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ORIGINAL ARTICLE

Rosiglitazone treatment and cardiovascular disease in the Veterans Affairs Diabetes Trial

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Aims: To evaluate the relationship between patterns of rosiglitazone use and cardiovascular (CV) outcomes in the Veterans Affairs Diabetes Trial (VADT).
Methods: Time-dependent survival analyses, case–control and 1 : 1 propensity matching approaches were used to examine the relationship between patterns of rosiglitazone use and CV outcomes in the VADT, a randomized controlled study that assessed the effect of intensive glycaemic control on CV outcomes in 1791 patients with type 2 diabetes (T2D) whose mean age was 60.4 ± 9 years. Participants were recruited between 1 December 2000 and 31 May 2003, and were followed for 5–7.5 years (median 5.6) with a final visit by 31 May 2008. Rosiglitazone (4 mg and 8 mg daily) was initiated per protocol in both the intensive-therapy and standard-therapy groups. Main outcomes included a composite CV outcome, CV death and myocardial infarction (MI).
Results: Both daily doses of rosiglitazone were associated with lower risk for the primary composite CV outcome [4 mg: hazard ratio (HR) 0.63, 95% confidence interval (CI) 0.49–0.81 and 8 mg: HR 0.60, 95% CI 0.49–0.75] after adjusting for demographic and clinical covariates. A reduction in CV death was also observed (HR 0.25, $p < 0.001$, for both 4 and 8 mg/day rosiglitazone); however, the effect on MI was less evident for 8 mg/day and not significant for 4 mg/day.
Conclusions: In older patients with T2D the use of rosiglitazone was associated with decreased risk of the primary CV composite outcome and CV death. Rosiglitazone use did not lead to a higher risk of MI.
Keywords: cardiovascular disease, older adults, rosiglitazone, type 2 diabetes

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Introduction

Cardiovascular (CV) morbidity and mortality in patients with type 2 diabetes (T2D) are major problems in clinical practice. Thiazolidinediones improve glycaemic control by reducing insulin resistance and have beneficial effects on various CV risk factors. Pioglitazone has been shown to reduce progression of atherosclerosis and possibly reduce CV events [1,2]; however, previously published meta-analyses have raised uncertainty about the CV safety of thiazolidinediones, and rosiglitazone in particular [3–6]. An analysis in the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial, a randomized, multicentre, open-label, non-inferiority study in patients with T2D who had inadequate glycaemic control while receiving metformin or sulphonylureas, showed an increased risk of congestive heart failure associated with rosiglitazone, but there were no statistically significant differences between the rosiglitazone group and the control group for myocardial infarction (MI) and death from CV causes or any cause [7,8]. Recently, the US Food and Drug Administration (FDA) released a drug safety communication requiring removal of some prescribing and dispensing restrictions for rosiglitazone-containing diabetes medicines [9]. This decision was based on a re-evaluation of RECORD endpoints (CV death, MI and stroke), performed by the Duke Clinical Research Institute and presented to an FDA advisory committee, which did not show an increased risk of MI associated with rosiglitazone.

A joint consensus statement from the American Diabetes Association (ADA) and American Heart Association has provided recommendations about the use of thiazolidinediones and the risk of fluid retention and congestive heart failure in patients with T2D, particularly when combined with insulin

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[10]. Increased sympathetic nervous system activity, altered interstitial ion transport, alterations in endothelial permeability, and peroxisome proliferator-activated receptor-γ-mediated expression of vascular permeability growth factor represent other possible mechanisms for oedema with these agents [11].

The Veterans Affairs Diabetes Trial (VADT) assessed the effect of intensive glycaemic control on a composite CV endpoint that included: MI, CV death, stroke, congestive heart failure, invasive revascularization, inoperable coronary artery disease and amputation for ischaemia [12]. In the present analysis we evaluated patterns of rosiglitazone use and its association with CV outcomes in older patients with T2D. Through *post hoc* analyses, we specifically tested the hypothesis that treatment with rosiglitazone in patients with T2D would not be associated with increased risk of MI, CV deaths and other CV outcomes.

Materials and Methods

Study Design

Details of the VADT study protocol, including patient selection criteria, and the primary study results have been reported previously [12,13]. In brief, the VADT was a prospective, randomized study of intensive versus standard glucose treatment [expected separation of at least 1.5% in glycated haemoglobin (HbA1c)] effects on CV events in patients with long-standing T2D. Blood pressure, lipids, diet and lifestyle were treated identically in both arms in accordance with ADA management recommendations. Study recruitment was initiated on 1 December 2000 and ended on 31 May 2003. Participant follow-up was completed on 31 May 2008, resulting in a treatment and follow-up duration of 5–7.5 years (median 5.6). The study protocol was approved by the institutional review board at each of the 20 participating sites. An independent data and safety committee monitored CV events related to group assignment and rosiglitazone use throughout the study duration.

Patients

Men and women aged ≥41 years with T2D and inadequate response to maximum doses of an oral agent or insulin therapy were included. Those with an HbA1c level <7.5%, as well as those with a CV event during the previous 6 months, advanced congestive heart failure (class III–IV), severe angina, a life expectancy of <7 years, a body mass index (BMI) >40 kg/m^2, a serum creatinine level of >1.6 mg/dl (141 μmol/l), and an alanine aminotransferase level of more than three times the upper limit of normal range were excluded. All patients provided written informed consent.

Treatment Protocol

In both intensive and standard glycaemic control groups, patients were started on two oral agents, one of which was rosiglitazone. The other agents were metformin (for those with BMI ≥27 kg/m^2) or glimepiride (for those with BMI <27 kg/m^2). Initiation of these agents was protocol-driven. A tool box of recommended treatment options was available for addition of other available drugs (except for incretin-based medications), or use of any combination of medications, needed to achieve study HbA1c goals, at the discretion of the investigator. Changes in medication, including insulin initiation and/or discontinuation of oral agents, were determined according to protocol guidelines and local assessment. This included protocol safety guidelines about rosiglitazone use and discontinuation that were consistent with the drug's FDA-approved prescribing information (package insert).

Statistical Analysis

The primary study results showed no significant difference between the intensive and standard glycaemic control groups for the primary composite outcome, any component of the primary outcome, or in the rate of death from any cause [13], but the effect of rosiglitazone on the CV outcomes remained unanswered; therefore, participants in both treatment groups were aggregated for the analyses in the present report.

Although the original study was based on the intention-to-treat principle, the present investigation is a *post hoc* analysis. The effect of rosiglitazone on CV outcomes was analysed using a time-dependent covariate survival analysis for the whole population, and scrutinized by two additional approaches to attempt to overcome the limitations of the *post hoc* analysis. Baseline variables are expressed as means and standard deviations or percentages or numbers. All analyses were conducted with SAS software (version 9.3; SAS Institute Inc., Cary, NC, USA) with a significance level <0.05 using a two-sided test.

Time-dependent Covariate Survival Analysis. Survival analysis compared the time from randomization to the occurrence of the first VADT composite outcome in patients treated with rosiglitazone (4 or 8 mg daily) compared with those not treated with rosiglitazone. Separate analyses were performed for individual events from the composite CV outcome, CV death, MI and coronary revascularization. For each outcome, three Cox proportional hazard models were used to calculate relative risk estimates and 95% confidence intervals (CIs): (i) unadjusted (except for the time of publication of Nissen and Wolski paper in 2007 [3]), (ii) additionally adjusted for baseline covariates; and (iii) adjusted for baseline and time-varying covariates, including baseline age, race/ethnicity, smoking status, education, diabetes duration, previous CV event, HbA1c, baseline and on-study BMI, blood pressure, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, severe hypoglycaemic episodes, and baseline and on-study use of insulin, other oral antihyperglycaemic agents, statins and aspirin. As the VADT did not randomize by the use of rosiglitazone, two other methods were used: case–control matching and 1 : 1 propensity matching.

Case–control Matching Method. Patients with the study outcome (cases) were matched to patients without the outcome (controls) using the case–control matching method [14]. Matching criteria included: age, diabetes duration, previous CV event, insulin use at baseline, duration of follow-up, BMI, systolic blood pressure, diastolic blood pressure, HbA1c, total cholesterol and HDL cholesterol. Rosiglitazone use was compared between cases and controls on: baseline use, on-study

Table 1. Cox proportional models for the primary outcome and other cardiovascular outcomes in Veterans Affairs Diabetes Trial participants according to rosiglitazone doses.

	Unadjusted		Adjusted for baseline covariates*		Adjusted for baseline and time-dependent covariates†	
Rosiglitazone doses	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Primary cardiovascular outcomes						
4 mg daily	0.495 (0.390, 0.628)	<0.0001	0.679 (0.523, 0.884)	<0.01	0.625 (0.483, 0.809)	<0.001
8 mg daily	0.471 (0.384, 0.578)	<0.0001	0.630 (0.496, 0.799)	<0.0001	0.659 (0.521, 0.834)	<0.001
CV death						
4 mg daily	0.203 (0.095, 0.434)	<0.0001	0.431 (0.193, 0.963)	<0.05	0.375 (0.165, 0.851)	<0.05
8 mg daily	0.169 (0.088, 0.324)	<0.0001	0.219 (0.106, 0.453)	<0.0001	0.228 (0.108, 0.483)	<0.0001
MI						
4 mg daily	0.604 (0.388, 0.939)	<0.05	0.852 (0.518, 1.400)	0.5	0.742 (0.457, 1.204)	0.2
8 mg daily	0.551 (0.376, 0.809)	<0.01	0.749 (0.473, 1.184)	0.2	0.838 (0.536, 1.311)	0.4
Coronary revascularization						
4 mg daily	0.704 (0.500, 0.992)	<0.05	0.907 (0.621, 1.324)	0.6	0.853 (0.587, 1.240)	0.4
8 mg daily	0.611 (0.451, 0.828)	<0.01	0.722 (0.509, 1.023)	0.07	0.803 (0.569, 1.134)	0.2

CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction.
*Baseline age, race/ethnicity, smoking status, education, diabetes duration, previous CV event, glycated haemoglobin.
†On-study (time-dependent change) body mass index, blood pressure, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, use of insulin, other oral antihyperglycaemic agents (metformin and glimiperide), statins and aspirin, and severe hypoglycaemic episodes.

use at any time, number of visits prescribed, and average dose per visit, using Student's *t*-test for continuous variables or a chi-squared test for categorical variables. This method enabled us to see the difference according to rosiglitazone use when the patients had the same level of baseline covariates between the cases and the controls.

Propensity Exact Matching Method. Patients were stratified into two groups; those who never used rosiglitazone and those who used it regularly (always) from the beginning to the end of the study. This analytical method [15] approximates to an intention-to-treat approach for the comparison of events among rosiglitazone-treated patients versus matched patients not treated with a thiazolidinedione. Using a stepwise logistic model, including baseline age, diabetes duration, HbA1c, BMI, blood pressure, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, creatinine, gender, blood pressure medication use, race, smoking status, previous CV event, insulin use and intensive glycaemic treatment, propensity scores were produced to match 1 : 1 between the two groups. The CV risk factors chosen were compared before and after matching (Tables S1 and S2), which suggested good balance between the two groups. After the matching, Cox proportional hazard regression models were used before and after adjusting for these CV risk factors to assess the association of rosiglitazone use (always vs never) with CV outcomes (Figure S2). This method was used in an attempt to draw a causal inference from rosiglitazone use with regard to the outcome after matching baseline variables between the two stratified groups.

Results

Overall, rosiglitazone was used more frequently and at a higher dose in the intensive treatment group than in the standard treatment group ($p < 0.05$); however, the use of rosiglitazone in both groups initially decreased gradually over time according to protocol safety prescription guidelines. After the publication of the meta-analysis by Nissen and Wolski (2007), a more marked drop-off was observed (Figure S1) and study participants required increasing use of other agents to maintain appropriate separation in HbA1c values (median HbA1c after 6 months: 6.9% in the intensive treatment group vs 8.4% in the standard treatment group). In particular, the median insulin dose progressively increased in both arms but was 20% higher in the intensive treatment arm throughout the study.

Time-dependent covariate analyses showed that both daily doses of rosiglitazone (4 and 8 mg) were associated with a lower risk of the primary composite CV outcome after adjustment for baseline and time-dependent risk factors (Table 1 and Figure 1A). These relationships remained significant in a separate analysis that accounted for the effect of rosiglitazone discontinuation after June 2007, related to the CV safety concerns raised in the meta-analysis by Nissen and Wolski [3]. A reduction of CV mortality risk associated with rosiglitazone use was also observed (Figure 1B); however, the association with a reduced incidence of MI and coronary revascularization was less evident after accounting for the contribution of the same baseline and time-dependent covariates (Figure 2A, B).

For the primary composite CV outcome in the case–control analysis, both groups had similar age, degree of obesity, blood

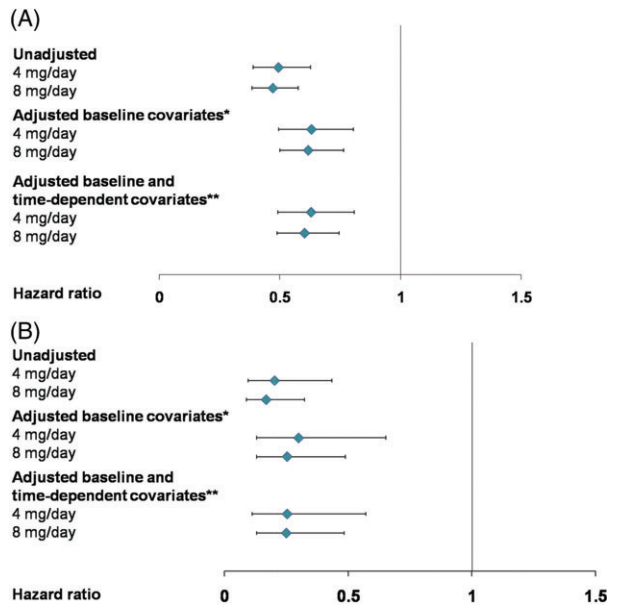

Figure 1. Effect of rosiglitazone dosage on time to (A) primary composite cardiovascular (CV) event and (B) CV death. *Baseline and **time-dependent covariates include: age, race, smoking status, diabetes duration, previous CV event, glycated haemoglobin, baseline and on-study body mass index, blood pressure, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, severe hypoglycaemic episodes and baseline and on-study use of insulin, other oral agents, statins and aspirin.

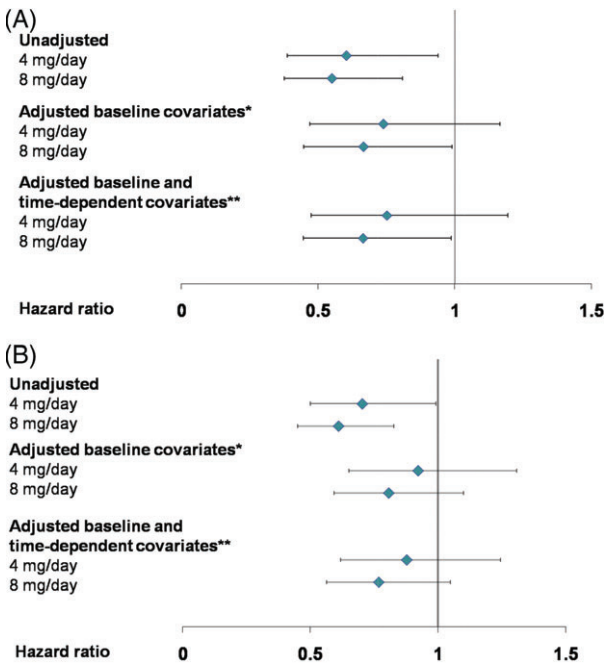

Figure 2. Effect of rosiglitazone dosage on time to (A) myocardial infarction and (B) coronary revascularization. *Baseline and **time-dependent covariates include: age, race, smoking status, diabetes duration, previous cardiovascular event, glycated haemoglobin, baseline and on-study BMI, blood pressure, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, severe hypoglycaemic episodes, and baseline and on-study use of insulin, other oral agents, statins and aspirin.

pressure and HbA1c and LDL cholesterol levels at baseline (Table 2), although diabetes duration was slightly longer and HDL cholesterol levels were lower in the cases. A similar percentage of cases and controls were using rosiglitazone in the first year (82.6 vs. 84.8%) but fewer participants who had the primary CV outcome (cases) used rosiglitazone at any time during the study compared with participants who did not [controls; 90.5 vs. 96.0%, respectively; $p < 0.01$ (Figure 3A)]. Similarly, the number of study visits with rosiglitazone prescribed (9.8 vs. 10.9; $p < 0.05$) and the average rosiglitazone dose (4.9 vs. 5.4 mg/day; $p < 0.01$) was lower in cases than in controls (Figure 3B).

In survival analysis with 1:1 propensity matching data, rosiglitazone use was associated with a lower incidence of the primary composite outcome [Hazard ratio (HR) 0.361, 95% CI 0.204-0.64; $p < 0.001$)], even after adjusting for age, previous CV event, BMI and baseline insulin use (HR 0.312, 95% CI 0.174-0.558, $p < 0.001$). Compared with the subjects who had never taken rosiglitazone, those who had taken rosiglitazone were 65% less likely to experience the primary CV outcome (Figure S2). Further analyses stratifying participants by obesity, smoking status and baseline HbA1c showed a similar association between rosiglitazone use and primary CV outcome (Table S3).

Discussion

The initial VADT report comparing standard with intensive glycaemic control found no significant difference in the risk of the primary composite endpoint between treatment groups [13]. Given the controversy about CV risk associated with rosiglitazone use and the recent FDA drug safety communication [7] about rosiglitazone after the re-evaluation of RECORD endpoints (CV death, MI and stroke), it seemed valuable to perform a *post hoc* analysis of rosiglitazone use and CV outcomes in the VADT. Three different but supportive approaches were used: a case–control analysis, a time-dependent covariate analysis and a survival analysis after propensity exact matching method.

Rosiglitazone was used more frequently and at a higher dose in the intensive treatment compared with the standard treatment group throughout the study duration. We found that rosiglitazone was not associated with increased CV risk, but conversely, may have been associated with a reduction in the occurrence of the primary composite outcome and CV mortality. Moreover, both daily doses of rosiglitazone (4 and 8 mg) were associated with a lower risk of these outcomes, even after adjusting for a broad array of covariates. These data are consistent with results from the PROactive Study [1] and a report suggesting that rosiglitazone use was associated with a 5%, non-significant, reduction in mortality [16]. These results also support preliminary analyses in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial that did not indicate an increased risk of CV events related to rosiglitazone use [17]. Furthermore, a recent *post hoc* analysis from the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial, using on-treatment and propensity-matched analyses, showed a lower incidence of the composite death, MI

Table 2. Baseline clinical characteristics in those with (cases) and without (controls) the primary study outcome.

Variable	Cases (n = 447)	Controls (n = 447)	p
% male	98	98	1.0
% white non-Hispanic people	70.9	66.7	0.17
Smokers, %	16.8	12.8	0.09
Previous CV event, %	64	64	1.0
Baseline insulin, %	59.7	59.7	1.0
Mean age, years	62.3 ± 8.2	62 ± 8	0.63
Mean T2D duration, years	12.7 ± 7.7	11.5 ± 7.2	0.01
Mean BMI, kg/m^2	31.4 ± 4.5	31.5 ± 4.1	0.76
Mean systolic blood pressure, mmHg	133.5 ± 18.2	131.4 ± 15.5	0.07
Mean diastolic blood pressure, mmHg	75.4 ± 11	74.7 ± 10	0.29
Mean total cholesterol, mmol/l	4.66 ± 1.0	4.63 ± 0.95	0.64
Mean HDL cholesterol, mmol/l	0.88 ± 0.23	0.93 ± 0.25	0.01
Mean LDL cholesterol, mmol/l	2.73 ± 0.77	2.74 ± 0.77	0.94
Mean baseline HbA1c, %	9.4 ± 1.5	9.3 ± 1.4	0.46
Mean baseline HbA1c, mmol/mol	79 ± 10.5	78 ± 9.5	0.46
Mean follow-up, days	873.4 ± 622	873.4 ± 622	1.00

BMI, body mass index; CV, cardiovascular; T2D, type 2 diabetes.

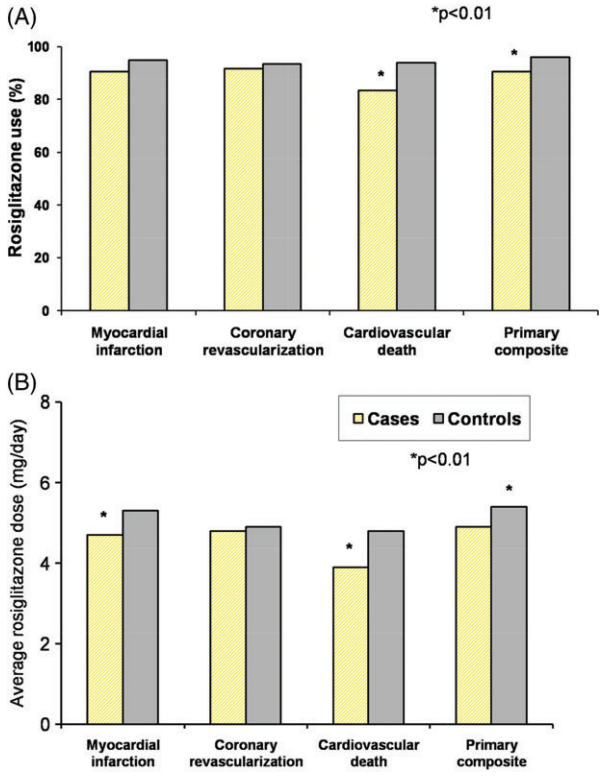

Figure 3. Rosiglitazone use in cases and controls according to myocardial infarction, coronary revascularization, cardiovascular (CV) death or primary CV outcome. (A) Percentage of cases and controls who had at least one prescription for rosiglitazone over the course of the study. (B) Average daily rosiglitazone dose in cases and controls.

and stroke outcomes (HR 0.72, 95% CI 0.55–0.93) associated with rosiglitazone treatment in patients with T2D and coronary artery disease [15].

These findings are not consistent with meta-analyses that suggested that an increased MI risk was associated with rosiglitazone [3–6]; however, there is ongoing debate as to the applicability of these findings to patients with T2D in general, with some criticism of the meta-analysis by Nissen and Wolski [3] on methodological grounds [18]. A potential harmful effect of thiazolidinediones was also surprising because thiazolidinediones reduce insulin resistance and therefore provide a therapy that directly corrects a key defect underlying T2D. In part because of this mechanism of action, thiazolidinediones not only lower blood glucose but also have beneficial effects on several processes associated with atherosclerosis, including inflammation, high blood pressure and microalbuminuria. Moreover, data from the PROactive trial suggested that addition of pioglitazone to existing therapy in high-risk patients with diabetes and atherosclerotic disease improved CV outcomes in that trial [1]. In addition, pioglitazone therapy has been reported to slow progression of atherosclerosis [2].

Further evidence that rosiglitazone does not cause increased CV events comes from the RECORD trial, which was designed specifically to study the CV effects of rosiglitazone treatment. Results from a well-designed, adequately powered clinical trial are usually more reliable than results from a meta-analysis [19]. Similarly to the VADT, the RECORD trial did not show an increased risk for MI or CV mortality associated with rosiglitazone use [8]. Furthermore, a recent comprehensive and independent re-evaluation of RECORD endpoints requested by the FDA showed no increased risk of CV death (HR 0.90, 95% CI 0.68–1.21), MI (HR 1.13, 95% CI 0.80–1.59) or stroke (HR 0.79, 95% CI 0.54–1.14) in those treated with rosiglitazone compared with a standard-of-care treatment combination (metformin and sulphonylurea) [9]. Since in the VADT changes in rosiglitazone use were determined based on protocol safety guidelines, consistent with FDA prescribing information, the results of the present analysis of the VADT provide additional perspectives on CV safety for this

drug, which is consistent with the FDA's risk and mitigation strategy.

A consensus statement of the ADA and the European Association for the Study of Diabetes (EASD) for hyperglycaemia management includes information on thiazolidinediones and advises caution in using these drugs on the basis of their increased risks of fluid retention and congestive heart failure as well as increased incidence of fractures in women and perhaps in men [20]. The ADA/EASD statement acknowledged that the meta-analyses reporting potential CV risk associated with rosiglitazone were not conclusive but still advised against using this thiazolidinedione on the basis of the possibility of increased risk of MI with rosiglitazone. By contrast, the evidence-based Canadian Diabetes Association clinical practice guidelines for the prevention and treatment of diabetes did not find that there was cause to exclude rosiglitazone based on the evidence from the ACCORD, RECORD and VADT studies, which did not show an increased risk of MI or CV mortality [21]. Despite the ongoing controversy, however, most organizations believe that the potential benefits and risks of these agents should be carefully considered before they are initiated. Both pioglitazone and rosiglitazone are contraindicated in patients with class III and IV heart failure. Patients with class II or worse heart failure were excluded from the PROactive study, and patients with any known congestive cardiac failure (class I–IV) were excluded from the ADOPT study [22]. Because patients with heart failure are more likely to be adversely affected by thiazolidinedione-associated fluid retention, any significant degree of heart failure, including class II or higher, could be regarded as a contraindication to use of thiazolidinedione.

Importantly, high-risk characteristics in patients with T2D, such as longer diabetes duration, insulin treatment and multiple comorbidities, may help identify those more susceptible to congestive heart failure and adverse CV outcomes, thus avoiding initiation or continuation of therapy in these individuals. This approach may have been followed in the VADT because a decline in the use of rosiglitazone was observed over time, as site investigators followed safety guidelines about its use. This pattern of discontinuation may have left a group of older adults with T2D who might have benefited from rosiglitazone treatment and therefore continued receiving this insulin sensitizer; however, as VADT rosiglitazone use and discontinuation guidelines were generally consistent with the FDA-approved prescription information, our results may apply to many patients with T2D who may have been suitable candidates for treatment with this thiazolidinedione. These results suggest that for patients on rosiglitazone who are achieving glycaemic goals and tolerating the therapy without apparent complications, rosiglitazone may be continued [23].

The present study results should be interpreted with caution because the analysis of the effect of rosiglitazone was not planned *a priori*. The approaches used in this VADT *post hoc* data analysis (i.e. epidemiological analyses of data collected within a randomized clinical trial) provide a lower level of evidence than that obtained from a carefully performed prospective randomized, controlled trial. A case–control approach, matching baseline risk factors between the case and the control, and to a lesser extent, a time-dependent covariate survival analysis may be limited by the potential role of confounding by indication [14], as investigators may have prescribed less rosiglitazone (or stopped it sooner) for patients with higher CV risk or comorbidities. Furthermore, there is also a possibility of bias associated with heart failure, oedema or physicians' views of interactions with other medications.

The low HRs associated with rosiglitazone use could thus be partly explained by the less healthy individuals being taken off this medication; however, because similar effects of rosiglitazone were seen in individuals receiving 4 or 8 mg, and the rosiglitazone dose regimen was part of the randomization medication treatment algorithm, there should be less confounding by indication. Moreover, even with propensity matching, there remained evidence for benefit, not harm, with rosiglitazone use.

In summary, treatment with rosiglitazone in older adults with T2D was not associated with increased risk of the primary composite CV outcome, CV death or MI in the VADT. These results are consistent with more recent evidence that rosiglitazone does not enhance CVD and supports the recent FDA panel recommendation easing restrictions on rosiglitazone. Concerns about specific adverse events (bone loss, oedema and congestive heart failure) with use of thiazolidinedione agents remain [24], however, and decisions to use these agents require careful balancing of risks and benefits.

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H. F. wrote manuscript; P. R. and N. E. contributed to discussion, and reviewed/edited the manuscript; G.B. and T. M. contributed to data research, and reviewed and edited the manuscript; S. W., J. M., D. R. and R. H. reviewed and edited the manuscript; W. D. and C. A. reviewed the manuscript.

G. B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of Interest

Sanofi-Aventis U.S. LLC, GlaxoSmithKline, Novo Nordisk, Roche Diagnostics, Sanofi-Aventis, Amylin Pharmaceuticals and KOS Pharmaceuticals provided financial support and donated study drugs to U.S. Department of Veterans Affairs Cooperative Studies Program (CSP) for the study. They had no role in study design, data analysis, or manuscript preparation.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Proportion of rosiglitazone use in the standard and intensive therapy groups throughout the duration of the Veterans Affairs Diabetes Trial.

Figure S2. Effect of rosiglitazone use on cardiovascular (CV) outcomes based on 1 : 1 propensity score matching method. It compares patients who took rosiglitazone regularly [always between the start and end of Veterans Affairs Diabetes Trial (VADT)] and those who never took it during the VADT. Outcomes include: myocardial infarction (MI); coronary revascularization (Cor Revas), cardiovascular-related death (CV-deaths), and the primary composite CV outcome. Each outcome is shown unadjusted and after adjusting for baseline CV risk factors. *Adjusted for age, prior CV event, BMI, and baseline insulin use.

Table S1. Baseline cardiovascular (CV) risk factors and CV events among patients who were always or were never on rosiglitazone therapy, *before* the propensity matching method was implemented.

Table S2. Baseline cardiovascular (CV) risk factors and CV events among patients who were always or were never on rosiglitazone therapy, *after* the propensity matching method was implemented.

Table S3. Cox proportional models for the primary composite cardiovascular outcome in participants in the Veterans Affairs Diabetes Trial according to rosiglitazone doses and stratified by obesity, smoking status and baseline glycated haemoglobin values.

File S1. Members of the VADT Research Group.

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