Use of Thiazolidinediones and Risk of Heart Failure in People With Type 2 Diabetes

A retrospective cohort study

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OBJECTIVE — To compare the incidence of heart failure in individuals with type 2 diabetes receiving thiazolidinediones (TZDs) versus other oral antihyperglycemic agents.

RESEARCH DESIGN AND METHODS — We conducted a retrospective cohort study using a health insurance claims database. The study sample included patients with type 2 diabetes who received an oral antihyperglycemic agent between January 1995 and March 2001. Those with any claims for TZDs were designated "exposed," and each was compared with five randomly selected unexposed patients. Those with diagnoses of heart failure or who received digoxin or a diuretic in the year before their index date were excluded. The primary measure of interest was incidence of heart failure, which was defined as a hospitalization or outpatient visit with a diagnosis of heart failure.

RESULTS — TZD patients ($n = 5,441$) were younger than control subjects ($n = 28,103$) but more likely to have coronary artery disease or diabetes complications, receive ACE inhibitors, β-blockers, metformin, or insulin, and have undergone HbA_{1c} tests or eye exams; they also had more comorbidities and higher costs (all $P < 0.05$). However, TZD use was predictive of heart failure even after controlling for these variables (hazard ratio = 1.7, $P < 0.001$). Adjusted incidence of heart failure at 40 months was 8.2% for TZD patients and 5.3% for control subjects.

CONCLUSIONS — The results of this observational study suggest that TZDs may increase the risk of heart failure. Physicians should use TZDs with caution in patients with heart failure, remain vigilant for manifestations of heart failure in those receiving these drugs (especially patients with cardiovasculopathy), and consider alternate therapies for patients who develop symptoms of heart failure, such as shortness of breath.

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Thiazolidinediones (TZDs) are widely used oral antihyperglycemic drugs that facilitate insulin action, increase insulin-stimulated glucose disposal, and thereby decrease insulin resistance (1,2). TZDs are effective in lowering HbA_{1c} levels and also may have beneficial β-cell and vasculo-protective effects (3,4). Three TZDs (troglitazone, pioglitazone, and rosiglitazone) have been approved for use in the U.S., although troglitazone was withdrawn from the market because of severe hepatic toxicity (5). Use of all of these drugs has been associated with weight gain, increased plasma volume, and edema (5–7), and it is possible that their use could contribute to heart failure in typical clinical practice. Since no published studies have addressed this issue, we tested the hypothesis by examining the relationship between use of TZDs and diagnoses of heart failure in a large health insurance claims database.

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Abbreviations: AGI, α-glucosidase inhibitor; CAD, coronary artery disease; SU, sulfonylurea; 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

Overview

We used a retrospective cohort design with concurrent control subjects and data from a large health insurance claims database to examine the relationship between use of TZDs and risk of heart failure in patients with type 2 diabetes. The primary measure of interest was the incidence of a new diagnosis of heart failure. We used multivariate Cox proportional hazards regression to compare the risk of heart failure in patients who received TZDs with that among those who received other oral antihyperglycemic therapies only.

Data source

At the time of this study, the Pharmetrics Integrated Outcomes Database included information from pharmacy, provider, and facility claims for members enrolled in 35 health plans across the U.S., representing ~17 million individuals. All claims in the database include a unique encrypted patient identifier that can be used to construct a longitudinal history of medical care utilization for each plan member. Age, sex, plan characteristics, and dates of benefit eligibility are available for members in selected plans. Data available for each pharmacy claim include the drug dispensed (in National Drug Code format), the dispensing date, and (for selected plans) the quantity and number of therapy-days dispensed. Data avail-

able for each provider or facility claim include dates of service and ICD-9-CM diagnosis codes. Provider claims also include Current Procedural Terminology, version 4 procedure codes. Data for this study spanned January 1995 to March 2001. The prevalence of diagnosed diabetes in the database is similar to that in the U.S. population (8).

Study sample

We selected all patients who had complete enrollment and demographic information, one or more paid provider or facility claims with a diagnosis of type 2 diabetes (ICD-9-CM 250.X0, 250.X2), and one or more pharmacy claim for an oral antihyperglycemic drug (i.e., a TZD, a sulfonylurea [SU], metformin, an SU/metformin combination, an α-glucosidase inhibitor [AGI], or a non-SU insulin secretagogue). From these patients, we identified all those who had one or more pharmacy claim for a TZD and for whom information on therapy-days dispensed was available for all TZD prescriptions. These data were required to accurately ascertain exposure to TZDs. These patients constituted the TZD group. For each patient, the date of the first claim for a TZD was identified and designated the index date. Patients with any claims with a diagnosis of heart failure (ICD-9-CM 402.11, 402.91, 428, 428.0, 428.1, and 428.9) during the 1-year period ending with the day before the index date (preindex period) were excluded.

To identify an unexposed control group, for each patient in the TZD group we randomly selected five patients who were not in the TZD group and who, during the preindex period of the corresponding TZD patient, *1*) had one or more pharmacy claim for an oral antihyperglycemic agent, *2*) had no diagnoses of heart failure, and *3*) were continuously enrolled over this period (the five-to-one ratio was chosen based on an analysis of statistical power suggesting that little additional power would be gained with a greater ratio). These patients were designated the no TZD group, and each was evaluated with respect to the same index date and preindex period as the corresponding TZD-group patient.

To ensure that patients with preexisting heart failure were not included in our sample, we excluded from both groups any patient with a pharmacy claim for digoxin or a diuretic during the preindex period. We also excluded those <18 years of age as of the index date.

Patient characteristics

Information on age, sex, and number of months of continuous enrollment during the pre- and postindex periods was obtained from enrollment files. Pharmacy claims in the 3 months before the index date were scanned to identify patients receiving drugs for heart disease or antihyperglycemic agents. We scanned diagnosis and procedure codes on professional service and facility claims during the 1-year preindex period to *1*) identify patients with a history of selected comorbid conditions (e.g., coronary artery disease [CAD] or complications of diabetes), *2*) calculate the Charlson Comorbidity Index (9,10), *3*) identify patients with emergency room visits or hospitalization for hyperglycemia or hypoglycemia, *4*) calculate the numbers of HbA_{1c} tests (as a measure of intensity of diabetes care; lab results were not available in the dataset) and dilated eye exams performed, and *5*) identify patients who underwent screening for diabetic nephropathy. Total health care costs (i.e., payments by health plans to providers) during the preindex period were also calculated for each patient.

Outcome measures

The primary measure of interest was the incidence of heart failure, defined as the occurrence during follow-up of one or more claims of any type (i.e., inpatient or outpatient, professional service or facility) with any diagnosis (i.e., primary or secondary) of heart failure. The follow-up period was defined as the period beginning with the index date and ending with the last date for which claims data were available, the date of health plan disenrollment (including death), or (for patients in the TZD group) the date of discontinuation of TZD therapy, whichever occurred first. TZD patients were assumed to have discontinued TZD therapy if 90 days passed without a new prescription for a TZD, starting from the date of the most recent prescription for a TZD plus the associated number of therapy-days dispensed. In calendar time, the potential period of follow-up in both groups thus ranged from August 1997 (the month of troglitazone's approval in the U.S.) to March 2001 (the last month for which claims were available).

In secondary analyses, we defined heart failure based on the occurrence during follow-up of *1*) two or more claims of any type with any diagnosis of heart failure (on different dates), *2*) one or more claim of any type with a primary diagnosis of heart failure, or *3*) one or more hospital inpatient claim with a primary diagnosis of heart failure (i.e., hospitalization for heart failure).

Statistical analyses

Patient characteristics were compared across treatment groups using Wilcoxon's rank-sum test for continuous variables and χ^2 tests for binary variables. Cox proportional hazards regression was employed to estimate hazard ratios (HRs) for heart failure given TZD use and other baseline demographic and clinical characteristics (11). Patients who did not experience heart failure were censored at the end of follow-up. Univariate and multivariate analyses were conducted. In multivariate analyses, we included treatment group plus all other patient characteristics as covariates. Unadjusted and adjusted estimates of the incidence of heart failure by treatment group and month were calculated using Kaplan-Meier methods (11) and the corrected group prognosis method (12), respectively.

We calculated HRs for heart failure given TZD use by index TZD (pioglitazone, rosiglitazone, or troglitazone) and, for each index TZD, by daily dosage (milligrams per day) of the index prescription (drug strength [in milligrams] times pills supplied divided by therapy-days prescribed). We used Wald's χ^2 to test the hypotheses of no difference in HRs by index TZD and, for each index TZD, the hypothesis of no difference in HR by daily dosage of index prescription. We generated multivariate HRs for heart failure given TZD use for subgroups of patients defined on the basis of selected covariates. Graphical and analytical methods were employed to assess the appropriateness of the proportional hazards assumption for the independent variable representing TZD use (13,14). In a secondary analysis, we compared the risk of heart failure in patients receiving TZDs with that in a propensity-matched sample of patients who did not receive these drugs (15,16) using multivariate Cox proportional hazards regression with stratification on matched pairs. All analyses were conducted using SAS Proprietary Soft-

Table 1—*Characteristics of study subjects*

	TZD	No TZD	*P*
n	5,441	28,103	
Age (years)	57.2 ± 12.2	58.8 ± 12.9	<0.001
Sex (male)	3,079 (56.6)	16,064 (57.2)	0.435
Conditions			
CAD	577 (10.6)	2,412 (8.6)	<0.001
Stroke/TIA	146 (2.7)	748 (2.7)	0.928
Diabetes complications			
Renal	125 (2.3)	387 (1.4)	<0.001
Opthalmic	576 (10.6)	2,438 (8.7)	<0.001
Neurological	494 (9.1)	1,982 (7.1)	<0.001
Peripheral arterial	365 (6.7)	1,365 (4.9)	<0.001
Cardiac arrhythmias	176 (3.2)	945 (3.4)	0.631
Hypertension	1,872 (34.4)	9,783 (34.8)	0.565
Diabetic emergency			
Hyperglycemia	80 (1.5)	199 (0.7)	<0.001
Hypoglycemia	33 (0.6)	135 (0.5)	0.228
Medications			
ACE inhibitor	1,505 (27.7)	7,143 (25.4)	<0.001
β-Blocker	504 (9.3)	2,402 (8.5)	0.086
Metformin	2,458 (45.2)	11,430 (40.7)	<0.001
SU	2,954 (54.3)	15,884 (56.5)	0.002
Non-SU insulin secretagogue	146 (2.7)	306 (1.1)	<0.001
α-Glucosidase inhibitor	94 (1.7)	198 (0.7)	<0.001
Insulin	956 (17.6)	2,009 (7.1)	<0.001
HbA_{1c} test	3,702 (68.0)	16,416 (58.4)	<0.001
Dilated eye exam	1,512 (27.8)	7,443 (26.5)	0.047
Screening for diabetic nephropathy	960 (17.6)	4,807 (17.1)	0.335
Charlson Comorbity Index ≥2	1,488 (27.3)	7,216 (25.7)	0.010
Preindex costs ($)	2,931 ± 7,727	2,816 ± 8,102	<0.001
Continuous enrollment (months)			
Preindex	26.0 ± 10.0	27.9 ± 11.3	<.001
Postindex	8.5 ± 7.3	8.7 ± 7.5	0.969

Data are means ± SD or *n* (%). All clinical characteristics assessed using claims during the 12 months prior to index date except for prescriptions, which were assessed using claims during the 3 months prior to the index date. TIA, transient ischemic attack.

ware, release 8.1 (SAS Institute, Cary, NC).

RESULTS

Patient characteristics

TZD patients (n = 5,441) were younger than those not receiving TZDs (n = 28,103) but were more likely to have CAD, complications of diabetes, and experienced hyperglycemic emergencies (Table 1). TZD patients were also more likely to have received ACE inhibitors, β-blockers, metformin, non-SU insulin secretagogues, AGIs, and especially insulin in the 3 months before their index date; however, they were less likely to have received SUs. They also were more likely to have received an HbA_{1c} test or dilated eye exam in the preindex period and to have a Charlson Index value >1. In addition, they had higher preindex health care costs and shorter periods of continuous enrollment both before and after the index date.

Incidence of heart failure

A total of 523 subjects experienced heart failure during follow-up (1.6%), including 126 in the TZD group (2.3%) and 397 of the control subjects (1.4%). Patient characteristics that were associated with an increased risk of heart failure in univariate analyses ($P < 0.05$) included advanced age; history of CAD, stroke/transient ischemic attack, complications of diabetes, arrhythmias, hypertension, and hyper- and hypoglycemic diabetic emergencies; receipt of ACE inhibitors, β-blockers, or insulin; dilated eye exam; Charlson index >1; and preindex health care costs (Table 2). Receipt of metformin in the 3 months before the index date was associated with a lower risk of heart failure, as was receipt of an HbA_{1c} test, screening for diabetic nephropathy, and longer duration of continuous enrollment before the index date. The unadjusted HR for risk of heart failure associated with TZD exposure was 1.69 (95% CI 1.38–2.06, $P < 0.001$). Kaplan-Meier estimates of the incidence of heart failure at 40 months (the maximum duration of follow-up) were 8.8% for TZD patients and 6.6% for control subjects.

Characteristics that were independently associated with increased risk of heart failure in the multivariate analysis included advanced age; a history of CAD, peripheral arterial complications of diabetes, or hyperglycemic emergencies; receipt of ACE inhibitors, β-blockers, or insulin; receipt of an HbA_{1c} test; a Charlson index >1; and higher preindex costs. After adjustment for all other covariates, the HR for heart failure given TZD use was 1.76 (95% CI 1.43–2.18, $P < 0.001$). The adjusted incidence of heart failure at 40 months was 8.8% among TZD patients and 5.5% among unexposed control subjects (Fig. 1).

When we identified heart failure based on the presence of two or more claims of any type with any diagnosis of heart failure, the multivariate HR for TZD use was 1.74 (95% CI 1.54–1.97, $P < 0.001$). The HR was 2.06 (1.65–2.58, $P < 0.001$) when we defined the outcome measure as the presence of one or more claims of any type with a primary diagnosis of heart failure and 3.57 (2.33–5.47, $P < 0.001$) when we defined the outcome measure as one or more hospital inpatient claim with a primary diagnosis of heart failure (i.e., hospitalization for heart failure). The adjusted incidence of hospitalization for heart failure by 40 months was estimated to be 2.5% among TZD patients and 1.0% among control subjects.

The test of the global hypothesis of a difference in HRs by index TZD was insignificant ($P = 0.091$) (Table 3). No relationship was observed between daily dose of index prescription and risk of heart failure for any TZD (all $P > 0.05$). In subgroup analyses (Fig. 2), the multivariate HR for TZD use was >1.0 in all strata and statistically significant ($P < 0.05$) in all strata except two (patients with insulin use in the 3 months before the index date

Table 2—*Cox proportional hazards analysis of time to heart failure* (n = 33,544)

	Univariate		Multivariate	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Receipt of TZD	1.69 (1.38–2.06)	<0.001	1.76 (1.43–2.17)	<0.001
Age (decade)	1.85 (1.72–1.99)	<0.001	1.77 (1.64–1.91)	<0.001
Sex (male)	1.04 (0.87–1.24)	0.658	1.08 (0.91–1.29)	0.384
Conditions				
CAD	2.55 (2.05–3.18)	<0.001	1.30 (1.02–1.67)	0.034
Stroke/TIA	2.62 (1.85–3.70)	<0.001	0.86 (0.59–1.25)	0.431
Diabetes complications				
Renal	2.66 (1.68–4.20)	<0.001	1.39 (0.86–2.23)	0.177
Opthalmic	1.52 (1.18–1.96)	0.001	1.19 (0.90–1.57)	0.217
Neurological	1.75 (1.34–2.29)	<0.001	0.96 (0.72–1.28)	0.783
Peripheral arterial	3.32 (2.62–4.21)	<0.001	1.71 (1.33–2.21)	<0.001
Cardiac arrhythmias	2.59 (1.87–3.59)	<0.001	1.28 (0.91–1.81)	0.154
Hypertension	1.40 (1.18–1.67)	<0.001	0.97 (0.81–1.18)	0.789
Diabetic emergency				
Hyperglycemia	2.29 (1.23–4.29)	0.009	1.98 (1.00–3.94)	0.052
Hypoglycemia	2.34 (1.05–5.24)	0.038	0.73 (0.30–1.78)	0.495
Medication use				
ACE inhibitor	1.38 (1.15–1.66)	<0.001	1.32 (1.09–1.60)	0.005
β-Blocker	1.83 (1.44–2.33)	<0.001	1.35 (1.05–1.74)	0.021
Metformin	0.82 (0.69–0.98)	0.031	0.90 (0.75–1.09)	0.282
SU	1.08 (0.91–1.29)	0.386	0.98 (0.82–1.19)	0.874
Non-SU insulin secretagogue	1.10 (0.49–2.47)	0.810	1.06 (0.47–2.39)	0.885
α-Glucosidase inhibitor	1.42 (0.67–2.98)	0.360	1.26 (0.60–2.67)	0.546
Insulin	1.76 (1.38–2.24)	<0.001	1.44 (1.10–1.89)	0.008
HbA_{1c} test	0.79 (0.66–0.94)	0.007	0.77 (0.64–0.93)	0.006
Dilated eye exam	1.30 (1.09–1.57)	0.004	0.91 (0.75–1.11)	0.377
Screening for diabetic nephropathy	0.76 (0.59–0.99)	0.041	0.88 (0.67–1.16)	0.372
Charlson Comorbity Index ≥2	2.29 (1.93–2.72)	<0.001	1.56 (1.26–1.93)	<0.001
Preindex costs, log ($)	1.23 (1.16–1.29)	<0.001	1.07 (1.01–1.14)	0.018
Preindex enrollment (years)	0.88 (0.79–0.98)	0.021	0.87 (0.78–0.98)	0.018

TIA, transient ischemic attack.

[n = 2,965] and those with no HbA_{1c} test, dilated eye exam, or nephropathy screen during the 12-month pretreatment period [n = 10,518]). The term representing the interaction of TZD use and the stratifying covariate was not significant in any subgroup analysis. There was no strong evidence of nonproportionality of the TZD effect. The multivariate HR for heart failure given TZD use in the propensity-matched samples (n = 5,440 in both groups) was 2.51 (95% CI 2.13–2.94, $P < 0.001$).

CONCLUSIONS — Using a large health insurance claims database, we found that use of TZDs was associated with an ~60% relative increase in the risk of heart failure after 40 months of follow-up. This relationship was consistently observed in a number of secondary analyses, including one based on a propensity-matched sample of control subjects. The multivariate HR for TZD use generally increased with the stringency of the criteria used to define heart failure. Although we did not observe a dose-response relationship between TZD use and heart failure, we characterized dosage based on index prescription only, and patients may have switched dosages over time. Also, the numbers of subjects and events within strata defined on index TZD and daily dosage were small and the probability of a type 2 error was therefore high.

TZDs could increase risk of heart failure via direct effects on the heart, the kidneys, and/or the vasculature (rosiglitazone can increase pulmonary endothelial cell permeability [17]), or indirectly by facilitating the action of insulin to promote renal sodium retention (18,19). Since patients with diabetes are at increased risk of heart failure (20), due in part to a specific diabetic cardiomyopathy (21), diabetic patients with underlying myocardial disease—including incipient cardiomyopathy—may be especially vulnerable to the effects of TZDs.

Our results are not inconsistent with the Food and Drug Administration–approved prescribing information for pioglitazone (7), which reports that in a 16-week, double-blind, placebo-controlled trial of insulin plus pioglitazone versus insulin alone in 566 patients with type 2 diabetes, 4 patients receiving pioglitazone (1.1%) developed heart failure compared with none in the group receiving insulin alone. Similar results have been reported for rosiglitazone when used in combination with insulin (6). Interestingly, we found no difference in the HR for heart failure given TZD use between people who did and did not use insulin before the index date, suggesting

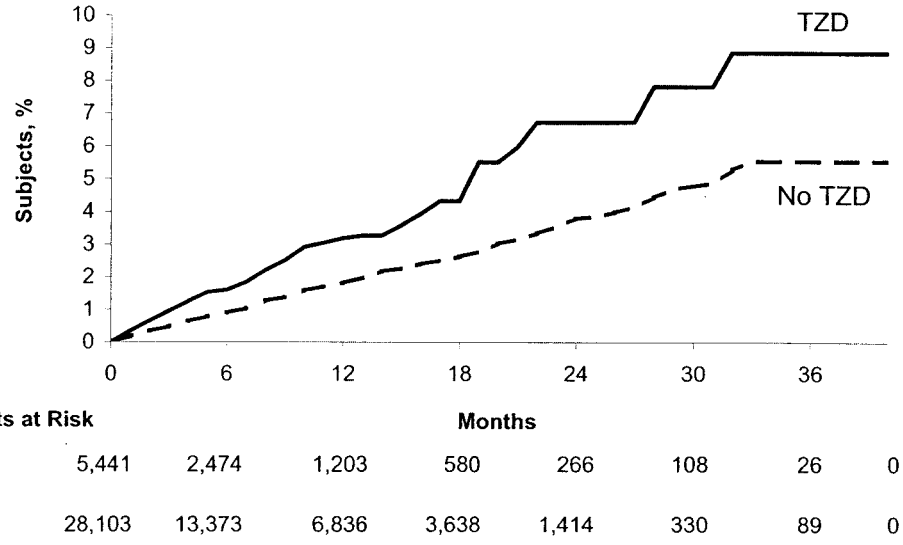

Figure 1—*Adjusted estimates of the percentage of subjects with diagnosis of heart failure by use of TZDs. The total number of subjects who experienced heart failure was 126 (2.3%) in the TZD group and 397 (1.4%) in the no TZD group.*

that the effects of TZDs on the risk of heart failure may not be limited to those receiving insulin therapy.

In absolute terms, TZD use was associated with a 1.1% increase in the annual risk of a new diagnosis of heart failure and a 0.5% increase in risk of heart failure hospitalization. Treatment of 200 individuals with a TZD might thus result in two additional cases of heart failure and one additional hospitalization for heart failure each year. Given the possibility of lifelong therapy with TZDs, and their widespread use, an increase in the risk of heart failure of this magnitude might have important clinical and economic consequences. However, potential risks must be weighed against potential benefits. The reductions in risk of vascular events with TZDs are unknown, although clinical trials to assess such benefits are underway.

Although the relative increase in risk of heart failure associated with TZD use was relatively constant across subgroups defined on baseline characteristics, the absolute increase in risk was greater in subgroups with a higher baseline risk of heart failure. It therefore may be prudent to use TZDs with particular care among those predisposed to the development of heart failure, such as the elderly or those receiving insulin.

Limitations of this study should be noted. First, TZD patients were slightly "sicker" than no TZD patients based on history of vascular disease, diabetes complications, and other comorbidities. However, TZD patients were younger and may have received "better" diabetes care than control subjects based on the frequency of HbA_{1c} tests. Although we sought to control for "confounding by indication" using multivariate regression and propensity score matching, we lacked data on clinical parameters that have been shown to be independently associated with risk of heart failure in diabetic patients, including weight, HbA_{1c} level, blood pressure, and serum creatinine (22). Also, because claims data are available only for a limited period of time for each patient, it was not possible to ascertain time since initial diagnosis of diabetes. Differences between groups in these and possibly other unobserved characteristics may have contributed to the ele-

Table 3.—*Multivariate Cox proportional hazards analysis of time to heart failure given exposure to TZDs by index TZD and daily dosage*

Index TZD/daily dosage	*n*	Heart failure [*n* (%)]	HR (95% CI) for treatment effect	*P*		
				Treatment effect	Daily dosage	Index TZD
No TZD	28,103	397 (1.41)	—	—	—	—
TZD						
Pioglitazone (mg/day)	1,347	22 (1.63)	1.92 (1.24–2.97)	0.003		
<45	1,150	18 (1.57)	1.81 (1.12–2.94)	0.003	0.272	
≥45	197	4 (2.03)	3.08 (1.14–8.31)	0.134		
Rosiglitazone (mg/day)	1,882	45 (2.39)	2.27 (1.65–3.13)	<0.001		
<8	1,272	31 (2.44)	2.21 (1.52–3.22)	<0.001	0.956	0.091
≥8	610	14 (2.30)	2.25 (1.31–3.87)	0.004		
Troglitazone (mg/day)	1,665	54 (3.24)	1.44 (1.07–1.94)	0.016		
<400	745	25 (3.36)	1.40 (0.93–2.13)	0.109	0.883	
≥400	920	29 (3.15)	1.46 (0.99–2.16)	0.055		

P value for daily dosage represent test of hypothesis of difference in risk by daily dosage on index prescription; *P* value for index TZD, test of hypothesis of difference in risk difference by index TZD. HRs are adjusted for all covariates. Patients for whom index TZD/daily dosage could not be identified were excluded.

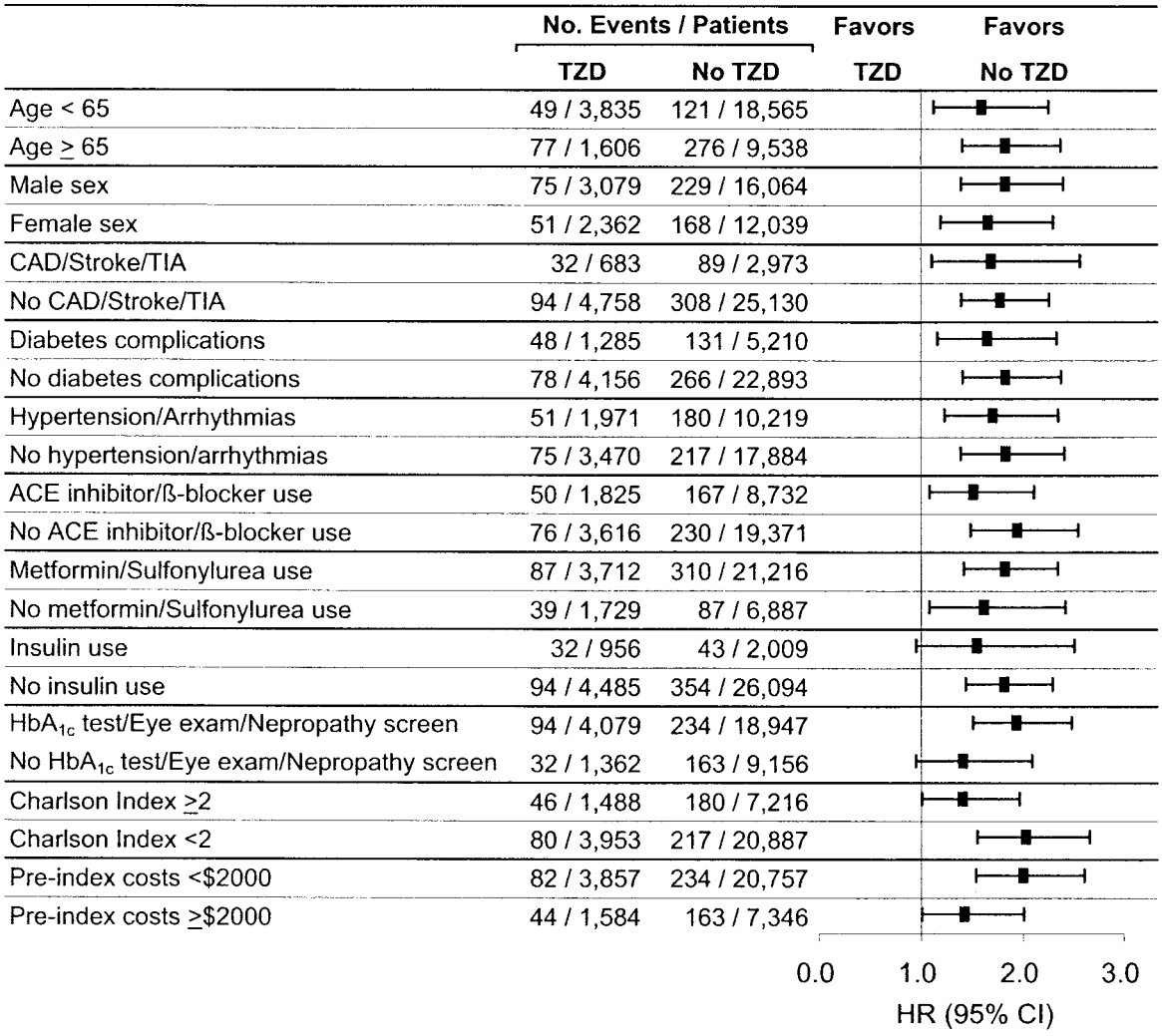

Figure 2—*Multivariate Cox proportional hazards analysis of time to heart failure given exposure to TZDs by subgroups. TIA, transient ischemic attack.*

vated risk of heart failure that we observed among TZD patients.

Second, some diagnoses may be omitted or coded incorrectly in administrative datasets (23). There is evidence to suggest that diagnoses of heart failure may be inappropriately used to obtain more favorable reimbursement (24). If TZD patients were more likely to be misdiagnosed with heart failure than control subjects (e.g., due to symptoms of edema), our results might be biased.

Third, treatment was not blinded and the increased risk of heart failure that we observed among TZD patients may have been due to heightened vigilance to the signs and symptoms of heart failure in TZD patients. While such detection bias is potentially problematic for "softer" outcomes such as that used in our primary analysis, it should be less so for "harder" outcomes such as hospitalization for heart failure, which we examined in a secondary analysis. However, it was not possible to assess mortality, as information on vital status is not available in the dataset.

In summary, we observed a strong, consistent, and independent association between the use of TZDs and risk of heart failure. However, the results of single observational study are not sufficient to establish causality. Nevertheless, our findings suggest that physicians should use TZDs with caution in patients with heart failure, remain vigilant for manifestations of heart failure in those receiving these drugs, especially patients with cardiovasculopathy, who may be predisposed to heart failure, and consider alternate therapies for patients who develop symptoms of heart failure such as shortness of breath.

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References

1. Petersen KF, Krssak M, Inzucchi S, Cline GW, Dufour S, Shulman GI: Mechanism of troglitazone action in type 2 diabetes. *Diabetes* 49:827–831, 2000
2. Mudaliar S, Henry RR: New oral therapies

for type 2 diabetes mellitus: the glitazones or insulin sensitizers. *Annu Rev Med* 52: 239–257, 2001
3. Inzucchi SE: Oral antihyperglycemic therapy for type 2 diabetes. *Scientific Review. JAMA* 287:321–328, 2002
4. Parulkar AA, Pendergrass ML, Granda-Ayala R, Lee TR, Fonseca VA: Nonhypoglycemic effects of thiazolidinediones. *Ann Intern Med* 134:61–71, 2001
5. Henney JE: New type 2 diabetes drugs. *JAMA* 282:932, 1999
6. Prescribing Information: *Avandia Brand of Rosiglitazone Maleate Tablets*. Philadelphia, SmithKline Beecham Pharmaceuticals, February, 2001
7. *Actos (Pioglitazone Hydrochloride) Tablets*. Lincolnshire, IL, Takeda Pharmaceuticals America, July, 2002
8. Harris MI, Flegal KM, Cowie CC, Eberhardt MS, Goldstein DE, Little RR, Wiedmeyer HM, Byrd-Holt DD: Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults: the Third National Health and Nutrition Examination Survey, 1988–1994. *Diabetes Care* 21:518–524, 1998
9. Deyo RA: Adapting a comorbidity index for use with ICD-9-CM administrative data. *J Clin Epidemiol* 45:613–619, 1992
10. Deyo RA: Adapting a comorbidity index for use with ICD-9-CM administrative data: a response. *J Clin Epidemiol* 46:1085–1090, 1993
11. Cantor AB: Extending SAS survival analysis: techniques for medical research. Cary, NC. SAS Institute, 1997
12. Ghali WA, Quan H, Brant R, van Melle G, Norris CM, Faris PD, Galbraith PD, Knudtson ML, APPROACH (Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease) Investigators: Comparison of 2 methods for calculating adjusted survival curves from proportional hazards models. *JAMA* 286:1494–1497, 2001
13. Harrell F, Lee KL: Verifying assumptions of the Cox proportional hazards model. In *Proceedings of the 11th Annual SAS User's Group International Conference*. Cary, NC, SAS Institute, 1986
14. Fisher LD, Lin DY: Time-dependent covariates in the Cox proportional hazards regression model. *Ann Rev Public Health* 20:145–157, 1999
15. Rosenbaum P, Rubin D: The central role of the propensity score in observational studies for causal effects. *Biometrika* 70: 41–55, 1983
16. Rubin DB: Estimating causal effects from large datasets using propensity scores. *Ann Intern Med* 127:757–763, 1997
17. Idris I, Gray S, Donnelly R: Rosiglitazone and pulmonary oedema: an acute dose-dependent effect on human endothelial-cell permeability. *Diabetologia* 46:288–290, 2003
18. Muscelli E, Natali A, Bianchi S, Bigazzi R, Galvan AQ, Sironi AM, Frascerra S, Ciociaro D, Ferrannini E: Effect of insulin on renal sodium and uric acid handling in essential hypertension. *Am J Hypertens* 9:746–752, 1996
19. Stenvinkel P, Bolinder J, Alvestrand A: Effects of insulin on renal haemodynamics and the proximal and distal tubular sodium handling in healthy subjects. *Diabetologia* 35:1042–1048, 1992
20. Sobel BE: Effects of glycemic control and other determinants on vascular disease in type 2 diabetes. *Am J Med* 113 (Suppl. 6A):12S–22S, 2002
21. Raev DC: Which left ventricular function is impaired earlier in the evolution of diabetic cardiomyopathy? An echocardiographic study of young type I diabetic patients. *Diabetes Care* 17:633–639, 1994
22. Nichols GA, Hillier TA, Erbey JR, Brown JB: Congestive heart failure in type 2 diabetes: prevalence, incidence, and risk factors. *Diabetes Care* 24:1614–1619, 2001
23. Newton KM, Wagner EH, Ramsey SD, McCulloch D, Evans R, Sandhu N, Davis C: The use of automated data to identify complications and comorbidities of diabetes: a validation study. *J Clin Epidemiol* 52:199–207, 1999
24. Psaty BM, Boineau R, Kuller LH, Luepker RV: The potential costs of upcoding for heart failure in the United States. *Am J Cardiol* 84:108–109, 1999