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Thiazolidinedione use is not associated with worse cardiovascular outcomes: A study in 28,332 high risk patients with diabetes in routine clinical practice
Brief title: Thiazolidinedione use and mortality

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ABSTRACT

Objective: Assess the cardiovascular safety of Thiazolidinediones (TZD) in routine clinical practice.
Background: TZD are insulin-sensitizing antidiabetic drugs commonly used in type 2 diabetes, but their cardiovascular safety has been questioned. We examined the association between TZD use and major cardiovascular outcomes.
Methods: We examined 2-year mortality, non-fatal myocardial infarction (MI), and congestive heart failure (CHF) rates among outpatients with high cardiovascular risk and diabetes according to TZD use in the REACH Registry. Multivariable adjustment and propensity scores were used in the analyses.
Results: A total of 4997 out of 28,332 patients took TZDs at baseline. During follow-up, 1532 patients died. The mortality rates (95% confidence interval [CI]) were 6.5% (5.5–7.6) with TZD and 7.2% (6.33–8.06) without; adjusted hazard ratio (HR) was 1.06 (0.89–1.26, $P=0.54$). The lack of association with mortality was consistent across subgroups regardless of history of atherothrombosis or CHF. Rates of non-fatal MI (HR 1.10, 95% CI 0.83–1.45, $P=0.50$) and non-fatal CHF (HR 0.90, CI 0.75–1.09, $P=0.27$) were similar in users and non-users. TZD use was associated with an increased risk of CHF in patients aged >80 years (HR 1.59, CI 1.06–2.40, $P=0.03$).
Conclusions: Use of TZD was not associated with increased incidence of major cardiovascular events in patients with diabetes from this large registry. Older patients experienced an increased risk of CHF over the study interval. Limitations of this study include its observational design, and thus unmeasured confounders cannot be excluded.

1. Introduction

Type 2 diabetes is a chronic condition associated with a high cardiovascular burden. Recent clinical trials suggest that an intensive glucose-control strategy may decrease the risk of myocardial infarction (MI), but it does not reduce mortality [1]. Conventional anti-diabetic therapy includes lifestyle modification, metformin, sulfonylurea, and insulin. The thiazolidinediones (TZD) are ligands of Peroxisome Proliferator Activated Receptor-gamma, a transcription factor expressed

Abbreviations: BMI, Body Mass Index; CHF, Congestive Heart Failure; CI, Confidence Interval; eGFR, estimated Glomerular Filtration Rate; HR, Hazard Ratio; MI, Myocardial infarction; RCT, Randomized Controlled Trial; ROC, Receiver Operating Characteristic; TZD, Thiazolidinedione.

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in the adipose tissue, but also in endothelial cells. The net effect on metabolism is sensitization to insulin and glucose lowering. The cardiovascular safety and efficacy of these drugs were tested in several trials; pioglitazone was tested as secondary prevention via the PROActive study (PROspective pioglitAzone Clinical Trial in macroVascular Events) and rosiglitazone as primary prevention via the RECORD (Rosiglitazone Evaluated for Cardiovascular outcomes in ORal combination therapy for type 2 diabetes study) trial [2,3]. These two trials did not show a clear connection between TZD and cardiovascular risk, but a meta-analysis has first raised concerns regarding the cardiovascular safety of rosiglitazone, particularly with respect to the risk of MI [4]. However, none of these studies was sufficiently powered for analyzing effects on mortality because the numbers of deaths were small; 363 of 5238 (6.9%) participants in the PROActive study and 293 of 4447 (6.6%) participants in the RECORD trial. Observational studies can complement randomized trials if they are dedicated to specific aims, are of sufficient size, and have a design allowing prospective and extensive collection of relevant characteristics of the participants in order to minimize potential confounding factors.

We compared mortality, non-fatal MI, and congestive heart failure (CHF) rates in patients with diabetes according to the use of TZD in the REACH (REduction of Atherothrombosis for Continued Health) Registry, an international prospective cohort of patients with either established atherosclerotic arterial disease or at risk for atherothrombosis.

2. Methods

The study design, as well as the baseline description of the REACH Registry has been published previously [5–7]. Consecutive outpatients aged ≥45 years, with established coronary artery disease, cardiovascular disease, or peripheral arterial disease, or patients with ≥3 atherothrombotic risk factors were enrolled by 5587 physician practices in 44 countries between December 2003 and December 2004. In each country, the protocol was submitted to the institutional review boards according to local requirements, and signed informed consent was obtained for all patients.

A standardized international case report form, completed at each study visit, was used and data were centrally collected. Diabetes was defined by anti-diabetic drug use by a patient. Overweight was defined by a body mass index (BMI) of 25–29, and obesity at BMI of ≥30. The estimated glomerular filtration rate was calculated according to the Modification of Diet in Renal Disease formula; stages of kidney function were defined according to the Kidney Disease Outcomes Quality Initiative guidelines (http://www.kidney.org/professionals/KDOQI/guideline_diabetes/guide1.htm). As prior investigations have shown race-related differences in the medical treatment and outcomes of high risk patients, race was self-reported and in instances of mixed-racial origin, patients were asked to choose the race that had the strongest personal influence [6,7]. In some countries, local rules did not allow the recording of race and data were considered missing.

Data were collected from participating physicians regarding patients' clinical outcomes, vascular procedures, employment status, weight and current smoking status, as well as any medications used, at each follow-up visit until 24 months after enrolment, and dates of the outcomes were collected if appropriate; events were not adjudicated. To ensure data quality, in each country 10% of all sites (that is, physicians) that enrolled ≥1 patient were chosen randomly 6% of the time, and an additional 4% were chosen due to the number of queries and missing data from the site to undergo onsite quality control by completing a site visit. For each of the sites undergoing monitoring, 100% of case report forms for patients enrolled at that site were monitored for source documentation and accuracy.

The present analysis focuses on 2-year rates for mortality, non-fatal MI, and non-fatal CHF (i.e. hospitalization for CHF) in the diabetic subset of the REACH Registry. Patients with only baseline data were not included in the analysis.

To take into account confounding factors we used the propensity score method [8]. This score represents the probability of receiving TZD given the characteristics of an individual. The list of co-variables was built in a two-step process. Bivariate analyses were first conducted to determine the variables associated with TZD prescription. In this preliminary selection, the *P* value limit was arbitrarily set at 0.20. These variables were then introduced in order to build a multivariable logistic regression model. To ensure the robustness of the score, the variables with >5% missing data were excluded. Finally, the propensity score was calculated for every patient using this model with the individual data of the patient. The quality of the model was assessed using global evaluation (Wald test) and by calculating the area under the corresponding receiver-operating characteristic (ROC) curve. To validate the score, a minimal value of 0.7 was expected.

Patient characteristics were presented as mean ± standard deviation, and compared using Student's t tests or chi-squared tests. Hazard ratios (HRs) for death, non-fatal MI, and non-fatal CHF were calculated using a Cox proportional-hazard model, involving survival time in any individual patient, with TZD use and propensity scores as co-variables, as well as other specified factors. Survival time was calculated according to the date of the outcome as collected in the registry. For patients who remained free of the outcome, data were censored at the time of the last visit with available information. Event rates are presented based on total sample sizes. The homogeneity of treatment effects across subgroups was tested by adding interaction terms to the relevant models. A *P* value of <0.05 was considered significant. All analyses were performed with the use of the SAS software, version 9.1.

3. Results

3.1. Patient characteristics

Of the 65,441 patients enrolled in the REACH Registry and with data during follow-up, 28,332 patients had type 2 diabetes and available data on TZD use; they represent our study population. The

Table 1
Baseline characteristics of the study population by TZD use.

Characteristics	TZD use		
	Yes ($n=4997$)	No ($n=23\,335$)	p-value*
Age (years)	67.1 ± 9.6	68.6 ± 9.6	<0.0001
Male sex	3034 (60.7)	14 165 (60.7)	0.99
Region of enrolment			<0.0001
North America	4063 (81.3)	8945 (38.3)	
Latin America	61 (1.2)	756 (3.2)	
Western Europe	338 (6.8)	6300 (27.0)	
Eastern Europe	27 (0.5)	1515 (6.5)	
Middle East	26 (0.5)	407 (1.7)	
Asia (excluding Japan)	309 (6.2)	2401 (10.3)	
Australia	19 (0.4)	844 (3.6)	
Japan	154 (3.1)	2167 (9.3)	
Racial origin			<0.0001
Caucasian	3255 (66.9)	13 001 (60.7)	
Hispanic	398 (8.2)	1222 (5.7)	
East Asian	403 (8.3)	3480 (16.3)	
South Asian	60 (1.2)	352 (1.6)	
Other Asian	189 (3.9)	1439 (6.7)	
Black	500 (10.3)	1184 (5.5)	
Other	60 (1.2)	735 (3.4)	
Clinical and biological variables			
Waist (cm)	104.9 ± 18.7	100.1 ± 16.3	<0.0001
BMI (kg/m^2)	31.6 ± 6.7	29.0 ± 5.9	<0.0001
Overweight (BMI 25–29)	1561 (31.8)	8704 (37.9)	<0.0001
Obese (BMI ≥30)	2642 (53.8)	8435 (36.7)	<0.0001
Smoking			0.13
Former smoker	1865 (38.5)	9028 (40.0)	
Current smoker	691 (14.3)	3072 (13.6)	
Serum creatinine (mg/L)	1.15 ± 0.73	1.13 ± 0.73	0.07
Fasting blood glucose (mg/dL)	145.1 ± 55.6	146.0 ± 53.1	0.31
Fasting total cholesterol (mg/dL)	185.4 ± 48.2	191.9 ± 48.6	<0.0001
Fasting triglycerides (mg/dL)	180.3 ± 113.7	173.4 ± 105.2	0.0002
Hypertension	4448 (89.0)	20 360 (87.3)	0.0006
Systolic blood pressure (mm Hg)	135.2 ± 18.3	139.9 ± 19.5	<0.0001
Diastolic blood pressure (mm Hg)	75.8 ± 10.9	78.4 ± 11.4	<0.0001
Prior arterial disease			<0.0001
None	2042 (40.9)	6686 (28.7)	
One bed	2314 (46.3)	12 834 (55.0)	
Two beds	561 (11.2)	3374 (14.5)	
Three beds	80 (1.6)	441 (1.9)	
Prior CHF	704 (14.3)	3845 (16.8)	<0.0001
Baseline therapies			
≥1 Antiplatelet agent	3718 (74.4)	17 196 (73.7)	0.32
Acetylsalicylic acid	3367 (67.4)	14 723 (63.2)	<0.0001
≥1 Lipid-lowering agent	4310 (86.3)	17 663 (75.7)	<0.0001
Statins	3981 (79.7)	16 047 (68.8)	<0.0001
Angiotensin II receptor blockers	1628 (32.9)	6158 (26.6)	<0.0001
Angiotensin-converting enzyme inhibitors	2575 (52.0)	11 486 (49.5)	0.0015
Beta-blockers	2115 (42.6)	10 363 (44.6)	0.0078
Calcium channel blockers	1654 (33.4)	8642 (37.2)	<0.0001
Diuretics	2465 (49.6)	10 731 (46.1)	<0.0001
Nitrates	792 (16.3)	5537 (24.1)	<0.0001
Other antihypertensive agents	541 (11.0)	2651 (11.5)	0.35
Sulfonylurea	2426 (49.3)	10 198 (43.8)	<0.0001
Metformin	2374 (48.2)	9399 (40.4)	<0.001
Insulin	1027 (20.8)	6546 (28.1)	<0.0001
Other anti-diabetic agent	417 (8.9)	2681 (11.6)	<0.0001

Data are n (%) or mean ± standard deviation.