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ORIGINAL REPORT

Association between serious ischemic cardiac outcomes and medications used to treat diabetes†

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SUMMARY

Purpose Data on cardiovascular outcomes among treated diabetics have been inconsistent. Our goal was to compare cardiovascular outcomes associated with different treatments for diabetes.

Methods This is a retrospective cohort study of diabetic patients at least 40 years of age treated in general practices participating in The Health Information Network (THIN) data system between 2002 and 2006. Our primary outcome was serious atherosclerotic vascular disease of the heart.

Results Among all diabetics ($N = 63\,579$), the fully adjusted hazard ratios of association with our outcome were 1.2 (1.1, 1.3) for insulin, 1.03 (0.97, 1.09) for sulfonylureas, 0.8 (0.7, 0.8) for biguanide, 1.2 (0.99, 1.5) for meglitinide, 0.5 (0.5, 0.6) for thiazolidinediones, and individually 0.6 (0.5, 0.6) for rosiglitazone, and 0.5 (0.4, 0.7) for pioglitazone. Among those individuals newly diagnosed and treated for diabetes after 2002 ($N = 13\,576$), the adjusted hazard ratios of association with our outcome were 2.4 (2.0, 2.9) for insulin, 1.4 (1.2, 1.7) for sulfonylureas, 0.5 (0.4, 0.5) for biguanide, 0.9 (0.4, 2.1) for meglitinide, 0.8 (0.7, 1.0) for thiazolidinediones, and individually 0.8 (0.6, 1.0) for rosiglitazone, and 0.9 (0.6, 1.4) for pioglitazone. Risk increased as total duration of therapy increased for insulin, sulfonylureas, and biguanide, but decreased with duration for rosiglitazone and pioglitazone.

Conclusions Overall, insulin was associated with an increased risk of myocardial infarction. Its risk increased with longer use, and risk emerged with longer use of sulfonylureas and biguanide. Conversely, a protective effect emerged with longer use of rosiglitazone or pioglitazone. Copyright © 2008 John Wiley & Sons, Ltd.

KEY WORDS — cardiac disease; myocardial infarction; diabetes; diabetes medications

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INTRODUCTION

Therapies for diabetes are generally approved for marketing on the basis of their ability to lower blood glucose. However, this is, at least in part, a surrogate endpoint. The prevention of complications like myocardial ischemia is one of the true goals of treatment success. Yet, this is not generally evaluated at the time of drug marketing.[1]

In this context, several recent studies have demonstrated conflicting results concerning the cardiovascular safety of rosiglitazone.[1–8] However, these studies varied by the length of time of observation, the duration of diabetes for an individual, the definition of the acute myocardial event, and the medications investigated. It should be noted that previously published observational studies have implicated other treatments with increased risk of

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cardiovascular disease as well.[9,10] In fact the tightest glycemic control arm of a national study, Action to Control Cardiovascular Risk in Diabetes (ACCORD), was recently stopped early due to increased cardiovascular death.[11]

The increasing prevalence of adult onset diabetes, the common use of medications as treatment, and the impact on the public's health that would result if these drugs increased the risk of cardiovascular disease all make it important to understand whether medications used to treat diabetes decrease or increase the risk of cardiovascular disease. Our study aimed, therefore, to evaluate the onset of new cardiovascular outcomes in those with diabetes treated in general practice.

METHODS

Design

This was a retrospective cohort study of diabetics treated in general practices participating in The Health Information Network (THIN).[12] We first studied the entire database and then, to minimize the potential for bias, we also conducted a sub-study, comprised of patients newly diagnosed with and treated for diabetes.

Data source

Created in 2002, THIN, as the general practitioner's (GP) only medical record, includes data from approximately 300 UK practices. It is similar in structure and scope to the General Practice Research Database.[12–14] Subjects in THIN are similar in age, gender, and geographic characteristics to the general UK population.[12–14] THIN includes records on 4.78 million patients, of which 2.26 millions are currently active. Only approximately 3% of patients are lost annually due to leaving a practice or death. The database contains information on all past and current medical diagnoses (acute and chronic), coded by using Read codes, and prescribed medications, coded using British National Formulary (BNF) codes.[12] Unlike many other databases, THIN also includes laboratory values, which are electronically captured, and some aspects of the physical exam. Using chart reviews and audits, the reliability of the database is confirmed by the National Health Service (NHS) or data vendors, such as EPIC (our data vendor), and validation studies have been published previously.[12,14–16]

In 2002, a series of pay-for-performance programs was adopted in the UK in which GPs were compensated based on their ability to document control of various major medical illnesses, including diabetes. The NHS made several examinations mandatory for those with diabetes, including assessments at least every 15 months of serum creatinine, body mass index (BMI), hemoglobin A1c, cigarette use, and arterial blood pressure.

Study population

All subjects enrolled in this study were required to have at least two records for diabetes between January 2002 and 2006 and to be at least 40 years old. The database diagnosis of diabetes was previously validated.[17]

In the first cohort studied, selected from all diabetics in the database, individuals could have been diagnosed with diabetes at any time since they had been enrolled and followed by their GP, including before 2002. Person-time was calculated from 1 January 2002 or the first diagnosis of diabetes in the database, whichever was later, until our primary outcome occurred, the study subject died or left the practice, or the date of the last data in the database. An individual could have had drug exposures or an outcome before 1 January 2002; such events did not contribute to our study.

For the second study a smaller sub-cohort representing 'incident cases' of treated diabetes was studied. Patients' first THIN diagnosis for diabetes and first drug treatment for diabetes must both have occurred after January 2002. Thus, individuals with either a pre-existing history of diabetes or treatment for diabetes before January 2002 were excluded from this population. Person-time was then calculated from the first diagnosis of diabetes and pharmaceutical treatment for diabetes.

Study variables

The primary exposure variable was a BNF code for insulin, sulfonylureas (e.g., chlorpropamide, glipizide, tolbutamine, etc.), biguanide (metformin), meglitinides (nateglinide and repaglinide), or thiazolidinediones (rosiglitazone and pioglitazone). Because of current concerns, rosiglitazone and pioglitazone were also evaluated separately. Individuals could use more than one of these agents.

Our primary outcome was the onset of any serious atherosclerotic vascular disease of the heart after the first date of exposure to each of the medications of interest between January 2002 and 2006. Included

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were codes for myocardial infarction, unstable angina, cardiac death, and coronary artery reperfusion procedures, including closed (e.g., angioplasty) and open (e.g., coronary artery bypass) procedures.[13,15,16] Further, we performed a sub-analysis with only a clinical diagnosis of myocardial infarction as the outcome.

The following potential confounding variables were also assessed: age; sex; BMI; hemoglobin A1c; cigarette use; chronic kidney disease (CKD), as estimated by glomerular filtration rate (eGFR); mean arterial blood pressure (MAP); history prior to entry into the cohort of myocardial infarction, unstable angina, or a cardiac procedure consistent with atherosclerotic vascular cardiac disease; and history of atherosclerosis of the lower extremity. We only considered the first laboratory evaluation available after the diabetes diagnosis. The eGFR was estimated using the modification of diet in renal disease (MDRD) equation,[18,19] and based on three categories frequently used in the literature (>60, $30 \leq X < 60$, or <30 ml/min/1.73 m^2).[19,20] Our analyses did not include a term for ethnicity/race. Not using this term is a common practice for eGFR estimation in the UK,[20] and was also necessary because race/ethnicity is not recorded in THIN. For the larger dataset we also included a term for diabetes duration. This term was based on the GP's documentation in THIN.

Statistical analysis

Descriptive analyses were followed by unadjusted hazard (incidence) ratios of the association between our drug categories and our outcome, calculating 95% confidence intervals (CIs) using proportional hazards regression. For each comparison the reference group was those who did not use the drug of interest. The fit of the models was assessed visually using Cox–Snell residuals and a graphical display of hazard rates over time among those who did and did not use each therapy. All estimates were confirmed using Poisson regression. These estimates were nearly identical and are not reported. The final multivariable models (adjusted models) were developed by using variables deemed clinically important, or that changed our point estimates by more than 10%. Using this approach or simultaneously using all of the variables listed above produced nearly identical hazard ratios.

All statistical analyses were performed using Stata 9.2 (College Station, TX). This study was approved by the Institutional Review Board of the University of Pennsylvania.

RESULTS

In our 'all diabetics' cohort, there were 63 579 individuals identified with diabetes who met our study criteria (Table 1). The median duration of diabetes at enrollment was 6.5 years (25%—3.2 years, 75%—12.1 years) with a mean of 8.7 years (SD 7.5) and more than 665 000 person-years of previous evaluation. Since 2002, outcomes occurred in 5644 individuals (24.4/1000 person-years). As expected, nearly all of our potential confounding variables were associated with our outcome (Table 1).

In the 'all diabetics' cohort, the fully adjusted hazard ratios of association with our outcome were 1.2 (95% CI: 1.1, 1.3) for insulin, 1.03 (0.97, 1.09) for sulfonylureas, 0.8 (0.7, 0.8) for biguanide, 1.2 (0.99, 1.5) for meglitinide, 0.5 (0.5, 0.6) for thiazolidinediones, and individually 0.6 (0.5, 0.6) for rosiglitazone, and 0.5 (0.4, 0.7) for pioglitazone (Table 2).

In our 'new onset' diabetes sub-cohort, there were 13 576 individuals (followed for 44 657 person-years) newly identified with and treated for diabetes between January 2002 and 2006. The outcome occurred in 744 individuals (16.7/1000 person-years). Again, nearly all of our potential confounding variables were associated with our outcome (Table 1).

In our ''new onset'' cohort, the adjusted hazard ratios with our outcome were 2.4 (2.0, 2.9) for insulin, 1.4 (1.2, 1.7) for sulfonylureas, 0.5 (0.4, 0.5) for biguanide, 0.9 (0.4, 2.1) for meglitinide, 0.8 (0.7, 1.0) for thiazolidinediones, and individually 0.8 (0.6, 1.0) for rosiglitazone and 0.9 (0.6, 1.4) for pioglitazone (Table 2).

Changing our outcome definition to include only individuals with a diagnosis of myocardial infarction had minimal effect on our point estimates (data not shown).

We also evaluated the likelihood of our outcome developing based on the length of exposure to each therapy, using our dataset of incident diabetics. Trends, some of which were statistically significant (Table 3), were noted for several drug exposures as the total duration of therapy increased. This included an increasing risk of myocardial infarction or equivalent for those receiving insulin, sulfonylureas, and biguanide, and a decreasing risk as the total duration of therapy increased for rosiglitazone and pioglitazone.

In both cohorts, we evaluated interactions with concomitant drug use for insulin and all other drugs and sulfonylurea or biguanide and the two thiazolidinediones. The interactions were not significant at the $p = 0.10$ level and had minimal effect on our hazard ratios.

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Table 1. The frequency of potential confounding variables in the dataset and the hazard ratio of association between the confounding variable and the outcome with 95% confidence interval*

Variable	All diabetics		New onset diabetics	
	Number (%)	HR	Number (%)	HR
Sex (male)	34 415 (54.1)	1.3 (1.2, 1.3)	6736 (54.0)	1.5 (1.3, 1.7)
Age category (years)				
40–50	8522 (13.4)	Ref	1593 (11.7)	Ref
50–60	14 235 (22.4)	1.8 (1.6, 2.0)	2782 (20.5)	1.3 (1.0, 1.8)
60–70	18 378 (28.9)	2.8 (2.5, 3.1)	3631 (26.8)	3.6 (2.4, 5.3)
70–80	15 514 (24.4)	3.3 (3.0, 3.7)	3302 (24.3)	4.2 (2.8, 6.1)
>80	6930 (10.9)	2.8 (2.5, 3.2)	2268 (16.7)	4.2 (2.8, 6.2)
eGFR ml/min/1.73 m^2				
>60	42 839 (72.3)	Ref	9767 (78.2)	Ref
30–60	15 226 (25.7)	1.7 (1.6, 1.8)	2598 (20.8)	1.59 (1.4, 1.9)
<30	1167 (2.0)	2.40 (2.1, 2.8)	125 (1.0)	1.3 (0.6, 2.8)
Hemoglobin A1C (%)				
<7	16 312 (27.3)	Ref	5388 (39.7)	Ref
7–9	27 367 (45.7)	1.0 (1.0, 1.1)	4204 (31.0)	1.2 (1.0, 1.4)
9–11	11 257 (18.8)	1.0 (1.0, 1.1)	2214 (16.3)	1.3 (1.0, 1.6)
>11	4965 (8.3)	0.8 (0.7,0.9)	1770 (13.0)	0.9 (0.7, 1.2)
Limb ischemia	8364 (13.2)	2.2 (2.0, 2.3)	1299 (10.0)	1.7 (1.4, 2.0)
MAP mm of Hg	101.6 (101.5, 101.7)	1.0 (1.0, 1.0)	101.0 (101.0, 101.2)	1.0 (1.0, 1.0)
BMI Kg/m^2				
Regular 18–25	11 787 (20.0)	Ref	1919 (16.3)	Ref
Low <18	442 (0.8)	1.1 (0.8, 1.5)	416 (3.5)	1.4 (1.0, 2.1)
Obese 25–30	21 664 (36.7)	1.1 (1.1, 1.2)	3941 (33.4)	1.2 (1.0, 1.5)
Morbid >30	25 140 (42.6)	1.1 (1.0, 1.2)	5499 (46.7)	1.6 (1.3, 2.1)
Cigs per month				
None	49 876 (78.4)	Ref	88 (2.70)	Ref
1–30 cigarettes	7965 (12.5)	1.1 (1.0, 1.2)	2930 (90.0)	1.1 (0.4, 2.6)
>30 cigarettes	5738 (9.0)	1.0 (0.9, 1.1)	239 (7.3)	1.0 (0.3, 2.7)
Duration of diabetes years (SD)	9.2 (8.7)	1.0 (1.0, 1.0)	3.3 (3.4)	n/a

*Please note due to missing data not all denominators are the same.
n/a = not applicable.

Finally, we directly compared the effect of rosiglitazone *versus* pioglitazone. In the larger dataset, 10 165 individuals were exposed to one of these drugs for a total of 36 174 person-years. The hazard ratio of association for rosiglitazone *versus* pioglitazone was 1.0 (0.8, 1.3) and 1.0 (0.8, 1.3) after adjustment. In our smaller cohort, this analysis was of 2185 individuals with 7405 person-years of follow-up. The hazard ratio

Table 2. The frequency of use of therapy by class and the hazard ratio with 95% confidence interval

	All diabetics			New onset diabetics		
Drug name or class	Number (%) 63 579	Unadjusted HR	Adjusted HR*	Number 13 576	Unadjusted HR	Adjusted HR*
Insulin	16 213 (25.5)	1.3 (1.2, 1.4)	1.2 (1.1, 1.3)	1315 (9.7)	2.0 (1.7, 2.5)	2.4 (2.0, 2.9)
Sulfonylureas	32 857 (51.7)	1.0 (1.0, 1.1)	1.0 (1.0, 1.1)	5049 (37.2)	1.6 (1.3, 1.8)	1.4 (1.2, 1.7)
Biguanide	43 801 (68.9)	0.7 (0.6, 0.7)	0.8 (0.7, 0.8)	10 022 (73.8)	0.4 (0.3, 0.6)	0.5 (0.4, 0.5)
Meglitinide	1061 (1.7)	1.0 (0.8, 1.2)	1.2 (1.0, 1.5)	109 (0.8)	1.0 (0.8, 1.2)	0.9 (0.4, 2.1)
Thiazolidinedione	9526 (15.0)	0.5 (0.4, 0.5)	0.5 (0.5, 0.6)	2185 (16.1)	0.8 (0.6, 1.0)	0.8 (0.7, 1.0)
Rosiglitazone	7282 (11.4)	0.5 (0.4, 0.5)	0.6 (0.5, 0.6)	1691 (12.5)	0.7 (0.6, 0.9)	0.8 (0.6,1.0)
Pioglitazone	2244 (3.5)	0.5 (0.4, 0.6)	0.5 (0.4, 0.7)	494 (3.6)	0.9 (0.6, 1.3)	0.9 (0.6,1.4)

An individual may have used more than one medication.
*All confounders in Table 1 evaluated. The only factors that changed point estimates by more than 10% were the five medications, age, and gender. All adjusted estimates included these seven variables.

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Table 3. The frequency of use and the hazard ratios based on months of use of the therapy for drugs or classes with sufficient numbers for analysis in the incident diabetic dataset

Variable	Number (%)	Unadjusted HR	Adjusted HR
Insulin			
0	12 261 (90.3)	Ref*	Ref*
1–5 months	668 (4.9)	1.6 (1.2, 2.2)	2.0 (1.5, 2.6)
6–11 months	268 (2.0)	2.4 (1.6, 3.5)	2.9 (2.0, 4.2)
12 months or more	379 (2.8)	2.4 (1.8, 3.3)	2.9 (2.1, 3.9)
Sulfonylureas			
0	8527 (62.8)	Ref*	Ref*
1–5 months	1929 (14.2)	1.0 (0.8, 1.3)	1.0 (0.8, 1.2)
6–11 months	1047 (7.7)	1.6 (1.2, 2.0)	1.5 (1.2, 2.0)
12 months or more	2073 (15.3)	2.0 (1.7, 2.4)	1.8 (1.5, 2.2)
Biguanide			
0	3554 (26.2)	Ref*	Ref*
1–5 months	3632 (26.8)	0.6 (0.5, 0.8)	0.7 (0.5, 0.8)
6–11 months	2454 (18.1)	1.0 (0.8, 1.2)	1.0 (0.8, 1.3)
12 months or more	3936 (29.0)	1.2 (1.0, 1.5)	1.3 (1.0, 1.5)
Thiazolidinediones			
0	11 391 (83.9)	Ref†	Ref
1–5 months	950 (7.0)	0.8 (0.6, 1.1)	0.9 (0.7, 1.2)
6–11 months	567 (4.2)	0.6 (0.4, 0.9)	0.6 (0.4, 1.0)
12 months or more	668 (4.9)	0.7 (0.5, 1.1)	0.7 (0.4, 1.1)
Rosiglitazone			
0	27 780 (96.0)	Ref†	Ref
1–5 months	517 (1.8)	0.8 (0.6, 1.2)	0.9 (0.7, 1.3)
6–11 months	342 (1.2)	0.6 (0.4, 1.0)	0.6 (0.4, 1.1)
12 months or more	288 (1.0)	0.7 (0.4, 1.1)	0.7 (0.6, 1.3)
Pioglitazone			
0	13 082 (96.4)	Ref	Ref
1–5 months	204 (1.5)	0.9 (0.5, 1.6)	0.9 (0.5, 1.7)
6–11 months	123 (0.91)	0.6 (0.2, 1.5)	0.6 (0.2, 1.7)
12 months or more	167 (1.2)	0.8 (0.6, 1.9)	0.8 (0.7, 1.1)

Test for trend *p-value <0.001 and †p-value <0.05.

of association for rosiglitazone *versus* pioglitazone was 1.1 (0.7, 1.8) and 1.1 (0.7, 1.7) after adjustment.

DISCUSSION AND CONCLUSIONS

This is one of the largest studies evaluating in general practice the association between diabetes medications and serious cardiovascular outcomes. In our larger cohort, the hazard ratios for both rosiglitazone and pioglitazone were substantially less than 1.0, meaning that these agents had a protective effect with respect to serious cardiac outcomes, with generally greater protection from longer use. This effect, but smaller, was also noted, in our 'new onset' cohort. The hazard ratios did change over time.

Notably, it appears that those who used either insulin or sulfonylureas were more prone to having a myocardial infarction, and this risk increased with increased duration of therapy. This has been noted in prior papers, but not emphasized as it has been considered a function of diabetes duration.[9,10] However, this observation was also present in our smaller dataset of 'new onset' diabetics, suggesting it may be an effect of hypoglycemia. This suggests the possibility that the early risk associated with the thiazolidinediones, previously noted as especially salient in the presence of insulin,[3] might result from the thiazolidinediones potentiating the hypoglycemic effects of insulin, an effect that disappears over time as the cardioprotective effects of thiazolidinediones become stronger. This same observation might explain the recent finding in the ACCORD study, such that very tight glycemic control might be associated with increased cardiovascular risk.

Many previous studies evaluated thiazolidinediones and each was designed differently from ours. Nissen and Wolski recently described a significant increased risk of myocardial infarction in individuals who used rosiglitazone to treat their diabetes (1.43 (1.03, 1.98)).[3] Their report was a meta-analysis of data from 42 trials of rosiglitazone. These trials all included a randomized comparator arm, at least 24 weeks of drug exposure, and all treatment groups received similar duration of treatments. They postulated that this risk might occur soon after commencing therapy (within the first 24–54 weeks of use) due to either a direct effect of rosiglitazone on serum lipids, an unknown mechanism that increases risk of congestive heart failure, or a decrease in hemoglobin.[3,9]

The Nissen study did not include information from all studies available. Studies that did not report any myocardial infarctions were excluded from their final analyses and therefore did not contribute to their total follow-up.[3,21] Adding these studies substantially diminishes the magnitude of the increased association between rosiglitazone and myocardial infarction.[21] Further, they did not have access to the primary data so their analysis was based on the table-level data made publicly available by GlaxoSmithKline, the myocardial endpoint was not validated but based on serious adverse event reporting by local investigators, and those studied had diabetes for varying lengths of time.[2,3]

While it is very difficult to directly compare our study to Nissen's study, the 'protective effect' of rosiglitazone that we observed is greatest for those on the agent for more than 6 months. Yet, most of the clinical trials analyzed by Nissen *et al*. lasted for less than 6 months.[22] Finally, the subjects of the studies included in their meta-analysis were enrolled in randomized trials not in general practice. It is possible

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that their results do not generalize to general practice.[22] In particular, and relevant to our results, one might expect that diabetics who enroll in clinical trials of drugs used to treat diabetes may have had a longer history of diabetes, may have had more treatment for their diabetes, and perhaps may have failed to respond to previous treatments. This is a very different clinical situation than the one we present. In fact, our 'new onset' cohort likely generalizes better to the vast majority of individuals who are likely to be newly treated with the agents that we studied. Nissen also found their highest risk of myocardial infarction in those who used rosiglitazone and insulin.[3] While we did not find an interaction between these agents, we did find an increased risk of myocardial infarction among insulin users.

A recent meta-analysis by Singh *et al*. looked at longer-term administration of rosiglitazone.[4] Follow-up in this study was from at least 1 year to up to 4 years. The hazard ratio for myocardial infarction was similar to the Nissen meta-analysis (1.42 (1.06, 1.91)).[3] However, Singh *et al*. found no increased risk of cardiovascular death (0.90 (0.63, 1.26)). It should also be noted that a recent meta-analysis of studies of at least 1 year duration by Lago *et al*. found an increased risk of congestive heart failure (1.72 (1.21,2.42)) due to thiazolidinediones but found no increased risk of cardiac death (0.93 (0.67,1.29)) and no difference between rosiglitazone and pioglitazone users.[23]

An unplanned preliminary analysis by Home *et al*. of an ongoing long-term randomized trial of rosiglitazone for those who failed other oral therapy *versus* individuals not using rosiglitazone revealed a hazard ratio of 1.08 (0.89, 1.31) with respect to their cardiovascular outcome.[7] This study had a mean follow-up of 3.75 years and between 10 and 20% of those assigned to a drug group were no longer using that medication.[7] Another study of pioglitazone showed a protective effect with respect to death, myocardial infarction, and stroke (0.84 (0.72, 0.98)).[24] Furthermore, a similar effect was noted in a high-risk subgroup (0.85 (0.67,1.06)).[25] Again, those studied likely had diabetes for varying lengths of time and it is impossible to know exactly when in the course of their illnesses an individual began to contribute person-time.

Retrospective cohort studies by McAfee *et al*. and Gerrits *et al*. used the same administrative claims database.[5,8] McAfee *et al*. showed that the association between rosiglitazone use and hospitalization for myocardial infarction or coronary revascularization as compared to other oral agents or insulin use varied from a hazard ratio of 1.07 (small increase) to 0.77 (a small decrease) depending on the comparator agent.[5] A study by Gerrits *et al*. used the same database as McAfee but directly compared only pioglitazone to rosiglitazone.[8] They found a lower risk of hospitalization for myocardial infarction with pioglitazone than rosiglitazone.[8] Gerrits *et al*. estimated a hazard ratio of 0.78 (0.63, 0.96).[8] They did not evaluate rosiglitazone or pioglitazone with respect to individuals who were using other medications to treat their hyperglycemia.[8] Again our study is substantively different. Our effect estimates for rosiglitazone were similar to McAfee's over a comparable observation period, but ours decreased with more prolonged use. Unlike Gerrits, we did not note differences between rosiglitazone and pioglitazone with respect to myocardial infarction.[5,8] Our methods of ascertainment of diabetes and myocardial infarction have been previously used and validated and we were able to evaluate the association between many other important medical illnesses as well as mandatory laboratory examinations.[16,17]

Of course, our study has limitations too. Our study could have suffered from selection bias. However, data for our study were collected prior to the publication by Nissen, which is the study that resulted in public concerns about an association between rosiglitazone and cardiovascular illness. One difference is that our study is a cohort study and the publications by Nissen were based on randomized clinical trials. We did have access to and used for statistical adjustment many covariates as well as laboratory values. Very few had an effect on our hazard ratios. It is however possible that unmeasured confounders exist that may have an important influence on our results. Finally, we could have misclassified our outcome. However, it is important to note that we used the actual medical record rather than claims data or unvalidated trial data, our outcome has been previously validated, our rate of

KEY POINTS

- We were not able to demonstrate an association between serious ischemic cardiac events and the thiazolidinediones.
- An association may exist between other compounds used to treat diabetes and serious ischemic cardiac events.
- These differences may represent intrinsic differences between those who participate in clinical trials and those treated in general practice.

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cardiovascular illness was similar to previous estimates in the UK population and a recent German study, and as expected many of our potential confounders were associated with our outcomes.[10,16,26]

In conclusion, we were unable to demonstrate an increased risk of myocardial infarction with the use of rosiglitazone or pioglitazone, as compared to other therapies used to treat diabetes. If a risk exists, it likely exists only in the first few months of rosiglitazone or pioglitazone use. Indeed, after the first few months of use there appears to be a progressive decrease in the risk of myocardial infarction associated with the use of these medications. Conversely, it appears that those who used insulin and sulfonylureas were *more* prone to having a myocardial infarction.

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