Risk of Heart Failure with the Use of Thiazolidinediones within a Medicaid Population

Fadia T. Shaya, PhD, MPH, James Y. Shin, PharmD, C. Daniel Mullins, PhD, Antoine C. El Khoury, PhD, and Howard Garber, MD, MPH

ABSTRACT

Objective: Controlling for demographic and clinical characteristics and drug exposure, we evaluated the risk of heart failure after the use of thiazolidinediones (TZDs) in a group of Medicaid beneficiaries. We explored the effects of demographics, including race, clinical characteristics, treatment with drugs commonly given to patients with diabetes or heart failure, and the duration of drug therapy.

Study Design: This was a retrospective cohort trial.

Methods: We analyzed the patients' prescription and medical claims from a managed care organization. The study sample included patients with diabetes mellitus who received a TZD or metformin HCl for two years (from June 2000 to June 2002), but patients were excluded if they had a history of heart failure prior using the study drugs. The primary variable of interest was the incidence of heart failure, as measured by the presence of medical claims with the diagnosis of heart failure. Two multivariate logistic regression models were used to assess the association of heart failure with exposure to the drug.

Results: Compared with the metformin patients (n = 2,079), TZD patients (n = 677) were older, more likely to have pre-existing diabetes complications, and were more likely to use insulin. More TZD patients (9.9%) than metformin patients (5.9%) developed heart failure. In an adjusted model, the use of TZDs was predictive for the development of heart failure (odds ratio = 1.6; \(P = .0061\)). An analysis that considered exposure to the drug showed consistent results.

Conclusion: The use of TZDs may be predictive of an increased risk of heart failure. These agents should be used with caution in high-risk and older patients.

Key Words: thiazolidinediones, metformin, diabetes mellitus, heart failure, Medicaid

BACKGROUND

For the year 2000, diabetes mellitus was the sixth leading cause of death in the U.S.\(^1\) More than 10 million Americans have type-2 diabetes, and an additional 5.5 million people may unknowingly have the disease.\(^2\) Diabetes typically progresses via the development of resistance to insulin in the peripheral tissues and via decreased insulin production by the pancreas.\(^3\) The oral insulin-sensitizing agents that are most commonly used to treat insulin resistance are the biguanide metformin HCl (Glucophage®, Bristol-Myers Squibb) and the thiazolidinediones (TZDs) pioglitazone (Actos®, Takeda/Eli Lilly) and rosiglitazone maleate (Avandia®, GlaxoSmithKline). A third TZD, troglitazone (Rezulin®, Parke-Davis), was approved for use in the U.S. but was withdrawn because of severe hepatic toxicity.\(^4\)

Diabetes has been identified as a significant risk factor for the development of heart failure, a disease with major public health implications.\(^5,6\) It has not been determined whether this is a result of associated comorbidities, such as hypertension and hypercholesterolemia; the acceleration of the development of coronary atherosclerosis with diabetes; or the existence of a specific diabetic cardiomyopathy.\(^7\) The prevalence of heart failure is estimated at 1% to 2% of non-institutionalized adults, and it increases with age.\(^8\)

More than 500,000 new cases of heart failure are reported each year.\(^9\) The exact percentage of cases of heart failure that are attributable to diabetes is unknown; in one study, however, the risk of heart failure was 1.3 times higher in diabetic patients than in those without diabetes.\(^5\)

Race can be a predicting factor in the development of heart failure. African-American men have a 33% greater risk for hospitalization because of heart failure, compared with white men, and African-American women have double the risk, compared with white women.\(^10\) Mortality rates are also higher in African-Americans who have been hospitalized with heart failure.\(^11\) Compounding this issue is the higher prevalence of risk factors for heart failure among African-Americans; these risk factors include diabetes and hypertension.\(^11\)

Racial disparities in cardiovascular health have been widely documented and have sometimes been attributed to system-specific problems such as access to health care.\(^12\) Medicaid populations, which typically include a large population of African-Americans, are at a higher risk for cardiovascular complications associated with diabetes.\(^13\) However, the literature is inconclusive as to the influence of race on health in disadvantaged populations.\(^12,14,15\)

Despite the efficacy of metformin and TZDs in reducing insulin resistance, precautions should be taken with these agents in patients with moderate-to-severe heart failure.\(^16-18\) TZDs may also pose a potential risk for causing or exacerbat-

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ing heart failure because they are associated with fluid retention. Several case studies have explored the link between TZD use and the development of heart failure, but no prospective controlled clinical trials have been completed to establish this association.

The purpose of our study was to determine the possible risk of heart failure associated with the use of metformin or TZDs in Medicaid recipients. We built a multivariate logistic regression model to predict the risk of heart failure as a function of TZD use while accounting for confounders (e.g., race, age, sex, pre-existing comorbidities, pharmaceutical treatment commonly given to patients with diabetes or heart failure, and duration of drug therapy).

**METHODS**

**Source of Data**

We obtained prescription and medical claims from Medicaid managed care organizations. Over the study period, none of the Medicaid plans had tiered co-pay designs that charged different amounts for brand and generic drugs. The plans did not apply step therapy or prior authorization criteria to obtain these study drugs during the data collection period.

**Study Sample**

Patients were selected if they were continuously enrolled during the study period, if they had both pharmacy and medical claims, and if they had at least one claim for either metformin or a TZD. Patients with claims for both metformin and a TZD during the study period were excluded.

To improve the likelihood of finding only new users of these drugs, patients who used metformin or TZDs within the first six months of the data set (January 15, 2000–June 14, 2000) were excluded. The initial study drug (metformin or TZD) was labeled as the index drug. The date of the first claim for the index drug was designated as the index date.

Inclusion criteria also consisted of the presence of a diagnosis of diabetes mellitus (ICD-9-CM 250.xx). Because previous studies had shown heart failure occurring at least one month after the initiation of TZDs, we required patients to have at least one month of medical claims after their index date to observe the development of heart failure. Patients with a claim for heart failure (ICD-9-CM 402.11, 402.91, 428.0, 428.1, and 428.9) prior to the initiation of an index drug were excluded. Patients under 18 years old were excluded.

Predictors of risk included race, age, and sex. We also included a variable denoting the presence of at least one of the following risk factors for heart failure:

- hypertension (ICD-9-CM 401.xx–405.xx and 997.91)
- coronary heart disease (ICD-9-CM 410.xx–414.xx)
- hypercholesterolemia (ICD-9-CM 272.0x)
- stroke (ICD-9-CM 430.xx–438.xx)

To account for the severity of diabetes, we included the following complications of diabetes that occurred before initiation of the index drug:

- nephropathy (ICD-9-CM 250.4x and 581.xx–583.8x)
- neuropathy (ICD-9-CM 250.6x, 337.1x, 344.61, 354.xx, 355.xx, 356.9x, 357.2x, 357.9x, 536.3x, 593.7x, 596.4x, 596.5x, 607.84, and 713.4x)
- retinopathy (ICD-9-CM 250.5x, 362.0x, and 362.1x)

Similarly, we identified any use of oral diabetes drugs by including dummy variables accounting for the categories of alpha glucosidase inhibitors, sulfonylureas, and insulin secretagogues and insulin prior to the index date. These dummies accounted for patients who had been prescribed insulin or oral diabetes drugs and who were initiated with TZD or metformin.

We also assessed the use of heart failure medications, angiotensin-converting enzyme (ACE)–inhibitors, and beta blockers. The use of ACE-inhibitors and beta blockers is encouraged in patients with heart failure because these drugs can reduce the progression of the disease and decrease the mortality risk.

**Statistical Analysis**

We identified the predictors of TZD initiation within the overall population by using a multivariate logistic regression model that assessed the independent effects of demographic and clinical characteristics. We also explored the association between index drug use and other variables among patients who developed heart failure. Logistic regressions were built to assess the combined effect of all variables on the probability of heart failure development. Predictor variables included race, age, sex, pre-index comorbidities, and pre-index prescription drug use.

We accounted for exposure to the index drug by building two different models. In the first model, we added a continuous variable to count claims of the index drug. In the second one, three or more claims of the index drug were required for analysis. We used SAS Version 8.2 software (SAS Institute, Cary, North Carolina) to perform all of the statistical analyses.

**RESULTS: PREDICTORS OF TZD/METFORMIN PRESCRIBING**

**Patient Characteristics**

A total of 2,756 patients met the inclusion criteria; 677 patients filled a prescription for at least one TZD, and 2,079 patients filled at least one prescription for metformin (Table 1). Compared with the patients who were prescribed metformin, TZD patients were older (OR, 1.09; 95% confidence interval [CI], 1.01–1.07; \( P = .0209 \)), were more likely to have pre-existing diabetes complications (OR, 1.42; 95% CI, 1.13–1.79; \( P = .0027 \)), and tended to use insulin (OR, 2.0; 95% CI, 2.11–3.22; \( P < .0001 \)). They were less likely to be African-American (OR, 0.54; 95% CI, 0.45–0.65; \( P < .0001 \)).

**Incidence of Heart Failure**

After therapy was initiated, 190 patients (6.9%) developed heart failure (Table 2). These patients were generally older than the overall study population. Among the TZD users, 67 patients (9.9%) developed heart failure, compared with 123 (5.9%) in the metformin cohort. The TZD patients were more likely to use oral diabetes medications (OR, 2.46; 95% CI, 1.13–5.33; \( P = .0223 \)) and insulin (OR, 4.04; 95% CI, 1.84–8.88; \( P = .0005 \)).

continued on page 279
Analytical Models

The first multivariate model (Table 3) assessed the association of demographic and clinical characteristics with risk of heart failure without regard to the length of exposure to the drug. In the adjusted model, patients taking TZDs were more likely to develop heart failure than those taking metformin (OR, 1.581; 95% CI, 1.140–2.193; P = .0061). Significant predictors of heart failure were older age and the use of ACE-inhibitors or beta blockers.

In a second model (see Table 3), we accounted for the intensity of exposure to the index drug by including a variable for the number of claims for the index drug. The model showed significance for (1) older age, (2) receipt of ACE-inhibitors, (3) prescriptions for beta blockers, and (4) higher counts of index drug claims. Incremental increases in the number of index drug claims were associated with an OR of 1.050 (95% CI, 1.028–1.073; P < .0001). After we adjusted for covariates, the risk of heart failure in TZD users was higher than that for metformin users (OR, 1.600; 95% CI, 1.151–2.226).

To further evaluate the length of drug exposure, we built a third model (see Table 3). This model excluded patients whose total number of index drug claims was less than three during the study period. This allowed for analysis of only patients with multiple refills (at least three) of either index drug. The two cohorts were reduced by roughly the same proportion: 29% with metformin and 31% with TZDs.

The characteristics associated with a higher risk of heart failure were (1) advanced age, (2) use of ACE-inhibitors, and (3) use of beta blockers. The use of other oral diabetes medications was associated with a lower risk of heart failure. In the

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**Table 1** Demographic and Clinical Characteristics in the Study Population by Drug Cohort (TZDs or Metformin)

<table>
<thead>
<tr>
<th>Variable</th>
<th>TZD No. (%)</th>
<th>Metformin No. (%)</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 2,756</td>
<td>677</td>
<td>2,079</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>50.7 ± 12.1</td>
<td>48.8 ± 12.2</td>
<td>1.009 (1.001–1.017)</td>
<td>.0209</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>195 (29)</td>
<td>583 (28)</td>
<td>1.015* (0.832–1.238)</td>
<td>.8846*</td>
</tr>
<tr>
<td>Race (African-American)</td>
<td>342 (51)</td>
<td>1,321 (64)</td>
<td>0.546† (0.454–0.657)</td>
<td>&lt;.0001†</td>
</tr>
<tr>
<td>Pre-existing comorbidities</td>
<td>387 (57)</td>
<td>1,023 (49)</td>
<td>1.176 (0.958–1.443)</td>
<td>.1207</td>
</tr>
<tr>
<td>Pre-index diabetes complications</td>
<td>161 (24)</td>
<td>299 (14)</td>
<td>1.425 (1.131–1.795)</td>
<td>.0027</td>
</tr>
<tr>
<td>Pre-index medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Oral diabetes drugs</td>
<td>219 (32)</td>
<td>622 (30)</td>
<td>1.107 (0.904–1.355)</td>
<td>.3252</td>
</tr>
<tr>
<td>• Insulin</td>
<td>231 (34)</td>
<td>350 (17)</td>
<td>2.609 (2.110–3.224)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>• ACE-inhibitors</td>
<td>232 (34)</td>
<td>59 (27)</td>
<td>1.083 (0.872–1.344)</td>
<td>.4700</td>
</tr>
<tr>
<td>• Beta blockers</td>
<td>95 (14)</td>
<td>246 (12)</td>
<td>0.938 (0.713–1.233)</td>
<td>.6452</td>
</tr>
</tbody>
</table>

* Female vs. male.
† African-American vs. others.
ACE = angiotensin-converting enzyme; CI = confidence interval; TZD = thiazolidinedione.

**Table 2** Demographic and Clinical Characteristics in a Population with Heart Failure by Drug Cohort (TZDs or Metformin)

<table>
<thead>
<tr>
<th>Variable</th>
<th>TZD No. (%)</th>
<th>Metformin No. (%)</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 190</td>
<td>67 (10)</td>
<td>123 (6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>54.4 ± 9.4</td>
<td>52.7 ± 8.8</td>
<td>1.023 (0.985–1.063)</td>
<td>.2415</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>18 (27)</td>
<td>34 (28)</td>
<td>1.047* (0.509–2.154)</td>
<td>.906*</td>
</tr>
<tr>
<td>Race (African-American)</td>
<td>37 (55)</td>
<td>81 (66)</td>
<td>0.612‡ (0.310–1.211)</td>
<td>.1589‡</td>
</tr>
<tr>
<td>Pre-existing comorbidities</td>
<td>42 (63)</td>
<td>75 (61)</td>
<td>0.957 (0.451–2.029)</td>
<td>.9082</td>
</tr>
<tr>
<td>Pre-index diabetes complications</td>
<td>13 (19)</td>
<td>28 (23)</td>
<td>0.497 (0.211–1.171)</td>
<td>.1097</td>
</tr>
<tr>
<td>Pre-index medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Oral diabetes drugs</td>
<td>24 (36)</td>
<td>34 (28)</td>
<td>2.464 (1.137–5.338)</td>
<td>.0223</td>
</tr>
<tr>
<td>• Insulin</td>
<td>26 (39)</td>
<td>26 (21)</td>
<td>4.044 (1.840–8.887)</td>
<td>.0005</td>
</tr>
<tr>
<td>• ACE-inhibitors</td>
<td>30 (45)</td>
<td>52 (42)</td>
<td>0.944 (0.447–1.991)</td>
<td>.8791</td>
</tr>
<tr>
<td>• Beta blockers</td>
<td>14 (21)</td>
<td>27 (22)</td>
<td>0.605 (0.257–1.427)</td>
<td>.2512</td>
</tr>
</tbody>
</table>

* Female vs. male.
‡ Others vs. African-American.
ACE = angiotensin-converting enzyme; CI = confidence interval; TZD = thiazolidinedione.
Risk of Heart Failure with TZDs

Using our Medicaid database, we found that treatment with TZDs was associated with a higher risk of heart failure. The relative OR was similar to that in prior studies.9,25 The characteristics that precipitated initiation of TZDs were older age, presence of a pre-index comorbidity, the pre-index use of insulin, and non–African-American race. The first three findings show that these drugs were used in a population that was at a higher risk of heart failure. Although insulin is not known to increase the risk of heart failure, its use is commonly associated with a higher likelihood of heart failure. We estimated TZD use by two methods. The first model included a variable for counting the number of claims for the index drug; this was included as a continuous variable in the multivariate model. The second model involved limiting the population to those with three or more claims for the index drug.

**DISCUSSION**

Using our Medicaid database, we found that treatment with TZDs was associated with a higher risk of heart failure. The relative OR was similar to that in prior studies.9,25 The characteristics that precipitated initiation of TZDs were older age, presence of a pre-index comorbidity, the pre-index use of insulin, and non–African-American race. The first three findings show that these drugs were used in a population that was at a higher risk of heart failure. Although insulin is not known to increase the risk of heart failure, its use is commonly associated with a higher likelihood of heart failure. We estimated TZD use by two methods. The first model included a variable for counting the number of claims for the index drug; this was included as a continuous variable in the multivariate model. The second model involved limiting the population to those with three or more claims for the index drug.

Clinically, we chose to use the number of 3 claims to ensure that patients had enough exposure to the index drug to account for an ADE. One study had noted the occurrence of heart failure after only one month of TZD use; therefore, we considered a period of three months to be appropriate.9 Statistically, the distribution of patients removed from each group would be similar, roughly 30% each.

Some characteristics that might have increased the risk of heart failure did not show statistical significance in affecting its development. Although the number of African-Americans (62%) was higher among patients with heart failure, compared with the overall study population (60%), race was not a significant predictor of heart failure in this population. The lower rate of TZD use among African-Americans may have influenced this result.

Because diabetes is a risk factor for the development of heart failure, we included pre-existing diabetes complications to assess the influence of severity of the disease on the incidence of heart failure. There was an increase in the number of patients with pre-existing diabetes complications from the study population (17%), compared with those who developed heart failure (22%). However, the severity of diabetes did not result in a statistically significant difference.

The duration of exposure to a drug is often correlated with an increased risk of an adverse drug event (ADE). For example, a longer duration of exposure to nonsteroidal anti-inflammatory drug (NSAID) therapy is known to increase the risk for gastrointestinal bleeding.25 The long-term use of steroids has been shown to cause Cushing’s disease.25 However, little is known about the influence of duration of TZD exposure on the development of heart failure.

In this study, two different models assessing the use of TZDs showed that higher numbers of TZD claims were associated with a higher likelihood of heart failure. We estimated TZD use by two methods. The first model included a variable for counting the number of claims for the index drug; this was included as a continuous variable in the multivariate model. The second model involved limiting the population to those with three or more claims for the index drug.

Clinical and statistical significance of our study is limited by the fact that only Medicaid patients were included. The data were subject to the inherent limitations of a retrospective observational study design. The study population was a subset of the Medicaid population; therefore, findings may not be generalizable to other populations. However, the findings regarding the increased risk of heart failure associated with the use of TZDs are consistent with other studies.26

### Table 3 Predictors of Heart Failure

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1* (n = 2,756)</th>
<th>Model 2† (n = 2,756)</th>
<th>Model 3‡ (n = 1,943)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OR (95% CI) P Value</strong></td>
<td><strong>OR (95% CI) P Value</strong></td>
<td><strong>OR (95% CI) P Value</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Index drug: TZD</strong></td>
<td>1.581 (1.140–2.193) .0061</td>
<td>1.600 (1.15–2.226) .0052</td>
<td>1.749 (1.205–2.538) .0032</td>
</tr>
<tr>
<td><strong>Sex: female vs. male</strong></td>
<td>1.070 (0.766–1.497) .6906</td>
<td>1.078 (0.770–1.509) .6631</td>
<td>1.139 (0.776–1.672) .5066</td>
</tr>
<tr>
<td><strong>Race: other vs. African-American</strong></td>
<td>0.819 (0.597–1.124) .2169</td>
<td>0.810 (0.590–1.113) .1935</td>
<td>0.885 (0.597–1.223) .3901</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>1.027 (1.014–1.041) &lt;.0001</td>
<td>1.026 (1.012–1.041) .0003</td>
<td>1.034 (1.018–1.051) &lt;.0001</td>
</tr>
<tr>
<td><strong>Pre-existing comorbidities</strong></td>
<td>1.020 (0.718–1.449) .9128</td>
<td>1.036 (0.730–1.471) .8438</td>
<td>0.943 (0.639–1.393) .7695</td>
</tr>
<tr>
<td><strong>Pre-index diabetes</strong></td>
<td>1.178 (0.802–1.731) .4046</td>
<td>1.235 (0.839–1.181) .2856</td>
<td>0.907 (0.561–1.466) .6908</td>
</tr>
</tbody>
</table>

* Model 1 = all variables except index drug count; no index drug count limitation.
† Model 2 = all variables; no index drug count limitation.
‡ Model 3 = all variables except index drug count; index drug count ≥3.

Pre-existing comorbidities include hypertension, coronary heart disease, and hypercholesterolemia.

ACE = angiotensin-converting enzyme; OR = odds ratio; TZD = thiazolidinedione.

Adjusted model, patients taking TZDs were more likely to have heart failure (OR, 1.749; 95% CI, 1.205–2.538; P = .0032).
Factors such as body weight and edema have been associated with an increase in the incidence of heart failure in patients treated with TZDs and insulin. However, we did not include these variables in this study.27

The limitations of our study pertain to assumptions inherent in the claims data. Although we validated the data field, there might have been undetected errors in coding. The study did consider predictors of the use of TZDs and the odds of developing heart failure; however, given that the design was a retrospective cohort, there was no true randomization of patients, as in randomized clinical trials, because the population studied was composed of Medicaid patients.

Even though the association of heart failure and TZD use had not been previously studied in a Medicaid population, the external validity of the results may be limited. As a result, we cannot generalize to the overall population or even to other Medicaid populations. In the absence of clinical indicators, we evaluated the severity of diabetes by applying proxy measures of insulin use and oral diabetes drug use. Encounter data (relating to treatment or services rendered by health care providers to patients) used in this study do not inform us whether patients are actually taking the medication. Furthermore, no data on adherence to therapy or on clinical measures are available.

Finally, TZDs are approved for administration with metformin in selected patients. This study did not consider the risk of heart failure with this combination therapy.

CONCLUSION
TZDs are maintenance medications used in the treatment of insulin resistance and diabetes. Their influence on the development of cardiovascular events, such as heart failure, is currently being investigated in clinical trials.27 While research is being published on their risks and benefits, it is important to keep one’s clinical judgment in perspective. Our results suggest that TZDs should be used with caution in high-risk and older patients. However, the decision to prescribe should be based on weighing the benefits and risks as well as other individual physician and patient considerations.

REFERENCES