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# The Impact of Thiazolidinedione Use on Outcomes in Ambulatory Patients With Diabetes Mellitus and Heart Failure

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- Objectives** This study sought to examine the relationship between thiazolidinedione (TZD) use and outcomes in ambulatory patients with diabetes and heart failure (HF).
- Background** Thiazolidinediones have been relatively contraindicated in diabetic patients with HF.
- Methods** We conducted a retrospective study of a national cohort of veterans with HF and diabetes treated in ambulatory clinics at Veterans Affairs medical centers. Patients were classified into those using TZDs and those not using insulin-sensitizing medication based on prescriptions filled 90 days before or 30 days after the index outpatient visit. The outcomes were time to hospitalization for HF and time to death.
- Results** Of 7,147 ambulatory HF patients receiving diabetic therapy, 818 (11.4%) were receiving a TZD and 4,700 (65.8%) were not receiving insulin sensitizers. Over 2 years of follow-up, 134 (16.4%) patients receiving TZDs and 741 (15.8%) patients not receiving insulin-sensitizing medications required HF hospitalization (adjusted hazard ratio 1.00, 95% confidence interval 0.81 to 1.24,  $p = 0.97$ ). A total of 168 (20.5%) patients receiving TZDs and 1,192 (25.4%) patients not receiving insulin-sensitizing medications died (adjusted hazard ratio 0.98, 95% confidence interval 0.81 to 1.17,  $p = 0.80$ ).
- Conclusions** In ambulatory patients with established HF and diabetes, the use of TZDs was not associated with an increased risk of HF hospitalization or total mortality when compared with those not receiving insulin-sensitizing medications. (J Am Coll Cardiol 2007;50:32–6) © 2007 by the American College of Cardiology Foundation

Diabetes mellitus and heart failure (HF) commonly coexist with a prevalence of diabetes in major HF trials of approximately 20% to 30% (1). Importantly, the coexistence of diabetes and HF portends a poor prognosis (2). Because of this adverse prognosis, efforts to adequately treat diabetes in individuals with HF become increasingly important.

See page 37

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Thiazolidinediones (TZDs), agonists for the nuclear transcription factor peroxisome-proliferator-activated receptor  $\gamma$ , have emerged as a therapeutic option in the treatment of diabetes (3). In addition to beneficial effects on insulin sensitivity and glucose homeostasis, activation of the peroxisome-proliferator-activated receptor  $\gamma$  system results in myriad potentially beneficial metabolic (3), vascular (4,5), and neurohormonal effects (6,7) that may be advantageous in the prevention of HF and/or treatment of diabetes in those with established HF. Despite these potential benefits, TZD use has been associated with increased weight gain and fluid retention (8) and some reports of increased HF (9–11). Because of these concerns, TZD use is not recommended for patients with New York Heart Association functional class III or IV symptoms (8).

Limited data exist regarding the association of TZDs and HF outcomes in diabetic patients with established HF (12,13), particularly in ambulatory patients with HF. We sought to determine the relationship between TZD use and

HF outcomes compared with the use of non-insulin-sensitizing agents in a national cohort of ambulatory patients with diabetes and HF treated at Veterans Affairs (VA) medical centers.

## Methods

**Study design and sample.** We performed a retrospective study of a national cohort of veterans with HF treated in ambulatory clinics at VA medical centers using the VA External Peer Review Program (EPRP) data between October 2000 and September 30, 2002. As described in detail previously (14,15), the sampling pool of outpatients for EPRP included ambulatory patients with common chronic diseases such as HF, diabetes, ischemic heart disease, and chronic obstructive pulmonary disease (COPD) identified by specific ICD-9 codes. Abstractors reviewed electronic medical records for validation of inclusion criteria, including documentation of an HF diagnosis in outpatient charts (15). Patient-level data from the EPRP HF cohort was linked with 5 existing national VA databases to obtain further demographic, laboratory, pharmacy, and outcome data.

Individuals from the EPRP HF cohort who had diabetes (as identified in the EPRP data) and were prescribed hypoglycemic medications (in the pharmacy database) were included. Diabetic therapy was ascertained using pharmacy data and was based on prescriptions filled 90 days before or 30 days after the index outpatient visit, and individuals were classified as users of TZDs and users of non-insulin-sensitizing antihyperglycemic medications. In addition, baseline demographics and concomitant cardiac medications were assessed at the index visit. Most recent laboratory data within 1 year before and up to 2 weeks after the index visit were used. Glomerular filtration rate was calculated using the 4-variable Modification of Diet in Renal Disease equation (16). Covariates that reflected diabetes severity included hemoglobin A1c and a variable documenting a diabetic complication including neuropathy, nephropathy, retinopathy, or peripheral vascular disease.

Our comparison groups were composed of patients receiving TZDs versus those patients not receiving insulin-sensitizing medications. Because of the potential confounding effects of biguanide therapy (12), we excluded individuals receiving biguanide therapy in the absence of concomitant TZD therapy ( $n = 1,629$ ). The primary outcome was time to hospitalization for HF, and the secondary outcome was time to death over 2 years of complete follow-up after the index outpatient visit.

**Statistical analysis.** Differences in baseline variables were ascertained using chi-square tests for categorical variables and  $t$  tests for continuous variables. Two-sided  $p$  values  $< 0.05$  were considered statistically significant. Univariate and multivariable Cox proportional hazards models were used to assess the relationship between diabetic therapy with TZD compared with non-insulin-sensitizing agents and the outcomes of interest. Multivariable Cox proportional hazards

models were constructed using forward stepwise selection with variables with  $p \leq 0.1$  being entered into the model. Candidate variables included age, gender, body mass index, left ventricular ejection fraction (LVEF), glomerular filtration rate, hemoglobin, hyponatremia, hemoglobin A1c, race, prior diabetic complications, atrial fibrillation, angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker use, beta-blocker use, statin use, prior HF hospitalization, hypertension, cancer, prior myocardial infarction, COPD, peripheral vascular disease, dementia, psychiatric disorders, severe liver disease, rheumatologic disease, medical school affiliation, and additional diabetic therapy. Missing laboratory values were imputed using the median value of the study cohort for that parameter (missing = 418 for serum sodium, 713 for serum creatinine, and 1,208 for hemoglobin), and a dummy variable was used to indicate replacement of missing data. Models including only patients without missing laboratory data yielded no significant change in overall results. Statistical analysis was performed using SAS software 9.1 (SAS Institute Inc., Cary, North Carolina).

## Results

**Baseline characteristics.** A total of 7,147 ambulatory HF patients with diabetes requiring diabetic therapy were identified. Of these, 818 (11.4%) patients were receiving a TZD, 1,837 (25.7%) patients were receiving a biguanide, and 4,700 (65.8%) patients were not receiving insulin sensitizers. The 1,629 individuals who were receiving biguanide therapy in the absence of TZDs were excluded from the study.

The TZD users were younger, had a higher body mass index, and were more likely to have a higher LVEF and to have had a prior diabetic complication than those who were not receiving insulin-sensitizing medications (Table 1). The TZD users were less likely to have cancer, atrial fibrillation, COPD, a prior myocardial infarction, or a HF hospitalization within 2 years before the index visit. In addition, they had a lower hemoglobin and a higher hemoglobin A1c, and were more likely to receive statin therapy, but less likely to receive care in a VA center affiliated with a medical school than those not receiving insulin sensitizers.

**Outcomes.** Over 2 years of follow-up, 134 (16.4%) patients receiving TZDs and 741 (15.8%) patients not receiving insulin-sensitizing medications required HF admission ( $p = 0.79$ ). After adjusting for age and other covariates, no significant difference was noted in the rate for HF hospitalization between the 2 groups (risk-adjusted hazard ratio

### Abbreviations and Acronyms

CI	= confidence interval
COPD	= chronic obstructive pulmonary disease
EPRP	= External Peer Review Program
HF	= heart failure
HR	= hazard ratio
LVEF	= left ventricular ejection fraction
TZD	= thiazolidinedione
VA	= Veterans Affairs

**Table 1** Baseline Characteristics of the Study Cohort

	TZD (n = 818)	No Insulin-Sensitizing Medication (n = 4,700)
Age, yrs (SD)	67.6 (9.4)	70.3 (9.3)*
Male (%)	774 (95)	4,397 (94)
Race (%)		
White	625 (76)	3,491 (74)*
Black	67 (8)	596 (13)
Other/unknown	126 (15)	613 (13)
Systolic blood pressure, mm Hg (SD)	130.9 (21.3)	131 (21.6)
Body mass index, kg/m <sup>2</sup> (SD)	34.3 (7.6)	31.0 (6.5)*
LVEF (%)		
Normal or mildly reduced (LVEF ≥40%)	430 (52)	2,004 (43)*
Moderate or severely reduced (LVEF <40%)	261 (32)	1,844 (39)
Unknown	127 (16)	852 (18)
Diabetes with complications (%)	537 (66)	2,647 (56)*
Dementia (%)	10 (1.2)	133 (2.8)*
Atrial fibrillation (%)	199 (24)	1,412 (30)*
Past myocardial infarction (%)	314 (38)	1,627 (35)†
Chronic obstructive pulmonary disease (%)	178 (22)	1,332 (28.3)*
Cancer (%)	120 (14.7)	871 (18.5)*
GFR, ml/min/m <sup>2</sup> (SD)		
≥60	291 (36)	1,686 (36)
30 to <60	436 (53)	2,514 (53)
<30	91 (11)	500 (11)
Sodium (mEq/l)	138.7 (3.4)	138.9 (3.4)
Hemoglobin, mg/dl (SD)	13.1 (1.8)	13.3 (1.8)*
Hemoglobin A1c, % (SD)	8.0 (1.7)	7.5 (1.6)*
Medication use (%)		
Insulin	437 (53)	2,483 (53)
Sulfonylurea	405 (50)	2,824 (60)
Biguanide	208 (25)	0*
ACE or ARB	676 (83)	3,841 (82)
Statin	558 (68)	2,516 (54)*
Beta-blocker	496 (61)	2,847 (61)
Prior HF hospitalization within 2 yrs (%)	135 (17)	930 (20)†
Medical school affiliation (%)	467 (57)	2,985 (64)*

\*p ≤ 0.01; †p ≤ 0.05.

ACE = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; GFR = glomerular filtration rate; HF = heart failure; LVEF = left ventricular ejection fraction; TZD = thiazolidinedione.

[HR] 1.00, 95% confidence interval [CI] 0.81 to 1.24, p = 0.97) (Table 2).

Furthermore, 168 (20.5%) patients receiving TZDs and 1,192 (25.4%) patients not receiving insulin-sensitizing

medications died during follow-up (p = 0.003). However, the risk-adjusted mortality rates were not significantly different between the 2 groups (risk-adjusted HR 0.98, 95% CI 0.81 to 1.17, p = 0.80) (Table 2).

Additional analyses were performed using Cox proportional hazard models in specific subgroups based on age, LVEF, renal insufficiency, concomitant insulin use, and prior HF hospitalization (Fig. 1). No statistically significant interaction was noted between subgroups with the exception of concomitant insulin use and HF hospitalization. In those patients not receiving insulin therapy (n = 2,598), TZD was associated with a higher risk of HF hospitalization compared with those not receiving insulin-sensitizing medications (HR 1.62, 95% CI 1.15 to 2.29, p value for interaction = 0.03) (Fig. 1).

## Discussion

Despite the common coexistence of HF and diabetes, few studies have examined the safety and efficacy of TZDs in individuals with established HF. In a smaller study of diabetic patients with systolic HF who were treated with TZDs, 17% developed fluid retention, a finding that tended to be more peripheral and appeared reversible after drug withdrawal (13). In a more recent large retrospective cohort study of Medicare beneficiaries with diabetes with a principal hospital discharge diagnosis of HF, TZD use was associated with a 13% reduced risk of death, despite a borderline increased risk of HF readmission (HR 1.06, 95% CI 1.00 to 1.09) (12).

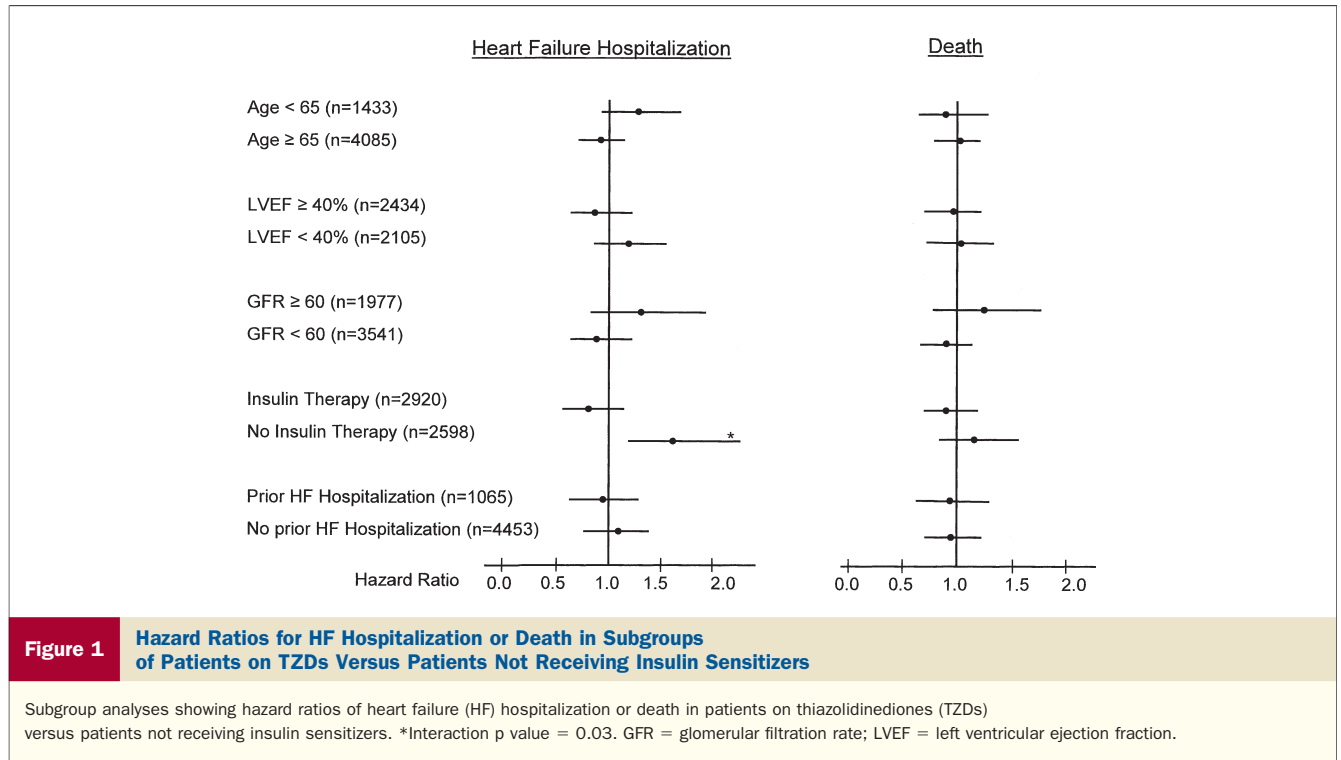
Our study extends the current body of literature regarding TZD use and HF to include a large cohort of ambulatory patients with established HF treated in VA medical centers. Similar to the study of Medicare beneficiaries (12), TZD use in individuals with established HF was relatively common and occurred in approximately 1 in 9 patients. Contrary to previous concerns, we found no evidence for increased rates of HF admission in diabetic HF patients treated with TZDs when compared with those patients who were not receiving insulin-sensitizing diabetic therapy. The unadjusted risk of death was reduced in those receiving TZD therapy, but was no longer significant in age-adjusted and fully adjusted models. The difference in results in mortality between this study and that of Masoudi et al. (12)

**Table 2** Heart Failure Hospitalization and Mortality by Diabetic Drug Category

	Heart Failure Hospitalization		Death	
	TZD (n = 818)	No Insulin-Sensitizing Medication (n = 4,700)	TZD (n = 818)	No Insulin-Sensitizing Medication (n = 4,700)
2-yr outcome (%)	134 (16.4)	741 (15.8)*	168 (20.5)	1,192 (25.4)†
Unadjusted hazard ratio (95% CI)	1.03 (0.85-1.23)	1.0	0.78 (0.67-0.92)	1.0
Age-adjusted hazard ratio (95% CI)	1.01 (0.84-1.21)	1.0	0.85 (0.72-1.00)	1.0
Fully adjusted hazard ratio (95% CI)	1.00 (0.81-1.24)	1.0	0.98 (0.81-1.17)	1.0

Hazard ratio compares heart failure hospitalization or death in patients on TZDs versus patients not on TZDs. \*p = 0.79; †p = 0.003.

CI = confidence interval; TZD = thiazolidinedione.



may relate to the lower severity of illness in our study of ambulatory patients compared with the cohort of recently hospitalized patients in the Medicare database.

In exploratory subgroup analyses, an increased risk of HF hospitalization was seen associated with TZD use in the group of diabetic patients not receiving insulin therapy. This finding contrasts previous data that suggest that insulin use is associated with more TZD-associated fluid retention in the general population (8) and in a smaller outpatient HF population (13). In the study by Masoudi *et al.* (12) of recently hospitalized Medicare patients, the risk of readmission for HF was similar among TZD patients treated with insulin and those not treated with insulin. Our finding may be a chance-related finding given the multiple analyses performed, but future studies will need to further explore risks and benefits of TZD use in various subgroups.

**Study limitations.** This study has limitations inherent to retrospective observational studies. Although multivariable statistical models were used to adjust for heterogeneity between groups, residual unmeasured confounding factors may remain. The younger age, lower frequency of prior HF hospitalization, and higher frequency of preserved LVEF in the TZD group may suggest less severe HF in this group compared with those using non-insulin-sensitizing medications. However, availability of LVEF, blood pressure, and laboratory data should provide robust risk-adjustment variables. Although the randomized clinical trials underway will be instrumental in defining the benefit-to-risk ratio of TZDs in HF, randomized trials may exclude patients included in observational studies, such as those patients with

advanced renal insufficiency. Finally, the primary end point of this study was HF hospitalization, and episodes of HF exacerbation that did not require hospitalization were not captured.

## Conclusions

In an ambulatory cohort of patients with established HF and diabetes, TZD use was not associated with an increased risk of HF hospitalization or with increased risk of death when compared with those not receiving insulin-sensitizing medications. Our data suggest that TZDs may be used safely in individuals with stable HF, and that TZDs could be included in the armamentarium to adequately treat diabetes in this group. However, until data from adequately powered randomized clinical trials are available to define the benefits and risks associated with TZDs, clinicians treating individuals with diabetes and HF must remain cautious when using this class of medications.

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