Thiazolidinediones and congestive heart failure in veterans with type 2 diabetes

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Aim: The thiazolidinedione (TZD) class of antihyperglycaemic agents has been shown to improve glycaemic control by improving peripheral insulin sensitivity but may worsen or precipitate congestive heart failure (CHF). Randomized controlled trials have shown an increased risk of CHF in patients treated with TZDs. The use of TZDs in clinical practice has the potential to increase morbidity and health care costs. The purpose of this study was to compare the incidence of CHF in TZD and non-TZD-treated patients in a clinical setting.

Methods: A retrospective cohort study of all male patients with type 2 diabetes seen in the South Central US Veterans Administration health care network between 1 October 1996 and 31 December 2004. We constructed a Cox proportional hazards model to evaluate the impact of TZD therapy on time to incidence of CHF.

Results: Of 3956 patients, 29% (n = 1157) developed CHF during the study period. The incidence of CHF was higher in patients who received TZD medications than in those who received TZDs. After adjustment for multiple cardiac risk factors, the hazard ratio for the development of CHF for TZD versus non-TZD-treated patients was 0.69 with a 95% confidence interval of 0.60–0.79.

Conclusions: Patients in this cohort who received TZD medications had a lower incidence of heart failure than patients who did not receive TZDs.

Keywords: adverse effect, antihyperglycaemic agents, congestive heart failure, glitazone, thiazolidinedione, type 2 diabetes

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Introduction

Congestive heart failure (CHF) is a major complication of diabetes and occurs as a result of both atherosclerotic coronary disease and non-ischaemic diabetic cardiomyopathy. It is theorized that diabetic cardiomyopathy is a direct result of pathologic characteristics of the diabetic state such as endothelial dysfunction, oxidative stress and glucose toxicity [1,2].

The thiazolidinedione (TZD) class of antihyperglycaemic agents acts by improving insulin sensitivity at peripheral sites of action. They have been shown to reduce levels of glucose and circulating insulin [3] and have beneficial effects on many markers of cardiovascular risk including blood pressure, waist to hip ratio, HDL levels [4,5], endothelial reactivity, C-reactive protein [6], fibrinolysis [7] and microalbuminuria [8,9]. Long-term outcome trials have not consistently shown reductions in cardiovascular events in TZD-treated patients [10].

TZDs are also associated with fluid retention, weight gain and peripheral oedema. TZDs may worsen the existing CHF or precipitate new-onset failure. In TZD trials, which included patients with New York Heart Association class I and II heart failure, the risk of CHF exacerbation was increased particularly for patients on TZDs in combination with insulin [11,12]. Findings from observational studies have been inconsistent, reporting negative, neutral and protective effects on the heart failure incidence and mortality [13–16].

Randomized controlled trials have uniformly shown an increase in the risk of heart failure for patients prescribed TZDs [17–20]. These trials were conducted with strict entry criteria and excluded patients with known heart failure or who were at high risk for CHF. These findings have raised concerns that the use of TZDs in practise may lead to a significant increase in CHF, which may in turn increase health care costs and have prognostic implications for patients. We therefore examined a large database of patients with type 2 diabetes to compare the incidence of new CHF in patients with type 2 diabetes receiving TZDs to that of patients with diabetes not receiving this class of medications.

Methods

This study was conducted as a retrospective cohort design. Data originated from the existing electronic data stored in the Veterans Administration (VA) Data Warehouse. These data are extracted from medical records of patients seen in the South Central US VA health care network (VISN 16). The primary measure of interest was the incidence of newly diagnosed CHF. The study protocol was approved by the Tulane University Health Sciences Center institutional review board.
Data Warehouse

VISN 16 serves nearly 400,000 patients in an eight-state region that includes Florida, Alabama, Mississippi, Louisiana, Arkansas, Missouri, Oklahoma, and Texas. It includes 10 medical centers, 30 community-based outpatient clinics, 7 nursing homes and 2 domiciliaries [21].

The data warehouse includes information abstracted from medical records, pharmacy records, and laboratory data. Recorded information includes demographic data, diagnosis codes for inpatient and outpatient visits, laboratory results, and pharmacy records including drug dispensed, date, quantity, and number of therapy days.

Study Population

The study population included male patients with at least one diagnosis of diabetes mellitus recorded during an inpatient or outpatient visit between 1 June 1999 and 31 December 2004 (ICD9 codes: 250.∗). Those patients who had an inpatient or outpatient visit with a diagnosis of CHF (ICD9 codes 428.∗) prior to their initial diabetes visit date were excluded. Patients with a record of filling a pharmacy prescription for either pioglitazone or rosiglitazone during the study period were designated as exposed. The remainder made up the unexposed (control) group.

Patient Characteristics

Information on age and body mass index (BMI) at the time of the first visit date for diabetes was obtained as well as the initial and average systolic blood pressure, glycosylated haemoglobin (HbA1c), low-density lipoprotein, high-density lipoprotein and triglyceride (TG) levels. In addition, a history of ICD9 diagnosis of vascular disease (coronary artery disease, cerebrovascular disease or peripheral vascular disease) and tobacco use was assessed. Finally, information about concurrent therapy with insulin, metformin, sulphonylureas, and non-sulphonylurea secretagogues, a-glucosidase inhibitors and 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors was gathered.

The initial sample size was 34,397. After removing observations with missing or invalid values for any of the predictor variables, such as negative or biologically implausible numbers, 11,239 subjects remained.

To ensure that the study groups were comparable, the cohort was restricted to those patients with a baseline HbA1c of 7% or greater who were being prescribed at least two antihyperglycaemic agents. This restriction was necessary because of the fact that TZDs were not usually prescribed as first-line agents. Thus, patients treated with TZDs most probably did not achieve optimal control after treatment with a first-line agent. The final data set contained 3,956 patients.

Outcome Measure

The primary measure of interest was the incidence of new CHF. This was defined as the occurrence of at least one inpatient or outpatient visit with a recorded diagnosis of CHF. The follow-up period began at the initial visit with a diagnosis of diabetes and ended on the last visit date, date of discontinuation of TZD, date of death or the end of the study period, whichever occurred first. The potential period of follow-up was from 1 June 1999 through 31 December 2006.

Excluded Patients

There were 7,283 patients excluded from the study because they had a baseline-HbA1c less than or equal to 7 (n = 5,133) or because they were being treated with less than two medications (n = 2,150). Excluded patients had an incidence of CHF (33%) slightly higher than that of the study population (29%). Two per cent (n = 114) of the excluded patients were receiving TZD monotherapy and a smaller proportion (23%) of these patients developed CHF than the larger population during the follow-up period.

Statistical Methods

All statistical analyses were conducted using SAS (version 9.1, SAS Institute, Cary, NC, USA). The demographic and clinical characteristics of exposed and unexposed patients at baseline were described with simple (unadjusted) summary statistics. Differences were assessed with chi-square tests for categorical variables and t-tests for continuous variables. Bivariate Cox proportional hazards models were generated to explore the effect of each predictor variable on time from study entry to initial diagnosis of CHF. Predictors that were related to survival time with p ≤ 0.20 were entered as potential covariates for the final model. Potential covariates were BMI, HbA1c, LDL cholesterol, TGs, systolic blood pressure, treatment with insulin, metformin, non-sulphonylurea secretagogues, HMG-CoA reductase inhibitors and TZDs, number of antihyperglycaemic medications prescribed, history of vascular disease and history of tobacco use. Although age at study entry did not meet the model entry criteria, the age variable was also entered because it is known to be strongly related to heart disease. The final model was generated using stepwise selection and the Efron method to handle tied event times.

Results

Statistically significant differences between the TZD-exposed and control groups were found for several of the baseline clinical and demographic covariates (Table 1). The mean length of follow-up was longer in the group exposed to TZDs by approximately 9 months. The exposed group was also more likely to have been prescribed more antihyperglycaemic agents and to have been treated with HMG-CoA reductase inhibitors. The unexposed group was more likely to have been treated with antihyperglycaemic agents other than TZDs (insulin, metformin or sulphonylureas). For the most part, the magnitude of the differences for the remaining covariates is small enough to question their clinical significance.

The length of follow-up ranged from 24 to 2557 days and the majority of patients were observed for over 2000 days. Approximately 29% (n = 1157) of the patients developed CHF during the 7.5-year study period. This incidence greatly exceeds that of the general population [22] but given that the presence...
Unadjusted Kaplan–Meier survival curves for TZD- and non-TZD patients are presented in figure 1. The plot shows that a smaller proportion of TZD-treated patients developed CHF than non-TZD patients for a given length of follow-up. Furthermore, this difference remained relatively constant throughout the duration of the follow-up period. Treatment with insulin was also associated with an increased risk of CHF on bivariate analysis (p = 0.02). However, when the data were stratified with respect to TZD exposure, insulin was no longer significantly related to CHF risk.

Parameters for the Cox proportional hazards model are summarized in Table 2 along with their associated hazard ratios, statistical significance and confidence intervals (CIs) for hazard ratios. Global tests on this model were highly significant (likelihood ratio = 368 on 12 df, p < 0.0001).

After adjustment for other variables, increasing age, BMI, low-density lipoprotein level, HbA1c level, TG level, systolic blood pressure and history of vascular disease were all predictors of increased CHF risk. Receiving a prescription for metformin, HMG-CoA reductase inhibitors and a higher total number of antihyperglycaemic agents were protective against the development of CHF. Finally, prescription for non-TZD-exposed patients is reported.

**Table 1.** Comparison of baseline characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean unexposed</th>
<th>Mean exposed</th>
<th>p value (t-test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up (days)</td>
<td>1836</td>
<td>2100</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62</td>
<td>61</td>
<td>0.0162</td>
</tr>
<tr>
<td>BMI</td>
<td>30.7</td>
<td>30.7</td>
<td>0.9529</td>
</tr>
<tr>
<td>First HbA1c (%)</td>
<td>8.96</td>
<td>8.93</td>
<td>0.6110</td>
</tr>
<tr>
<td>First LDL (mg/dl)</td>
<td>118.7</td>
<td>121.6</td>
<td>0.0059</td>
</tr>
<tr>
<td>First HDL (mg/dl)</td>
<td>39.8</td>
<td>39.3</td>
<td>0.0987</td>
</tr>
<tr>
<td>First TG (mg/dl)</td>
<td>205.8</td>
<td>204.9</td>
<td>0.8584</td>
</tr>
<tr>
<td>First SBP (mmHg)</td>
<td>144</td>
<td>144</td>
<td>0.9713</td>
</tr>
<tr>
<td>Number of drugs</td>
<td>2.28</td>
<td>2.99</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Bivariate analysis showed that the risk of CHF was increased by the history of vascular disease (p < 0.0001) and higher levels of BMI (p < 0.0001), HbA1c (p < 0.0001), low-density lipoprotein (0.0002), TGs (p < 0.0001) and systolic blood pressure (p < 0.0001). Having been prescribed metformin (p < 0.0001), HMG-CoA reductase inhibitors (p < 0.0001) or TZDs (p < 0.0001) were associated with lower risk of developing CHF as was having been prescribed a higher total number of antihyperglycaemic agents (p < 0.0001). Unadjusted Kaplan–Meier survival curves for TZD- and non-TZD-exposed patients are shown in figure 1. The plot shows that a smaller proportion of TZD-treated patients developed CHF than non-TZD patients for a given length of follow-up. Furthermore, this difference remained relatively constant throughout the duration of the follow-up period. Treatment with insulin was also associated with an increased risk of CHF on bivariate analysis (p = 0.02). However, when the data were stratified with respect to TZD exposure, insulin was no longer significantly related to CHF risk.

Parameters for the Cox proportional hazards model are summarized in Table 2 along with their associated hazard ratios, statistical significance and confidence intervals (CIs) for hazard ratios. Global tests on this model were highly significant (likelihood ratio = 368 on 12 df, p < 0.0001).

After adjustment for other variables, increasing age, BMI, low-density lipoprotein level, HbA1c level, TG level, systolic blood pressure and history of vascular disease were all predictors of increased CHF risk. Receiving a prescription for metformin, HMG-CoA reductase inhibitors and a higher total number of antihyperglycaemic medications were protective against the development of CHF. Finally, prescription for non-TZD-exposed patients is reported.

**Table 2.** Cox proportional hazards model.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>s.e. (Coefficient)</th>
<th>p</th>
<th>HR</th>
<th>Lower 95</th>
<th>Upper 95</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.01113</td>
<td>0.00324</td>
<td>0.0046</td>
<td>1.01</td>
<td>1.005</td>
<td>1.018</td>
</tr>
<tr>
<td>BMI</td>
<td>0.03074</td>
<td>0.00672</td>
<td>&lt;0.0001</td>
<td>1.03</td>
<td>1.018</td>
<td>1.045</td>
</tr>
<tr>
<td>First HbA1c</td>
<td>0.05514</td>
<td>0.02094</td>
<td>0.0085</td>
<td>1.06</td>
<td>1.014</td>
<td>1.101</td>
</tr>
<tr>
<td>Average HbA1c</td>
<td>0.12893</td>
<td>0.02344</td>
<td>&lt;0.0001</td>
<td>1.13</td>
<td>1.087</td>
<td>1.191</td>
</tr>
<tr>
<td>Average LDL</td>
<td>0.00551</td>
<td>0.00105</td>
<td>&lt;0.0001</td>
<td>1.06</td>
<td>1.003</td>
<td>1.008</td>
</tr>
<tr>
<td>Average TG</td>
<td>0.00150</td>
<td>0.00022</td>
<td>&lt;0.0001</td>
<td>1.00</td>
<td>1.001</td>
<td>1.002</td>
</tr>
<tr>
<td>Average SBP</td>
<td>0.00637</td>
<td>0.00249</td>
<td>0.0106</td>
<td>1.00</td>
<td>1.001</td>
<td>1.011</td>
</tr>
<tr>
<td>Metformin</td>
<td>-0.31429</td>
<td>0.10028</td>
<td>0.0017</td>
<td>0.73</td>
<td>0.600</td>
<td>0.889</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>0.31682</td>
<td>0.06086</td>
<td>&lt;0.0001</td>
<td>1.37</td>
<td>1.218</td>
<td>1.547</td>
</tr>
<tr>
<td>Statin</td>
<td>-0.63088</td>
<td>0.07022</td>
<td>&lt;0.0001</td>
<td>0.53</td>
<td>0.464</td>
<td>0.611</td>
</tr>
<tr>
<td>TZD</td>
<td>-0.36748</td>
<td>0.07007</td>
<td>&lt;0.0001</td>
<td>0.69</td>
<td>0.604</td>
<td>0.794</td>
</tr>
<tr>
<td>Number of drugs</td>
<td>-0.16326</td>
<td>0.04813</td>
<td>0.0007</td>
<td>0.84</td>
<td>0.773</td>
<td>0.933</td>
</tr>
</tbody>
</table>

BMI, body mass index; HbA1c, glycosylated haemoglobin A1c; HR, heart rate; LDL, low-density lipoprotein; SBP, systolic blood pressure; TG, triglyceride; TZD, thiazolidinedione.
TZDs remained significantly predictive of lower risk of CHF [hazard ratio (HR) = 0.69, 95% confidence interval 0.60–0.79]. Figure 2 compares the adjusted survival estimates for TZD exposed and unexposed patients.

Discussion

Using a large electronic medical records database, we found that the use of TZDs was associated with a lower risk of heart failure in male VA patients with uncontrolled type 2 diabetes over follow-up periods ranging from 24 days to over 7 years. These results contrast with the results from several large and long-term clinical trials that show an increase in the incidence of CHF with TZDs.

Patients exposed to TZDs appeared to have been in treatment for longer time periods and to have received more intensive pharmacological risk reduction than unexposed patients. One reason for this difference could be that patients who were ultimately prescribed TZDs had failed to achieve glycaemic control with other agents. In this situation, one would have expected to see lower baseline HbA1c values in the exposed group. Alternatively, the correlation between TZD exposure and treatment with other medications could reflect a more aggressive management approach on the part of a subset of providers. If this were the case, one might expect to see lower endpoint HbA1c values in the exposed group. However, there were no significant differences in baseline, average or final HbA1c values between the two groups.

Limitations

We recognize several limitations to this study. First, a large subset of the study population had to be excluded because of invalid values for one or more of the covariates. Such values point to a high rate of data entry errors. Second, as the study was conducted as a retrospective design, assignment to treatment was neither random nor blinded. It is possible that prior evidence of association between TZDs and oedema influenced health care providers to limit TZD prescription to patients with a low risk of CHF. In addition, information about the length of treatment with TZDs and reasons for discontinuation were unavailable. It is possible that exposed patients who showed early signs of fluid retention discontinued the medication prior to the development of heart failure.

Third, as it was not possible to ascertain the length of time since the diagnosis of diabetes, we were unable to control for this important factor. Fourth, the analysis used the first instance of entering an ICD9 code for heart failure as a proxy for the outcome measure, incidence of new CHF. The accuracy and timeliness of ICD9 coding are unknown and, in the outpatient setting, may be based on the presence of oedema or dyspnoea rather than the assessment of cardiac function.

Another potential limitation is the presence of a survivor effect if patients with acute heart failure received care at a non-VA facility and did not subsequently return to the VA system. However, studies on dual use of VA and non-VA health care systems have shown that the great majority of patients who use non-VA care continue to receive some care at the VA [24,25]. Finally, the study population was limited to male veterans and the findings may not be widely generalizable.

Conclusions

In summary, this study found that treatment with TZDs was associated with a significantly lower risk for the development of CHF after controlling for several known cardiac risk factors. The development of CHF in patients with type 2 diabetes is mediated by an array of risk factors, including many which contribute to atherogenesis and others which are involved in the development of diabetic cardiomyopathy unrelated to atherosclerosis. The TZD class of antihyperglycaemic agents has been shown to have positive effects on many cardiovascular risk factors, initially raising expectations that they might decrease the risk of cardiac complications. Prospective trials have shown that TZDs increase the risk of CHF but their effect on cardiovascular outcomes is still unclear.

Acknowledgements

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Conflict of Interest

Vivian Fonseca received research grants from GlaxoSmithKline, Novartis, Novo Nordisk, Takeda, AstraZeneca, Pfizer, Sanofi-Aventis, Eli Lilly, Daiichi Sankyo, National Institutes of Health and American Diabetic Association. He also received honoraria for consulting and lectures from GlaxoSmithKline, Novartis, Takeda, Novo Nordisk, Sanofi-Aventis, Eli Lilly and Daiichi Sankyo.

A. T. contributed to design, conduct/data collection and analysis. All authors had access to the data and a role in writing the manuscript.

References