Thiazolidinediones and Heart Failure

A teleo-analysis

SONAL SINGH, MD[1]
YOON K. LOKE, MBBS, MD[2]
CURT D. FURBERG, MD, PHD[3]

OBJECTIVE — Thiazolidinediones (TZDs) are known to increase the risk of heart failure in patients with type 2 diabetes. We aimed to evaluate the magnitude of the risk of heart failure with TZDs and classify this adverse effect under the novel dose-time-susceptibility system.

RESEARCH DESIGN AND METHODS — Evidence from randomized trials, controlled observational studies, anecdotal case reports, case series, and spontaneous reports in the Canadian Drug Reaction Monitoring Program (CADRMP) was analyzed in a teleo-analysis.

RESULTS — A random-effects meta-analysis of three randomized controlled trials showed an odds ratio (OR) of 2.1 (95% CI 1.08–4.08; $P = 0.03$) for the risk of heart failure in patients randomized to TZDs compared with placebo. Four observational studies revealed an OR of 1.55 (1.33–1.80; $P < 0.00001$) for heart failure with TZDs. A dose-time-susceptibility analysis of 28 published reports and 214 spontaneous reports from the CADRMP database showed that heart failure was more likely to occur after several months (with median treatment duration of 24 weeks after initiation of therapy). Heart failure equally occurred at high and low doses. The adverse reaction was not limited to the elderly, with 42 of 162 (26%) of the reported cases occurring in patients aged <60 years.

CONCLUSIONS — Our teleo-analysis confirms the increased magnitude of the risk of heart failure with TZDs. We estimate the number needed to harm with TZDs to be ~50 over 2.2 years. Existing guidelines and package inserts may have to be revised to incorporate these risk characteristics of TZDs.

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Thiazolidinediones (TZDs) have an important role in the management of type 2 diabetes. Clinicians have been urged to exercise caution, since several published case reports and guidelines have raised concerns that these drugs may increase the risk of heart failure (1–9). However, there is uncertainty surrounding the exact magnitude of the risk of heart failure and the susceptibility factors that may potentiate this risk. It would be helpful if specific characteristics of the adverse reaction, such as dose responsiveness and duration of onset to heart failure, were defined.

Information on this topic has expanded with the publication of new studies on TZDs (10). In this study, we aimed to *1*) estimate the magnitude of the risk of heart failure with TZDs using data from controlled observational studies and randomized controlled trials (RCTs) and *2*) classify this adverse effect under the novel dose-time-susceptibility system using data from published case reports and spontaneous reports from the Canadian Drug Reaction Monitoring Program (CADRMP) (11).

RESEARCH DESIGN AND METHODS

— Data from RCTs, observational studies, and anecdotal case reports were analyzed in a teleo-analysis. A teleo-analysis attempts to determine the adverse effect of a drug by complementing information from different study designs across all grades of evidence (12). Controlled data from randomized trials and observational studies are used to evaluate the statistical association between a drug and its adverse effect and estimate the frequency of the adverse event. This is complemented by data from individual case reports, allowing for the evaluation of specific characteristics of adverse effects such as dose, time, and susceptibility factors. We searched without language restrictions and contacted authors when specific aspects of the data required clarification.

RCTs

We retrieved potentially relevant citations by examinging trials identified in existing published meta-analyses (13,14). PubMed was searched from January 2003 to September 2006 for recent trials by applying the "Randomized Controlled Trial" search filter to the medical subject heading terms "pioglitazone" or "rosiglitazone," which yielded 221 citations. We retrieved unpublished RCTs for rosiglitazone from the manufacturer's Web site (15). No unpublished RCTs were available for pioglitazone. Included RCTs *1*) were at least 6 months' duration of TZD for treating or preventing type 2 diabetes, *2*) were direct head-to-head evaluations between a TZD alone (rosiglitazone or pioglitazone) and placebo alone, and *3*) provided numerical data on patients experiencing heart failure.

Observational studies

PubMed was searched using the medical subject heading terms "thiazolidinediones" and "case-control studies" or "cohort studies" in September 2006. We used the bibliographies of relevant studies, the "Web of Knowledge Cited References"

From the [1]Section of General Internal Medicine, Wake Forest University School of Medicine, Winston-Salem, North Carolina; the [2]School of Medicine, Health Policy and Practice, University of East Anglia, Norwich, U.K.; and the [3]Division of Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, North Carolina.

Address correspondence and reprint requests to Sonal Singh, Section of General Internal Medicine, Wake Forest University School of Medicine, 1 Medical Center Blvd., Winston-Salem, NC 27157. E-mail: sosingh@wfubmc.edu.

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S.S. and Y.K.L. contributed equally to this work.

Abbreviations: CADRMP, Canadian Drug Reaction Monitoring Program; NYHA, New York Heart Association; RCT, randomized controlled trial; TZD, thiazolidinedione.

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

Table 1—*RTCs of TZDs that evaluated heart failure outcomes*

Study (ref.)	Heart failure rates in the treatment arm	Heart failure rates in the control arm	Participants	Drug and daily dosage	Duration of treatment	Case ascertainment and definition
DREAM 2006 (10)	14 of 2,635	2 of 2,634	Impaired glucose tolerance and/or fasting glucose, not on hypoglycemic medication. Patients with heart failure excluded.	8 mg rosiglitazone	3 years (median)	Active surveillance. Confirmed heart failure was secondary outcome adjudicated by blinded independent monitoring committee. Prespecified definition was patient requiring acute treatment plus 2 of 3 criteria from: *1*) typical signs/symptoms; *2*) radiologic findings; *3*) use of diuretics, vasodilators, or inotrope.
ProActive 05 (18)	281 of 2,605	198 of 2,633	Type 2 diabetic patients with vascular disease. Less than one-third on insulin. Excluded if greater than NYHA Class II.	15–45 mg titrated pioglitazone	34.5 months	Active surveillance but no independent monitoring. We extracted data on all reported heart failure events. Post hoc independent blinded adjudication using clinical, radiologic, and laboratory criteria confirmed accuracy of original diagnoses.
GlaxoSmithKline 211 (17)	19 of 110	10 of 114	Type 2 diabetic patients with NYHA Class I or II; single blinded. No information on concomitant medications.	4–8 mg titrated rosiglitazone	12 months	Active surveillance and worsening heart failure a prespecified secondary outcome. We extracted data on all investigator-reported cardiac failure events. No information on diagnostic criteria or adjudication.

list, and the "Related Articles" link in PubMed to identify additional studies. Included articles were controlled observational studies containing data that enabled us to calculate the OR of new onset of heart failure developing in patients receiving TZDs compared with patients receiving other oral antidiabetes medications with or without insulin.

Case reports

PubMed, Embase, and Google Scholar were searched using the terms "thiazolidinediones" and "heart failure" to identify case reports and case series in September 2006. We used the bibliographies of relevant studies, the "Web of Knowledge Cited References" list, and the "Related Articles" link in PubMed to identify additional studies. We identified 28 published reports. All adverse drug reactions reported with pioglitazone (n = 195) or rosiglitazone (n = 830) to Health Canada's spontaneous adverse event reporting system (CADRMP), the only English language regulatory authority database that allows easy and unrestricted Web access, were reviewed in September 2006 to identify reports of heart failure or pulmonary edema (16). Reports describing only edema were excluded. A total of 51 reports of heart failure with pioglitazone and 163 reports of heart failure with rosiglitazone were identified. Information on age, sex, duration, dose of TZD, outcome of reaction, and concomitant medications was abstracted from both the published case reports and the spontaneous reports.

Data synthesis

We used RevMan 4.28 to calculate summary ORs (random-effects model) and heterogeneity.

RESULTS

RCTs

We identified three trials of 10,731 patients that provided numerical information on heart failure events (Table 1) (10,17,18). The pooled OR for heart failure was 2.1 (95% CI 1.08–4.08; P = 0.03) (Fig. 1). There is moderate heterogeneity around this estimate (I^2 = 59%), which is attributable to the different populations and varying criteria for ascertaining heart failure events.

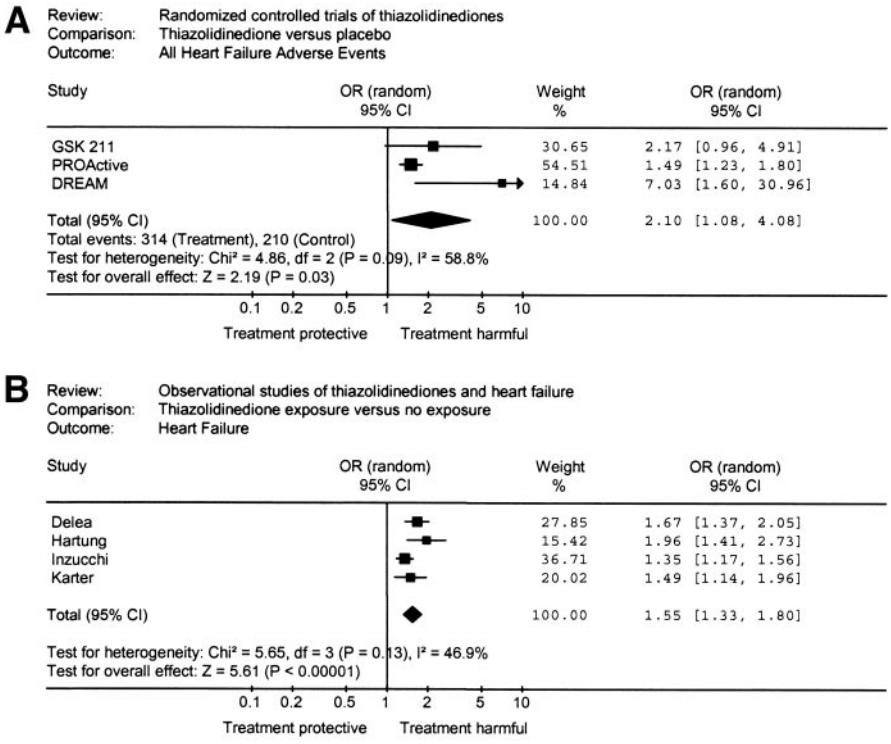

Figure 1—*Meta-analysis of the risk of heart failure in patients exposed to TZDs.*

Observational studies

Four observational studies of 67,382 patients were included (19–22). The pooled OR for heart failure with TZDs was 1.55 (95% CI 1.33–1.80; $P < 0.00001$) (Fig. 1). Moderate heterogeneity was found ($I^2 = 47\%$) due to the differences in population and coexisting morbidity. If we exclude the study by Inzucchi et al. (21), which focused on diabetic patients after myocardial infarction rather than on diabetic patients in general, sensitivity analysis shows the heterogeneity to have an I^2 of 0%.

Excluded observational studies

Two observational studies were excluded because they did not fulfill the selection criteria (Table 2) (23,24). The study by Masoudi et al. (23) studied readmission rates for patients on TZDs who already had a recent admission for heart failure, whereas the study by Rajagopalan et al. (24) compared the rates of heart failure solely between patients on pioglitazone and insulin. Our selection criteria were based on patients potentially being able to receive other oral hypoglycemic agents, with or without insulin. The use of a control group comprising patients on insulin is particularly prone to confounding, as patients with the most severe type 2 diabetes are likely to receive insulin.

Case reports

Age. A dose-time-susceptibility analysis of 162 analyzable case subjects showed that the age ranged from 31 to 88 years, with a median age of 67 years. The adverse effect was not limited to the elderly because 42 of 162 case subjects (26%) were aged <60 years.

Dose and duration. Among 99 analyzable cases, the median duration for the onset of heart failure was 24 weeks (range 1–260), suggesting that the reaction is delayed or late onset in nature (Fig. 2). Patients on low doses were also at risk of developing heart failure soon after starting treatment. One patient on pioglitazone and nine patients on rosiglitazone developed heart failure in the first 4 weeks of low-dose therapy (defined as ≤15 mg pioglitazone or ≤4 mg rosiglitazone). Heart failure did not develop much earlier in those receiving TZDs in the high-dose range (Fig. 3). Heart failure due to TZD use also did not occur as a function of the cumulative ingested dose. Heart failure can occur even at doses below those used for therapeutic benefit, and the relatively low daily doses of 15 mg pioglitazone or 2 mg rosiglitazone are already at the top end of the dose-effect curve for triggering episodes of heart failure.

Susceptibility. We were unable to identify any particular susceptibility factors, and heart failure occurred equally among 110 men and 88 women. Death occurred in nine patients.

CONCLUSIONS — Our teleo-analysis provides useful clinical information on the increased risk of heart failure with TZDs. This evidence should be judged in the context of a recent systematic review of pioglitazone, which found little evidence for beneficial effects on hard clinical end points (25).

Diabetes and the use of any therapy for the treatment of diabetes is associated with an increased risk of heart failure (26). The background incidence of heart failure in patients with diabetes is ~1.9% over 2.2 years (27). The estimated number needed to harm with TZDs, based on an OR of 2.10, would be ~50 over a 2.2 year follow-up period.

Biological basis of the reaction

The development of heart failure is a class effect of the TZDs, mediated through increased plasma volume rather than through a direct effect on the myocardium (9,17,28). A recent meta-analysis of RCTs found the OR for edema with TZDs to be 2.26 (95% CI 2.02–2.53) (14), similar to our estimates of heart failure. Fluid retention due to TZDs may trigger (clinically apparent) episodes of heart failure in susceptible individuals or may unveil the disease in those with latent heart failure (no previous cardiac history). This theory is supported by echocardiographic evaluation of heart failure patients where no deterioration in left ventricular function was found with TZDs therapy (5,17). Similarly, a 52-week study of rosiglitazone did not show any decline in the left ventricular ejection fraction (29). Fluid retention appears to be mediated through increased sodium reabsorption by the renal peroxisome proliferator–activated receptor-γ–dependent pathway in the collecting tubules, suggesting a possible therapeutic role for amiloride rather than loop diuretics, for which resistance has been reported (30).

The rosiglitazone package insert warns against the use of rosiglitazone in New York Heart Association (NYHA)

Table 2—*Observational studies of TZD exposure and association with heart failure*

Study (ref.)	Study type and data source	Study population	Outcome ascertainment	Key findings
Hartung 2005(19)	Case control. Oregon Medicaid insurance claims database.	Diabetic patients (288 case and 1,652 control subjects) with prescription claims data for OHAs within 60 days of hospital admission.	ICD codes used to verify cases with first hospital admission due to heart failure. Control subjects had admission for other reasons.	59 of 229 cases of heart failure had been exposed, whereas 216 of 1,436 controls were exposed.
Karter 2005 (20)	Retrospective cohort. Kaiser Permanente Northern California Diabetic registry.	23,440 patients initiating diabetes medication ("new user") with no history of heart failure.	ICD codes used to identify admissions for heart failure.	Heart failure rates in 67 of 3,556 exposed vs. 253 of 19,884 unexposed.
Inzucchi 2005 (21)	Retrospective cohort. Medicare National Heart Care Project.	Diabetic patients with recent admission for myocardial infarction discharged on hypoglycemic agents.	Readmission events (including heart failure) recorded for up to 1 year after discharge.	Heart failure rates in 402 of 819 exposed compared with 3,294 of 7,914 unexposed.
Delea 2003 (22)	Retrospective cohort, based on Pharmetrics Insurance database.	Diabetic patients with pharmacy claim for oral hypoglycemic drugs. Patients with existing heart failure excluded.	Follow-up data for 43 months to diagnose new heart failure cases. Verification through ICD codes for claims.	Heart failure rates in exposed: 126 of 5,441 vs. unexposed: 397 of 28,103.
Masoudi 2005 (23)*	Retrospective cohort. From a Medicare database.	16,417 diabetic patients with a pre-existing history of hospital admission for heart failure.	1-year follow-up to estimate risk of readmission for heart failure.	Heart failure rates in 1,505 of 2,226 exposed vs. 8,912 of 13,093 unexposed.
Rajagopalan 2004 (24)*	Retrospective cohort. Pharmetrics insurance database in U.S.	1,668 matched pairs initiating pioglitazone or insulin between January 1999 and December 2001. Those with existing heart failure were excluded.	Follow-up data of at least 3 months, using ICD codes for claims arising from heart failure.	Heart failure rates in 33 of 2,226 on pioglitazone compared with 66 of 1,668 on insulin.

*Observational studies excluded from the meta-analysis. OHA, oral hypoglycemic agent.

Stage III and IV heart failure patients and cautions about the increased risk of heart failure in combination with insulin (31). Similarly, the package insert of pioglitAzone cautions against this increased risk of heart failure (32). However, this increased risk is not confined to patients on insulin. None of the patients in the DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial were on insulin (10), and only one-third of patients required insulin in the PROActive (PROspective pioglitAzone Clinical Trial In macroVascular Events) Study (18). We were unable to obtain information on concomitant medications in GlaxoSmithKline Study 211 (17) (Table 1).

A 2003 consensus review by the American Heart Association and the American Diabetes Association rightly recommends that TZDs be avoided in patients with NYHA Stage III and IV heart failure (as RCTs of TZDs excluded these patients) (9). However, they also recommend that TZD therapy be initiated at a low dose, slowly increased, and closely monitored in diabetic patients with NYHA Stage I and II heart failure and in those with depressed ejection fractions (<40%) and one or more cardiac risk factors without heart disease (9). Recommendations for their use, even at low doses in NYHA Stage 1 and II heart failure patients and in those with risk factors for heart failure, may need to be carefully revaluated as heart failure occurred even among patients with no history of heart failure in the DREAM Trial and observational studies. Heart failure also occurred at the lowest-dose range for TZDs in spontaneous reports and at both low (4 mg) and high (8 mg) doses of rosiglitazone used in clinical trials. The occurrence of heart failure several months after initiation of TZDs suggests a long-term effect of the drug, which may not be avoided by slow-dose titration, and mandates the need for long-term vigilance.

Further research studies should evaluate intraclass differences in the risk of heart failure between the TZDs and optimal management strategies in patients experiencing heart failure on TZDs, including immediate withdrawal and the role of diuretics such as amiloride or spironolactone (33). Studies distinguishing between heart failure requiring hospitalization versus heart failure that can be managed as an outpatient are also needed.

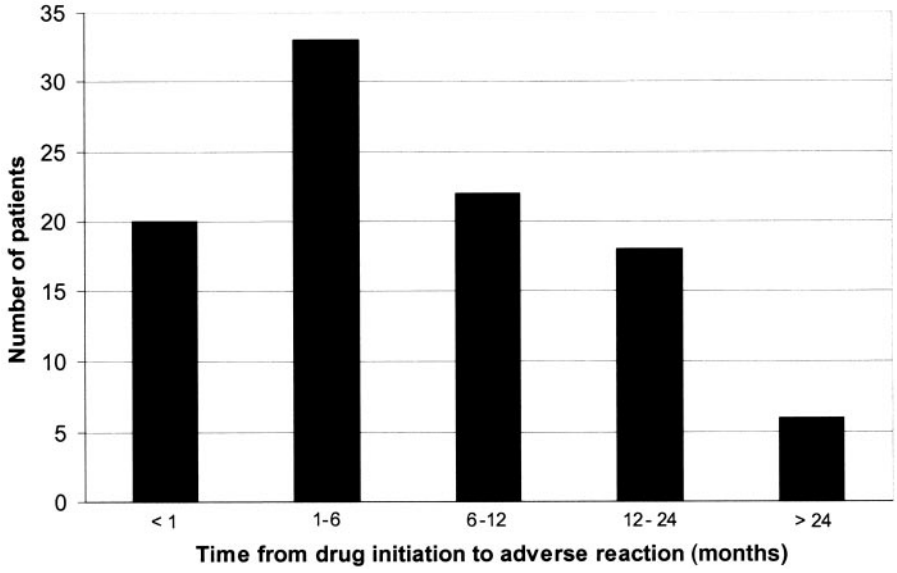

Figure 2—*Duration of TZD therapy prior to adverse reaction.*

Limitations

There are a number of limitations to our study. Diagnosing heart failure is challenging and may require subjective clinical interpretation of symptoms, signs, and additional investigations (such as chest radiographs or echocardiography). Inconsistent diagnostic criteria across studies may have led to some heterogeneity. Patients with progressive pedal edema from fluid retention could potentially have been erroneously classified as heart failure cases. This, however, seems unlikely here, since all three included RCTs were designed to actively seek out cases of heart failure and heart failure information in two of the large published studies was subjected to independently masked adjudication based on prespecified criteria (Table 1). Moreover, three of the four observational studies used fairly stringent criteria in that the patients required hospital admission due to heart failure.

In addition, anecdotal case reports may not be entirely representative of the population, were often incomplete, and were not necessarily causal, as they cannot rule out the role of concomitant medicines (metformin and insulin) in exacerbating heart failure. Case reports are subject to publication bias, which was minimized by the use of spontaneous reports from the CADRMP database. Spontaneous reports and case reports represent the observation of the individual health professionals and layperson and should not be used for numerically estimating the risk of advanced diabetic retinopathy, as the denominator is unknown. We used data from RCTs and observational studies to statistically determine the association between TZDs and heart failure. Observational studies are susceptible to confounding. We corroborated observational data with results from RCTs, and the risk of heart failure was consistent in magnitude and direction.

In conclusion, our teleo-analysis confirms the increased magnitude of the risk of heart failure with TZDs. The number needed to harm with TZDs was estimated to be ~50 over 2.2 years. Heart failure can occur at both high and low doses, usually weeks to months after initiation of TZDs. It can occur in the absence of insulin, even in patients without a history of heart failure. Existing guidelines and package inserts may have to be revised to incorporate these risk characteristics of TZDs.

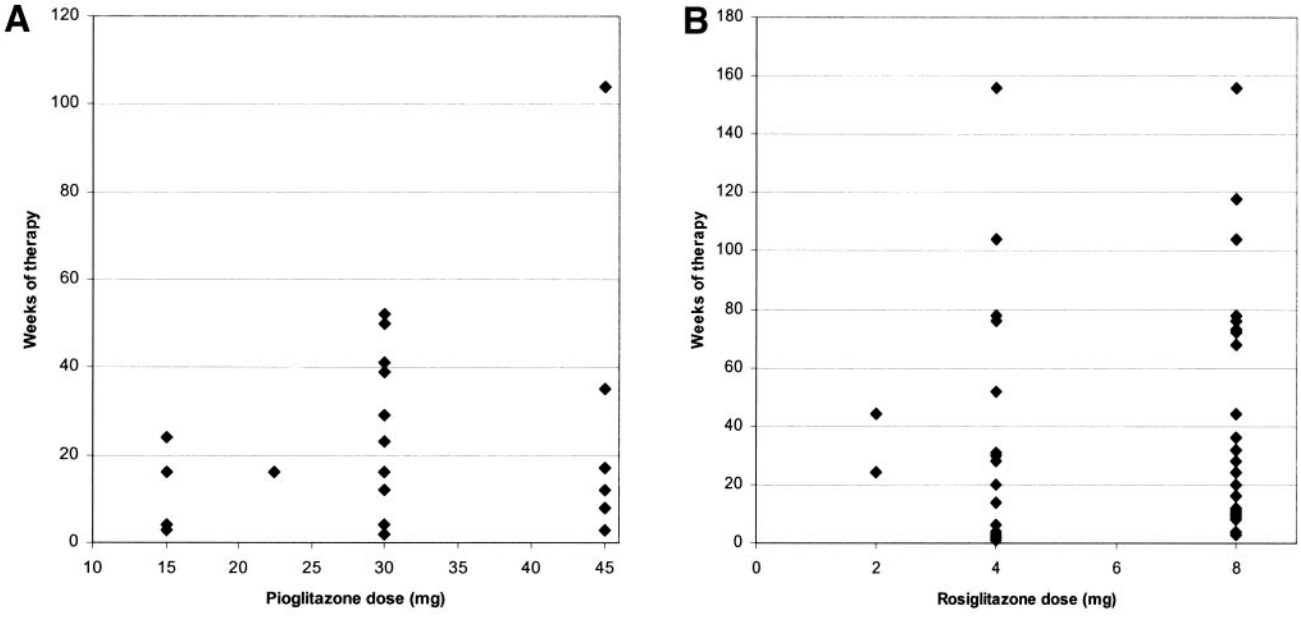

Figure 3—*Dose and duration of TZD therapy prior to occurrence of heart failure.* A*: Pioglitazone.* B*: Rosiglitazone.*

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