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Heart failure events with rosiglitazone in type 2 diabetes: data from the RECORD clinical trial

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See page 773 for the editorial comment on this article (doi:10.1093/eurheartj/ehp604)

Aims

Thiazolidinediones are insulin sensitizers, and are associated with fluid retention and increased risk of heart failure (HF) in people with type 2 diabetes. We assessed fatal and non-fatal HF events and their outcome, and identified HF predictors in the RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes) trial population.

Methods and results

In a multicentre, open-label study, we randomized 4447 people with type 2 diabetes on metformin or sulfonylurea monotherapy with a mean HbA1c of 7.9% to add-on rosiglitazone (n = 2220) or to a combination of metformin and sulfonylurea (n = 2227) and followed them over 5.5 years on average. Heart failure hospitalizations and deaths were adjudicated by a Clinical Endpoint Committee using pre-specified criteria. Independent predictors of HF events were identified out of a group of 30 pre-specified clinical, demographic, and biological variables. In the rosiglitazone group, the risk of HF death or hospitalization was doubled: HR = 2.10 (95% CI, 1.35–3.27): the excess HF event rate was 2.6 (1.1–4.1) per 1000 person-years. An excess in HF deaths was observed (10 vs. two), including four HF deaths as first HF events. By contrast, there was no increase in cardiovascular mortality or hospitalization (HR = 0.99, 95% CI, 0.85–1.16) or in cardiovascular deaths (60 vs. 71). Independent predictors of HF were rosiglitazone assignment, age, urinary albumin : creatinine ratio, body mass index, and systolic blood pressure at baseline. A history of previous cardiovascular disease was not predictive of HF. Duration of HF hospitalization and rate of HF re-hospitalization were similar in the two groups.

Conclusion

These findings confirm the increased risk of HF events in people treated with rosiglitazone and support the recommendation that this agent should not continue to be used in people developing symptomatic HF while using the medication. Close follow-up for the risk of HF should be offered to elderly people, people with markedly increased body mass index, people with microalbuminuria/proteinuria, and people with increased systolic blood pressure.

Keywords

Type 2 diabetes • Thiazolidinediones • Heart failure • Clinical trials

Introduction

Thiazolidinediones (TZDs) are peroxisome proliferator-activated receptor (PPAR-γ) agonists that improve insulin sensitivity in the liver, adipose tissue, and skeletal muscle, thus improving glycaemic control. In 2000, rosiglitazone and pioglitazone received marketing authorization for use in combination with metformin or sulfonylurea in type 2 diabetes in Europe. Although it was recognized that TZDs caused fluid retention, the suggestion that these agents might precipitate or aggravate heart failure (HF) was

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more controversial. International guidelines advised against the use of TZDs in patients with New York Heart Association class III and IV HF, but accepted cautious use in those with less severe symptoms or asymptomatic structural heart disease.1–4 Subsequently, the PROActve study, which enrolled type 2 diabetes patients with macrovascular disease, showed that the incidence of HF was increased by ~30% with pioglitazone.5

A recent meta-analysis including more than 20 000 patients treated with TZDs showed an increased risk of HF events of 72% and suggested that this risk was a class effect of TZDs.6 Observational studies have also confirmed that HF events are increased in elderly diabetic patients treated with TZDs.7 However, these findings have to be treated with caution as HF was generally an investigator-reported outcome, with the concern that fluid retention and oedema may have been misdiagnosed.

RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes) showed that rosiglitazone in combination therapy did not increase the risk of overall cardiovascular mortality or of morbidity compared with a combination of metformin and sulfonylurea.8

Here, we report a detailed analysis of HF events in the RECORD trial which accumulated around 25 000 person-years of follow-up and provides the opportunity to address the issue of HF in a large population with an adjudication based on predefined criteria performed by a Clinical Endpoint Committee (CEC) the members of which were blind to treatment allocation. Fatal and non-fatal outcomes following HF hospitalization were also determined.

**Methods**

**Study design and conduct**

RECORD was a prospective randomized, multicentre clinical trial of dual therapy in type 2 diabetes, comparing rosiglitazone plus either metformin or a sulfonylurea with metformin plus sulfonylurea, as the active control arm. It is registered on www.clinicaltrials.gov as NCT00379769.

The study design has been described in detail previously.9 Briefly, people with type 2 diabetes on monotherapy with either metformin or sulfonylurea and in less than optimal blood glucose control, showed that the incidence of HF was increased by ~30% with pioglitazone.5

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The study design has been described in detail previously.9 Briefly, people with type 2 diabetes on monotherapy with either metformin or sulfonylurea and in less than optimal blood glucose control (HbA1c > 7.0–9.0%) were randomized to receive in an open-label design addition of rosiglitazone or metformin (if already on sulfonylurea) or of rosiglitazone or sulfonylurea (if already on metformin).

The study had an open-label design, and its aim was to assess the non-inferiority of rosiglitazone combination to metformin/sulfonylurea for cardiovascular outcomes, the primary endpoint being the time to first cardiovascular hospitalization or cardiovascular death including HF. Data on glucose control and ambulatory blood pressure have been published.10,11 The study was conducted in 364 centres in 25 countries in Europe and Australasia.

Randomization was by telephone from a dedicated centre, using random-permuted blocks stratified by background medication. The study was not blinded because of planned differences in the strategy for rescue therapy (see below), and the need to allow different types and doses of comparator sulfonylurea therapy. Choice of sulfonylurea from gliclazide, gliclazide, or glibenclamide (glyburide) was according to local investigator practice. Other glucose-lowering therapies were not permitted.

**Patients**

We recruited patients for the study from April 2001 through April 2003. Eligible patients had type 2 diabetes, as defined by criteria of the World Health Organization, were between the ages of 40 and 75 years, had a body mass index (weight in kilograms divided by the square of height in metres) of >25.0 kg/m², and had a glycated haemoglobin level of >7.0% and ≤9.0% while receiving maximum doses of metformin or a sulfonylurea. Exclusion criteria were the current use of other glucose-lowering agents, hospitalization for a major cardiovascular event in the previous 3 months, a planned cardiovascular intervention, HF, clinically significant hepatic disease, renal impairment, and uncontrolled hypertension. The study protocol was approved by ethics committees or institutional review boards in accordance with the laws and customs of each country participating in the study. Written informed consent was obtained from all patients.

**Oral glucose-lowering medications**

Oral therapies were managed throughout to a target HbA1c of ≤7.0%. Rosiglitazone (Avanda, GlaxoSmithKline, UK) was begun at 4 mg/day, and titrated to 8 mg/day any time after 8 weeks of therapy if not to target. The starting dose of metformin and sulfonylurea varied by local practice, with dose increases permitted from 8 weeks. Maximum daily dose of 2550 mg metformin, 15 mg glibenclamide (or equivalent for different preparations), 240 mg gliclazide, or 4 mg glimepiride were stipulated. The criterion for ‘rescue’ therapy by the addition of the third oral agent (if in the rosiglitazone arm) was a confirmed HbA1c of ≥8.5%. Subsequently, if participants taking triple therapy, including rosiglitazone, had a confirmed HbA1c ≥8.5%, rosiglitazone was to be stopped and insulin therapy substituted.

**Heart failure events**

Deaths and investigator-identified cardiovascular events were identified through adverse event reporting and/or direct questioning at study visits using trial record forms. Data from all relevant clinical sources were collected by a clinical trials organization (Quintiles, Bracknell, UK) and provided to an independent CEC the members of which were blind to treatment allocation. This Committee comprised five cardiologists, one diabetologist, and one stroke specialist (see Appendix 1). All events were randomly allocated to a pair of members of the CEC. In case of disagreement, events were discussed by the full committee.

Heart failure diagnosis required the presence of typical signs and symptoms of HF plus objective evidence of cardiac dysfunction plus objective change in HF medications. Heart failure death and hospitalization were defined as death/hospitalization due to the onset and progression of symptoms defining definite HF as described above. Change in current HF medication was defined by an increase in dose or IV medication or introduction of a new class of medication specific for the treatment of HF.

**Statistical analysis**

Statistical methods used for the sample size calculation and the endpoint analysis for the RECORD study have been reported previously.8 The analysis was performed on an intention-to-treat basis and included all patients who were randomized and treated. A sensitivity ‘per-protocol’ analysis was conducted restricted to each participant’s time on dual-combination therapy plus 30 days thereafter. The (unadjusted) incidence of HF (fatal and non-fatal) was analysed by fitting a Cox proportional hazards regression stratified for background medication and using time from randomization to the first event of HF. The comparison between the rosiglitazone group and the active
control group was estimated as a hazard ratio (HR) with 95% CI and a two-sided P-value derived from an asymptotic Wald test.

Multivariable regression analysis was used to identify factors predictive of HF (fatal and non-fatal). Variable selection was carried out using a stepwise selection algorithm at the significance level of 5%. This analysis considered 30 baseline characteristics identified a priori by the steering committee (see Appendix 2), along with randomized study treatment. The multivariable analysis was based on the subset of patients who had complete data available on these variables. The statistical contribution of each variable to the prediction of outcome was assessed by the $\chi^2$ statistic.

To evaluate the potential effects of related variables on the findings, the modelling was repeated combining some variables based on clinical judgement: myocardial infarction, other ischaemic heart disease (IHD) items, peripheral vascular disease, and cerebrovascular disease were pooled into prior cardiovascular disease; medical history of hypertension, systolic blood pressure $>130$ mmHg, and diastolic blood pressure $>80$ mmHg were pooled into hypertension; variables related to any lipid disorder, to the use of diuretics, and to the use of antihypertensive therapy were also combined. The model adjusted for the effects of rosiglitazone assignment, age, gender, and years from the first diagnosis of diabetes.

Simple descriptive summaries and figures were otherwise used to compare the two treatment groups.

The statistical analysis was done by the sponsor’s statistician according to predefined agreement by the steering committee, with SAS software version 8.2 (Cary, NC, USA).

## Results

### Participants

The design of the study is shown in Figure 1. In the study, 2222 people on metformin were assigned to additional rosiglitazone (1117) or sulfonylurea (1105) and 2225 patients on sulfonylurea were assigned to additional rosiglitazone (1103) or metformin (1122). Mean follow-up was 5.5 years, which corresponded to 12 338 person-years in the rosiglitazone group and 12 272 person-years in the comparator group. In the rosiglitazone group, 75% of person-years follow-up were on dual oral therapy and 13% on triple oral therapy (88% in total). In the control group, 83% of person-years follow-up were on dual oral therapy. While $\sim$61% (rosiglitazone) and 51% (control group) of participants completed the study to the final visit on randomized treatment, the proportion of person-time exposed to randomized treatment is a more relevant indicator of time on study drug (88% rosiglitazone, 83% control).

A significant increase in the use of cardiovascular medications was observed during the course of the trial. In particular, there was more use of loop diuretic agents in the rosiglitazone group at 5 years (11.3 and 7.2% on rosiglitazone and active control, respectively).

The primary outcome of the first occurrence of cardiovascular mortality or hospitalization has been published elsewhere, and showed that rosiglitazone in combination therapy was not inferior to standard combination therapy with metformin and sulfonylurea.

The incidence of HF events (either fatal or non fatal) was approximately doubled: 61 cases were observed in the rosiglitazone group vs. 29 in the active control group (HR = 2.10, 95% CI 1.35–3.27), $P = 0.0010$. The estimated excess event rate for HF was 2.6 (1.1–4.1) per 1000 person-years. Figure 2A shows the Kaplan–Meier curve for HF events in the intention-to-treat analysis. The curves started to diverge early and continued to diverge during the whole course of the trial. Of the 61 patients with either fatal or non-fatal HF on rosiglitazone, the first event was non-fatal in 57 patients. In the active control group, the first HF event was non-fatal in all 29 patients (36 HF hospitalizations). A ‘per-protocol’ analysis censoring any participant 30 days after transfer from dual therapy gave similar results [HR 1.91 (95% CI, 1.15–3.19), $P = 0.013$]. 40 people with HF events on rosiglitazone vs. 23 on active control, with exposures of 9310 and 10 236 person-years, respectively. Figure 2B shows the Kaplan–Meier curves for the per-protocol analysis.

The mean duration of admission for HF hospitalization (69 events in the Rosiglitazone group, 36 in the active control group) was similar in the two groups [10.5 ± 6.6 days (SD) in the rosiglitazone group vs. 9.6 ± 5.3 days (SD) in the control group].

Post-admission outcome in patients who developed a first HF event is shown in Table 1. Ten people in the rosiglitazone group died of HF vs. two in the active control group. Four of these events were the first HF event and another six events occurred after the occurrence of the first HF event. Seventeen (30%) of the 57 patients who survived a first HF episode died subsequently in the rosiglitazone group including six HF deaths when compared with 8/29 patients (28%) in the control group with two additional HF deaths. Seven further non-fatal HF events (12%) were observed in the rosiglitazone group when compared with five (17%) in the control group.

There were more first HF events in the rosiglitazone group compared with the active control group, although a similar proportion of patients had recurrent episodes of HF in the both groups (12/57 vs. 6/29).

Forty-five of the 57 people in the rosiglitazone group who survived the first non-fatal HF event were still taking rosiglitazone at the time of the event. Nineteen had rosiglitazone discontinued and 26 were maintained on rosiglitazone.

The risk of HF was assessed in people with/without a history of IHD. Table 2 shows that the relative increase in risk was similar in
the two subgroups (interaction \( P = 1.00 \)), but the absolute risk of HF events was doubled for both the rosiglitazone and the active control group in the IHD patients.

Table 3 compares the baseline characteristics of patients who developed HF over time vs. those without HF events.

A modelling analysis of predictors of HF events was performed using 30 demographic, clinical, and biological baseline characteristics. Table 4 shows the independent predictors of HF that were identified through the modelling analysis: assignment to rosiglitazone, increased age, increased BMI, urinary albumin:creatinine ratio (microalbuminuria/proteinuria), and increased systolic blood pressure. A history of myocardial infarction, peripheral vascular disease, or diagnosed hypertension were not identified as predictors in the stepwise regression. However, interpretation is limited by the relatively low number of HF events in the study and by the small proportion of people within some of the factors investigated, such as myocardial infarction.

In the modelling analysis combining some variables by clinical judgement, four variables were identified as significant predictors (in addition to assignment to rosiglitazone and age already in the model): body mass index, urinary albumin:creatinine ratio (microalbuminuria/proteinuria), antihypertensive drug use, and

Figure 2 Kaplan–Meier plots of time to heart failure (fatal or non-fatal) in the RECORD study (yellow, rosiglitazone group, blue, active control group). (A) Intent-to-treat analysis and (B) per-protocol +30 days analysis.
uncontrolled hypertension at baseline, whereas a previous cardiovascular disease was not predictive \( (p = 0.070) \) in the final model of stepwise regression.

Within this further analysis, the HRs (95% CI) were: 1.10 (1.07–1.13) for age per 1-year increase; 2.95 (1.90–4.57) for the presence of microalbuminuria/proteinuria vs. normoalbuminuria; 1.11 (1.06–1.15) for body mass index per 1 kg/m\(^2\) increase; 2.34 (1.47–3.72) for rosiglitazone assignment vs. control; 2.74 (1.40–5.36) for baseline antihypertensive therapy yes vs. no; 1.66 (1.06–2.62) for uncontrolled hypertension yes vs. no, all \( p \leq 0.03 \). Gender and years since the first diagnosis of diabetes were not significant.

**Discussion**

**Fluid retention and heart failure with thiazolidinediones**

The use of TZDs has been limited by the knowledge that these agents can cause fluid retention and lead to the development of HF.\(^1\) This has led to marketing contraindications in patients with HF and to guidelines cautioning the use of these compounds in some patients with pre-existing cardiovascular disease.\(^4\)

We report here that rosiglitazone added to either metformin or sulfonylurea was associated with a two-fold increase in the risk of HF hospitalizations or death when compared with standard dual therapy. These results, observed in a population of more than 4400 people with a mean follow-up of more than 5 years confirm and extend previous observations. Unlike previous studies, we used predefined criteria for HF based on the European Society of Cardiology guidelines, and a specific CEC prospectively adjudicated all HF endpoints. This process limited the risk of not capturing or of misdiagnosing HF events, and the incidence of HF observed in RECORD is likely to reflect the size of the problem in patients treated with TZDs.

In particular, the magnitude of the excess risk observed here is in line with data from a recent meta-analysis which reported an overall excess risk of 72%, with no heterogeneity between pioglitazone and rosiglitazone.\(^6\)

The mechanism of TZD-induced fluid retention and oedema remains unclear. In vitro and animal studies suggest that the PPAR\(\gamma\) agonists stimulate sodium re-absorption in the distal nephron by up-regulating the expression and translocating the collecting duct epithelial sodium channel.\(^13\) By contrast, no direct effect of TZDs on cardiac function or structure has been reported.\(^17\)

In people with pre-existing cardiac disease or HF, fluid retention and plasma volume expansion can induce HF decompensation. People with diabetes are prone to develop coronary artery disease and diastolic dysfunction, and poor glycaemic control is associated with increased incidence of HF.\(^18\) Thus, TZD-induced fluid retention is therefore of particular concern in this population at risk of developing HF: in clinical trials which excluded people with a history of HF, TZDs induced a small increase in HF episodes,\(^20\) whereas in the PROactive study pioglitazone was associated with a 6% incidence of HF hospitalizations over a follow-up of almost 3 years in people with type 2 diabetes and macrovascular disease, half of these with a previous myocardial infarction. The risk of HF episodes with TZDs increases with the prevalence of the underlying cardiac disease. This finding is confirmed in RECORD, although a minority of participants had a history of prior documented IHD or of a previous macrovascular event. In the subgroup which had a previous IHD, the incidence of HF events was higher (4.4%) than in people without previous IHD (2.4%) in the rosiglitazone group. However, the same was true for the metformin/sulfonylurea control group (HF incidence with previous IHD 2.1%; incidence without 1.1%) giving similar relative risk, rosiglitazone vs. control (2.16 and 2.10) in the two subgroups. These findings

### Table 1: Outcome of patients with heart failure events (fatal and non-fatal)

<table>
<thead>
<tr>
<th></th>
<th>Rosiglitazone (n = 2220)</th>
<th>Control (n = 2227)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with HF events (fatal and non-fatal)</td>
<td>61/2220 (2.7%)</td>
<td>29/2227 (1.3%)</td>
</tr>
<tr>
<td>First HF event fatal</td>
<td>4/2220</td>
<td>0/2227</td>
</tr>
<tr>
<td>Survived first HF event</td>
<td>57/2220 (25.7%)</td>
<td>29/2227 (12.9%)</td>
</tr>
<tr>
<td>All-cause death (%)</td>
<td>17/2220 (7.7%)</td>
<td>8/2227 (3.7%)</td>
</tr>
<tr>
<td>HF death</td>
<td>6/2220</td>
<td>2/2227</td>
</tr>
<tr>
<td>Other CV deatha</td>
<td>9/2220</td>
<td>2/2227</td>
</tr>
<tr>
<td>Other death</td>
<td>2/2220</td>
<td>4/2227</td>
</tr>
<tr>
<td>Further non-fatal HF event (%)</td>
<td>7/111 (6.3%)</td>
<td>5/111 (4.5%)</td>
</tr>
<tr>
<td>Other non-fatal CV event (%)</td>
<td>13/111 (11.8%)</td>
<td>10/111 (9.0%)</td>
</tr>
<tr>
<td>No other CV event (%)</td>
<td>26/111 (23.4%)</td>
<td>15/111 (13.5%)</td>
</tr>
</tbody>
</table>

Data are number of patients (per cent of those surviving first HF event). Note: participants may experience multiple events (both HF and CV), so numbers in each category will not sum to the number surviving the first HF event.

aOther CV death includes one fatal MI on same day as first HF hospitalization.

### Table 2: Relative risk for heart failure events in patients with and without prior ischaemic heart disease

<table>
<thead>
<tr>
<th></th>
<th>Rosiglitazone</th>
<th>Control</th>
<th>Relative risk (95% CI)</th>
<th>( P )-value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>61/2220 (2.7%)</td>
<td>29/2227 (1.3%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Prior ischaemic heart disease</td>
<td>17/383 (4.4%)</td>
<td>8/389 (2.1%)</td>
<td>2.16 (0.94, 4.94)</td>
<td>–</td>
</tr>
<tr>
<td>No prior ischaemic heart disease</td>
<td>44/1837 (2.4%)</td>
<td>21/1838 (1.1%)</td>
<td>2.10 (1.25, 3.51)</td>
<td>1.00 (NS)</td>
</tr>
</tbody>
</table>

Data are patients with HF events/number of patients randomized and treated (%).
Heart failure events with rosiglitazone

Table 3  Baseline characteristics of patients who developed heart failure over time

<table>
<thead>
<tr>
<th>Variable</th>
<th>Participants with HF adjudicated event (n = 90)</th>
<th>Participants without HF adjudicated event (n = 4357)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.8 (7.3)</td>
<td>58.3 (8.3)</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>50 (55.6)</td>
<td>2244 (51.5)</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>25 (27.8)</td>
<td>747 (17.1)</td>
</tr>
<tr>
<td>Stable angina</td>
<td>17 (18.9)</td>
<td>440 (10.1)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>5 (5.6)</td>
<td>213 (4.9)</td>
</tr>
<tr>
<td>Coronary angioplasty</td>
<td>5 (5.6)</td>
<td>129 (3.0)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>3 (3.3)</td>
<td>47 (1.1)</td>
</tr>
<tr>
<td>Stroke</td>
<td>7 (7.8)</td>
<td>101 (2.3)</td>
</tr>
<tr>
<td>Transient ischaemic attack</td>
<td>3 (3.3)</td>
<td>95 (2.2)</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>12 (13.3)</td>
<td>398 (9.1)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>9 (10.0)</td>
<td>183 (4.2)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>2 (2.2)</td>
<td>19 (0.4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>85 (94.4)</td>
<td>3478 (79.8)</td>
</tr>
<tr>
<td>Statins</td>
<td>13 (14.4)</td>
<td>810 (18.6)</td>
</tr>
<tr>
<td>Fibrates</td>
<td>3 (3.3)</td>
<td>246 (5.6)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>33 (36.7)</td>
<td>883 (20.3)</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>25 (27.8)</td>
<td>748 (17.2)</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>8 (8.9)</td>
<td>135 (3.1)</td>
</tr>
<tr>
<td>β-Adrenergic blockers</td>
<td>35 (38.9)</td>
<td>964 (22.1)</td>
</tr>
<tr>
<td>ACE-inhibitors/A2R blockers</td>
<td>55 (61.1)</td>
<td>2038 (46.8)</td>
</tr>
<tr>
<td>Calcium-channel blockers</td>
<td>32 (35.6)</td>
<td>881 (20.2)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>10 (11.1)</td>
<td>262 (6.0)</td>
</tr>
<tr>
<td>Antiplatelet agents</td>
<td>26 (28.9)</td>
<td>844 (19.4)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>11 (12.2)</td>
<td>695 (16.0)</td>
</tr>
<tr>
<td>Previous smoker</td>
<td>30 (33.3)</td>
<td>1074 (24.6)</td>
</tr>
<tr>
<td>Microalbuminuria or proteinuriaa</td>
<td>41 (44)</td>
<td>810 (22)</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>7.5 (4.9)</td>
<td>7.1 (4.9)</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>110.9 (13.2)</td>
<td>104.6 (11.7)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>93.1 (17.8)</td>
<td>88.9 (16.0)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>33.5 (5.6)</td>
<td>31.4 (4.8)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.84 (0.69)</td>
<td>7.90 (0.70)</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sBP (mmHg)</td>
<td>148.7 (18.9)</td>
<td>138.6 (15.3)</td>
</tr>
<tr>
<td>dBP (mmHg)</td>
<td>84.5 (9.8)</td>
<td>82.9 (8.3)</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>73.1 (9.7)</td>
<td>73.7 (8.6)</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>3.3 (0.9)</td>
<td>3.3 (0.9)</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.2 (0.3)</td>
<td>1.2 (0.3)</td>
</tr>
<tr>
<td>Haemoglobin (g/L)</td>
<td>141.5 (12.7)</td>
<td>141.7 (11.6)</td>
</tr>
<tr>
<td>Serum creatinine (µmol/L)</td>
<td>68.8 (18.0)</td>
<td>64.6 (17.6)</td>
</tr>
<tr>
<td>Uric acid (µmol/L)</td>
<td>237.0 (82.9)</td>
<td>297.4 (78.1)</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>140.4 (2.4)</td>
<td>140.1 (2.3)</td>
</tr>
<tr>
<td>Blood urea nitrogen (mmol/L)</td>
<td>6.2 (1.4)</td>
<td>5.7 (1.5)</td>
</tr>
</tbody>
</table>

Data are number (%) or mean (SD). HbA1c, haemoglobin A1c.

aMicroalbuminuria: ACR ≥2.5 to <30.0 mg/mmol in males and ACR ≥3.5 to <30.0 mg/mmol in females. Proteinuria: ACR ≥3.5 mg/mmol.

Table 4  Significant baseline predictors of heart failure risk by multivariable analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>χ²</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 1-year increase)</td>
<td>1.10</td>
<td>(1.07–1.14)</td>
<td>39.71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urinary albumin : creatinine ratio (microalbuminuria/proteinuria vs. normoalbuminuria)</td>
<td>3.09</td>
<td>(2.01–4.77)</td>
<td>26.12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index (per 1 kg/m² increase)</td>
<td>1.11</td>
<td>(1.06–1.15)</td>
<td>23.94</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rosiglitazone assignment (rosiglitazone vs. control)</td>
<td>2.33</td>
<td>(1.46–3.70)</td>
<td>12.74</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure (per 1 mmHg increase)</td>
<td>1.02</td>
<td>(1.01–1.03)</td>
<td>9.18</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Model based on n = 3849 (86%) patients with n = 84 (93%) HF events with complete data on the four baseline characteristics identified as predictors (via stepwise selection and 5% significance).

must, however, be interpreted with caution, given the small size of the population with prior IHD and therefore the small number of events observed in this group.

Four baseline factors were independent predictors of HF in addition to rosiglitazone treatment: elderly people, people with increased body mass index, those with microalbuminuria or overt proteinuria, and people with increased systolic blood pressure were at a substantially increased risk of HF events. Albumin/creatinine ratio is a recognized marker of diabetic nephropathy, and interventions which reduce the development or the progression of this complication have been associated with a significant reduction in HF events. Of note, a history of previous cardiovascular disease was not predictive in our model, but the absolute risk of HF was increased in patients with previous IHD. In another study, pioglitazone use, renal dysfunction, diuretic use, LDL cholesterol, previous myocardial infarction, age, duration of diabetes, HbA1c, and body mass index were identified as independent predictors of HF events. Most of these factors have been previously recognized as predictors of HF in people with diabetes. Elderly patients with obesity or increased body mass index or with proteinuria, renal dysfunction, or hypertension should therefore be closely followed for signs and symptoms suggestive of HF when treated with TZDs.

Heart failure and cardiovascular outcomes

It has been suggested that the increased event rate of HF with TZDs is not associated with an increase in cardiovascular mortality.

In the PROactive study, the number of deaths from HF was similar in the pioglitazone group (25) and in the placebo group (22), and in patients reported to have a serious HF event, the subsequent rate of death from any cause, myocardial infarction, or stroke was lower in the pioglitazone group. The number of
patients with serious HF for whom the HF event resolved during follow-up was also similar between treatment groups. In the RECORD trial, the number of primary events (cardiovascular mortality or cardiovascular hospitalization) was similar in the two treatment groups, and there were somewhat fewer cardiovascular deaths in the rosiglitazone group (60) than in the control group (71). This was also true for specific causes of cardiovascular death, including sudden cardiac death, myocardial infarction, or stroke, and for all-cause deaths, but as with cardiovascular death, the difference was not significant.

By contrast, we observed an excess in HF deaths (10 vs. two), including four fatal initial HF events in the rosiglitazone group. Six additional patients surviving an initial HF event subsequently experienced an HF death when compared with two in the control group. We therefore cannot conclude that HF events with rosiglitazone are all benign episodes of reversible fluid retention.

The fatal and non-fatal HF event rate was higher in PROactive than in RECORD. This is probably because all patients in PROactive had prior macrovascular disease, including myocardial infarction in 47%.

The length of hospitalizations related to HF events was ~10 days and was similar in both groups. This finding is consistent with the observation of HF hospitalizations in the PROactive study and with the average length of hospitalization for an HF population in Europe.

More people in the rosiglitazone group experienced multiple episodes of HF than in the control group. However, in survivors of a first HF event, the number of people who experienced a further HF event or a further other cardiovascular event was similar in the two treatment groups.

The comparison of HF events in the two large outcome studies with TZDs, RECORD and PROactive, is difficult due to differences in design and inclusion criteria. Furthermore, the duration of follow-up in PROactive was shorter than in RECORD (34.5 vs. 66 months), a factor which may have played a role in the long-term assessment of events and outcome of a chronic condition such as HF. Finally, it is noteworthy that HF was not a protocol-defined centrally adjudicated event in PROactive.

Strengths and limitations
The detailed analysis of HF events in the RECORD trial provides incremental information on the risk of developing this adverse event in a broad clinically representative population of people with type 2 diabetes exposed to rosiglitazone for a long period of time and carefully followed-up. Heart failure is a potentially ‘soft’ endpoint in this population due to confounding disorders such as obesity or non-cardiac peripheral oedema. The prospective adjudication of all hospitalizations or deaths by an endpoint committee blinded to medications and using pre-specified criteria based on the European Society of Cardiology guidelines limited the risk of misdiagnosis of HF in our study. In particular, the diagnosis of HF systematically required the documentation of cardiac dysfunction and of HF medication changes in addition to the presence of signs and symptoms of HF.

There are some weaknesses in this secondary analysis: somewhat higher use of loop diuretics (~4% by 5 years) in the rosiglitazone group may have attenuated the incidence of HF, although we are unable to attribute the reason for investigator’s prescription of these medications. The mean age of the population was ~60 years, and we cannot extend our conclusions to the elderly or the very elderly, a population at high risk of HF. Owing to the limited number of HF events and of the non-randomized nature of the decision to continue or discontinue rosiglitazone after an event, we cannot draw any conclusion on the risk of HF in patients experiencing an HF event and continuing rosiglitazone.

Finally, we examined only HF hospitalizations or deaths. The actual incidence of fluid retention cannot therefore be assessed from our analysis, although the CEC examined all presumed cardiovascular serious adverse events.

Conclusion
We found that HF events were twice as common in people with type 2 diabetes and increased body mass index treated by rosiglitazone added to metformin or a sulfonylurea than in the conventional dual-therapy group. A number of factors were identified as predictors of HF in addition to treatment with rosiglitazone. Elderly people, people with markedly increased body mass index, people with microalbuminuria/proteinuria, and people with increased systolic blood pressure are particularly at risk of HF and should be offered close follow-up.

Finally, although rosiglitazone was not associated with increased cardiovascular mortality or morbidity, an excess number of HF deaths was observed. Overall, our findings support the guidelines issued for the management of patients treated with TZDs in the presence of HF. The development of HF in patients treated with this compound should lead to discontinuation.

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Appendix 1
Clinical Endpoint Committee: M.K. (chair), M. Bohm, A. Gavazzi, K. Lees, M. Marre, P. Ponikowski, M. Syvanne.
Appendix 2. List of baseline variables included in the predictive modelling analysis

Demographics/diabetes history
- Age (years)/gender
- BMI (kg/m²)
- Waist circumference (cm)
- HbA₁c (%)
- Duration of diabetes (years)

Medical history
- Previous smoker vs. non-smoker
- Current smoker vs. non-smoker
- Diagnosed hypertension
- Peripheral vascular disease
- Cerebrovascular disease
- Myocardial infarction

Baseline medications
- Nitrates
- ACE-inhibitor/ARBs
- Diuretics
- Calcium-channel blockers
- Beta-blockers
- Anti-platelets
- Statins

Haematology and chemistry
- LDLC (mmol/L)
- HDLC (mmol/L)
- Heart rate (bpm)
- Systolic BP (mmHg)
- Diastolic BP (mmHg)
- Haemoglobin (g/L)
- Creatinine (µmol/L)
- Urinary albumin/creatinine ratio (microalbuminuria/proteinuria vs. normoalbuminuria)
- Uric acid (µmol/L)
- Sodium (mmol/L)
- Blood urea nitrogen (mmol/L)

References