefits observed with pioglitazone were attenuated by the higher reported rates of serious heart failure. Our findings are corroborated by a retrospective study of 16,417 Medicare claims in people with diabetes who were discharged after hospitalization for heart failure, 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 heart failure was not included in the composite end point and therefore was not evaluated as an independently adjudicated event. Additionally, no diagnostic criteria were provided to the investigators to ensure a systematic, consistent reporting of heart failure across sites during the study. Because of this, there was concern as to the accuracy of heart failure reports. To address this concern, an independent expert group of cardiologists (under the Chairmanship of Lars Rydén, Karolinska Institut, Stockholm, Sweden) reviewed all cases of serious heart failure and pneumonia. After a review of all available documentation for each case of serious heart failure, 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 serious heart failure with pioglitazone than placebo. The committee's findings validate the accuracy of the investigators' diagnoses of serious or fatal heart failure: episodes of adjudicated serious heart failure were more frequent in patients with advanced cardiovascular disease treated with pioglitazone than in patients given placebo (144 [5.5%] vs. 111 [4.2%] patients, respectively), and mortality due to heart failure was the same in each group (15 [0.6%] patients) (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 peroxisome proliferator–activated receptor-γ 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 heart failure, funded by the American Diabetes Association (18), argues against the possibility that TZDs cause heart failure. Another limitation is that the focus of PROactive was the evaluation of outcome in regard to major cardiovascular events. Because 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 serious heart failure episode.

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

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