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ORIGINAL ARTICLE

The risk of developing coronary artery disease or congestive heart failure, and overall mortality, in type 2 diabetic patients receiving rosiglitazone, pioglitazone, metformin, or sulfonylureas: a retrospective analysis

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Abstract Oral anti-diabetic agents have been associated with adverse cardiovascular events in type 2 diabetes (DM2). We investigated the risk of coronary artery disease (CAD), congestive heart failure (CHF), and mortality using multivariable Cox models in a retrospective cohort of 20,450 DM2 patients from our electronic health record (EHR). We observed no differences in CAD risk among the agents. Metformin was associated with a reduced risk of CHF (HR 0.76, 95% CI 0.64–0.91) and mortality (HR 0.54, 95% CI 0.46–0.64) when compared to sulfonylurea. Pioglitazone was also associated with a lower risk of mortality when compared to sulfonylurea (HR 0.59, 95% CI 0.43–0.81). No other significant differences were found between the oral agents. In conclusions, our results did not identify an increased CAD risk with rosiglitazone in clinical practice. However, the results do reinforce a possible increased risk of adverse events in DM2 patients prescribed sulfonylureas.

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Introduction

Controversy still surrounds the selection of oral anti-diabetic agents for the treatment of type 2 diabetes. There has been a discrepancy in the reported risk of coronary artery disease (CAD), congestive heart failure (CHF), and/or death in type 2 diabetics taking the various oral anti-diabetic agents, starting with the University Group Diabetes Project (UGDP) which raised concern that administration of a sulfonylurea (tolbutamide) may increase the risk of cardiovascular death [1]. The United Kingdom Prospective Diabetes Study (UKPDS) did not support the suggestion by the UGDP that sulfonylureas were associated with an increased risk of death, and demonstrated that metformin use in obese patients with type 2 diabetes reduced all-cause mortality when compared to the conventional treatment group, and a greater risk reduction was observed in the metformin group than in the groups assigned intensive therapy with sulfonylurea or insulin [2, 3]. However, the addition of metformin to sulfonylurea therapy was associated with a 96% increased risk of diabetes related death and a 60% increased risk of death from any cause [3]. The controversy has now encompassed the new oral anti-diabetic agents rosiglitazone and pioglitazone, particularly with respect to the risk of CAD.

A recent meta-analysis by Nissen and Wolski concluded rosiglitazone was associated with a significant increase in the risk of myocardial infarction (OR 1.43, 95% CI 1.03–1.98) [4]. Subsequent meta-analyses by GlaxoSmithKline, and Singh et al. reported similar results (OR 1.31, 95% CI 1.01–

1.70 and RR 1.42, 95% CI 1.06–1.91 respectively) [5, 6]. These meta-analyses included many of the same studies. A time-dependent medication analysis by Lipscombe et al. [7] found monotherapy with a thiazolidinedione was associated with an increased risk of acute myocardial infarction when compared with other oral anti-diabetic agent combination therapies (RR 1.40, 95% CI 1.05–1.86). The increased risk of myocardial infarction appeared limited to rosiglitazone; however, the study appeared underpowered to detect an increased risk with pioglitazone, as it had a relatively small number of persons prescribed pioglitazone monotherapy. An interim analysis of RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes), a prospective study assessing CAD risk, did not show a statistically significant risk for myocardial infarction with rosiglitazone therapy (HR 1.16, 95% CI 0.75–1.81) [8]. Likewise, a retrospective cohort of 26,931 patients found no increase in the risk of coronary heart disease (CHD) outcomes with rosiglitazone compared to metformin monotherapy (HR 1.07, 95% CI 0.85–1.34) or sulfonylurea monotherapy (HR 0.82, 95% CI 0.67–1.02) [9]. The literature has been saturated with conflicting results with respect to an increased risk of myocardial infarction with rosiglitazone therapy, and the United States Food and Drug Administration (FDA) ordered that myocardial infarction be added to the black box warning of rosiglitazone, a measure based largely on the results of meta-analyses investigating outcomes/events which many of the studies used in the meta-analyses were not originally intended, or powered to detect.

Unlike the reported increased risk of CAD with rosiglitazone, recent data suggests that pioglitazone is associated with a decreased risk of CAD. PROactive (Prospective Pioglitazone Clinical Trial in Macrovascular Events) showed that in high-risk patients with type 2 diabetes and previous myocardial infarction, pioglitazone significantly reduced the occurrence of fatal and nonfatal myocardial infarction and acute coronary syndromes [10]. A meta-analysis by Lincoff et al. [11] examining pioglitazone and the risk of cardiovascular events included both high- and low-risk patients (including PROactive) and showed that pioglitazone was associated with a lower risk of death, myocardial infarction, or stroke compared to controls (HR 0.82, 95% CI 0.72–0.94). The PERISCOPE trial (comparison of pioglitazone vs. glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes) suggested treatment with pioglitazone resulted in a significantly lower rate of progression of coronary atherosclerosis compared with glimepiride [12]. This suggests that agents may have varying effects on endpoints independent of glycemic control.

The treatment of type 2 diabetes with thiazolidinediones has been limited by weight gain and fluid retention. Studies have found a higher incidence of CHF in those treated with thiazolidinediones secondary to the therapy itself and independent of the severity of underlying diabetes [6–8, 10, 11, 13–15]. This literature prompted the FDA to add black box warnings to rosiglitazone and pioglitazone reminding physicians that these drugs should not be used in people with heart failure. Retrospective studies investigating the risk of CHF with non-thiazolidinedione therapies suggested it was the severity of diabetes, duration of diabetes, and the need for drug therapy that imparted risk, and not the antidiabetic therapies themselves [16, 17]. However, ADOPT (A Diabetes Outcome Progression Trial) found the risk of developing CHF was similar in the rosiglitazone and metformin treatment cohort, suggesting metformin may also impart risk independent of the underlying diabetes severity [14].

The discrepancy in the reported risks of CAD, CHF, and all cause mortality, particularly with rosiglitazone and pioglitazone, and the recent actions taken by the FDA, prompted this study to compare mortality and cardiovascular outcomes in a large cohort of type 2 diabetics, stratified by medication, to assess the relationship of the initial medication choice with these adverse outcomes.

Methods

Source population

The source population was obtained from an electronic health record (EHR) derived clinical data repository at the Cleveland Clinic. This study was approved by the Institutional Review Board.

Study groups

For the period 10/24/1998 to 10/12/2006, we identified all newly and previously diagnosed type 2 diabetics with documented International Classification of Diseases Version 9 codes (ICD-9) (see "Appendix") and by identifying patients with at least two encounters for diabetes after visiting the Cleveland Clinic main campus or family health centers and who had a prescription for rosiglitazone, pioglitazone, metformin, or a sulfonylurea entered into the EHR. Patients were stratified into four medication groups according to the initial prescription entered in the EHR at baseline. All patients were $\geq$18 years of age and had no history of dialysis, CAD or CHF (see "Outcomes" section for criteria constituting CAD or CHF) at baseline. Patients prescribed insulin or other injectable diabetic medications (as monotherapy or in conjunction with oral agents), and those on multiple oral agents at baseline, were excluded.

Follow-up

Follow-up began on the day after the first prescription of the qualifying study drug was entered in the EHR and continued until the date of the outcome of interest or censoring. For CAD and CHF, patients with no observed event were censored on the date of their last encounter or laboratory value in the EHR. For mortality, patients with no observed event were censored on the last clinic encounter or the date of extraction of vital status from the Social Security Death Index (SSDI) minus a 6 month lag, whichever came last.

Multivariable analysis

In order to compare patients in each medication group, we used a multivariable analysis, which allowed us to adjust for differences in baseline characteristics. Variables were chosen and derived based on prior considerations of their clinical relevance with respect to the risk of cardiovascular events (CAD or CHF) and mortality. The baseline medical history variables chosen for the CAD, CHF, and mortality models can be seen in Table 3.

We were unable to use family history or alcohol use as predictor variables due to inconsistent documentation in the EHR. The baseline variables were derived from the EHR on the date closest to the date of the first oral antidiabetic agent up to 21 days after baseline. Missing baseline values were imputed by chained equations (mice) package version 1.16 for R, without regard to the outcomes, using regression techniques that included all patients and all baseline values to predict the missing value.

Outcomes

CAD was defined by documentation of coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, myocardial infarction, or a diagnosis of CAD via ICD-9 documentation under encoded diagnosis or problem list in the EHR after baseline. CHF was defined by documentation of CHF via ICD-9 code and/or a post-baseline LVEF <40%. See "Appendix" for a list of the ICD-9 codes utilized. Mortality was determined by documentation in the EHR and/or SSDI. In most instances, the EHR and SSDI were congruent. Patients were considered to be deceased if either system classified them as dead. The SSDI was able to identify those deceased individuals who were lost to follow in the EHR. However, we identified 49 patients who were classified as dead according to the SSDI, but who continued to have follow-up visits in the EHR. Since these patients were obviously still alive at the time of their follow-up visits, they were counted as alive.

Analysis

Analyses were performed using the statistical package R for Windows version 2.3.1 (Copyright 2006, The Foundation for Statistical Computing). Survival curves for CAD, CHF, and mortality were estimated with the Kaplan–Meier procedure. Multivariable Cox proportional hazards models were used to derive hazard ratios for each baseline medication group comparison. Restricted cubic splines were used to relax linearity assumptions for the continuous variables. After adjustments were made for the baseline covariates, the following comparisons were made:

- Rosiglitazone versus metformin
- Rosiglitazone versus sulfonylurea
- Pioglitazone versus metformin
- Pioglitazone versus sulfonylurea
- Metformin versus sulfonylurea
- Pioglitazone versus rosiglitazone

Results

Using the EHR we were able to identify 2,587 initiators of monotherapy with a thiazolidinedione (1,079 rosiglitazone and 1,508 pioglitazone), 10,436 initiators of monotherapy with metformin, and 7,427 initiators of monotherapy with a sulfonylurea, without a history of CAD or CHF, and not on insulin or a non-insulin injectable at baseline. The distribution of baseline characteristics, categorical and continuous variables, among the medication groups, can be seen in Tables 1 and 2 respectively.

The cohorts contained a total of 1,797 outcomes for CAD, 661 outcomes for CHF, and 1,783 outcomes for mortality. The survival curves for CAD, CHF, and mortality can be seen in Figs. 1, 2, 3 respectively. There were 3,579 patients lost to follow-up in the EHR, but with vital status from the SSDI. They were excluded from the Kaplan–Meier estimates for CAD and CHF as they did not have follow-up for the two end-points. The hazard ratios with 95% confidence intervals for the monotherapy comparisons for CAD, CHF, and mortality can be seen in Table 3 after adjusting for baseline variables.

For the period 10/24/1998 to 10/12/2006, no difference in the risk of developing CAD was found across medications, see Table 3.

A 24% risk reduction in developing CHF with metformin versus sulfonylurea was observed (HR 0.76, 95% CI 0.64–0.91, $P = 0.003$). An increased risk of CHF with pioglitazone when compared to metformin was of borderline significance (HR 1.38, 95% CI 1.0–1.90, $P = 0.05$). The results of the remaining monotherapy comparisons, with respect to CHF, can be seen in Table 3.

Table 1 Baseline characteristics: categorical variables

Characteristics	Rosiglitazone ($N = 1,079$)		Metformin ($N = 10,436$)		Sulfonylurea ($N = 7,427$)		Pioglitazone ($N = 1,508$)	
	N	%	*N*	%	*N*	%	*N*	%
Male								
Yes	491	45.5	4,362	41.8	3,678	49.5	729	48.3
No	588	54.5	6,074	58.2	3,749	50.5	779	51.7
Caucasian								
Yes	893	86.8	7,703	76.9	5,588	78.0	1,214	83.5
No	136	13.2	2,317	23.1	1,580	22.0	240	16.5
Missing	50	–	416	–	259	–	54	–
Smoking								
Never	388	50.1	4,259	51.3	2,501	49.0	524	47.1
Passive	1	0.1	45	0.5	20	0.4	7	0.6
Quit	273	35.3	2,647	31.9	1,824	35.8	388	34.9
Yes	112	14.5	1,349	16.3	757	14.8	193	17.4
Missing	305	–	2,136	–	2,325	–	396	–
ACE/ARB inhibitors								
Yes	529	49.0	4,602	44.1	3,580	48.2	787	52.2
No	550	51.0	5,834	55.9	3,847	51.8	721	47.8
Alb/creatinine ratio								
0–29.9	59	72.0	1,152	81.4	352	70.4	91	77.1
30–300	17	20.7	226	16.0	115	23.0	24	20.3
>300	6	7.3	37	2.6	33	6.6	3	2.5
Missing	997	–	9,021	–	6,927	–	1,390	–
Renal disease								
Yes	22	2.0	33	0.3	132	1.8	25	1.7
No	1,057	98.0	10,403	99.7	7,295	98.2	1,483	98.3
Cholesterol lowering med								
Yes	542	50.2	4,455	42.7	2,852	38.4	797	52.9
No	537	49.8	5,981	57.3	4,575	61.6	711	47.1
Clopidogrel								
Yes	79	7.3	354	3.4	435	5.9	88	5.8
No	1,000	92.7	10,082	96.6	6,992	94.1	1,420	94.2
Aspirin								
Yes	221	20.5	2,062	19.8	1,498	20.2	325	21.6
No	858	79.5	8,374	80.2	5,929	79.8	1,183	78.4

A 41% risk reduction in mortality with pioglitazone versus sulfonylurea (HR 0.59, 95% CI 0.43–0.81, $P < 0.001$) and a 46% risk reduction with metformin versus sulfonylurea (HR 0.54, 95% CI 0.46–0.64, $P < 0.001$) were observed. The results of the remaining monotherapy comparisons, with respect to mortality, can be seen in Table 3.

Discussion

The present study did not find a statistically significant difference in the incidence of CAD among the various treatment options. With respect to CHF, patients treated initially with metformin monotherapy had substantially less CHF than those treated initially with sulfonylurea monotherapy. Comparison of initial monotherapy with pioglitazone versus metformin suggests an increased risk of CHF of borderline significance. The present study also suggests patients treated initially with pioglitazone or rosiglitazone monotherapy are associated with a risk reduction in mortality when compared to patients treated initially with sulfonylurea monotherapy (although only pioglitazone vs. sulfonylurea was statistically significant). In addition, patients treated initially with metformin monotherapy experienced a reduction in mortality compared to those treated initially with sulfonylurea monotherapy.

The results of this study were not supportive of the assertion that rosiglitazone results in an increased risk of

Table 2 Baseline characteristic: continuous variables

Characteristics	Rosiglitazone		Metformin		Sulfonylurea		Pioglitazone		Missing
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	%
Days from diagnosis/first med to start of oral med	35.9	167.1	58.5	210.1	31.1	186.3	38.2	180.4	0.00
Age (years)	61.4	13.7	56.8	13.9	66.1	13.5	61.6	13.1	0.00
BMI (kg/m^2)	32.7	7.6	33.8	7.4	31.1	6.9	33	7.4	43.50
BP Systolic (mmHg)	134.7	19.4	133.5	18.4	138.4	21.4	134.7	19.4	21.40
BP Diastolic (mmHg)	75.6	11.2	78.7	10.6	76.7	11.6	76.5	11.1	21.40
HDL (mg/dL)	45.7	12.8	47.5	14.1	47.2	15	47.1	14.6	52.60
LDL (mg/dL)	111.8	39.1	113.5	38.3	112	38.2	109.7	40.5	55.10
Triglycerides (mg/dL)	222.7	187.9	210.1	250.4	201.3	187.6	228.5	390	53.20
Hba1c (%)	7.3	1.7	7.7	2	7.6	1.9	7.3	1.7	52.10
MDRD eGFR truncated at 90	73.6	19.2	81.2	12.7	72.8	19.4	71.2	19.8	35.00
Zip median income (US dollars)	44,724	13,695	45,435	14,822	44,183	14,714	44,242	13,392	0.1

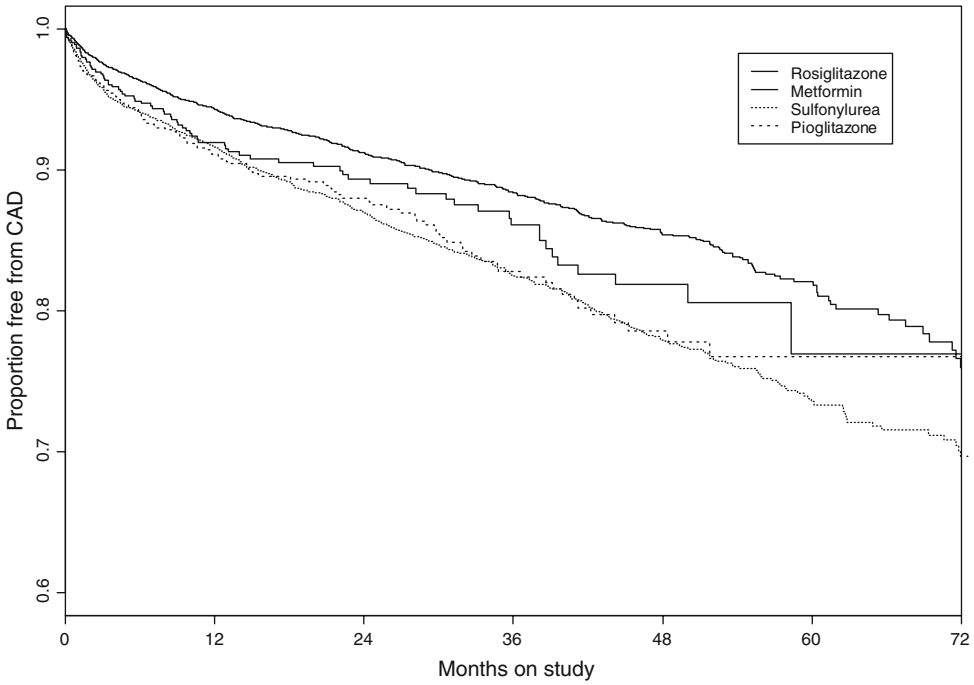

Fig. 1 CAD in the monotherapy group

Number of people at risk for CAD

Drugs	0 Months	12 Months	24 Months	36 Months	48 Months	60 Months	72 Months
Rosiglitazone	831	414	280	170	78	15	4
Metformin	8684	4959	3328	2213	1220	309	118
Sulfonylurea	6189	3680	2598	1806	1062	337	181
Pioglitazone	1167	568	352	221	103	17	4

developing CAD in type 2 diabetics observed by the recent meta-analyses by Nissen and Wolski, Glaxo-SmithKline, and Singh et al. [4–6]. The observed differences between the cohorts do support the hypothesis of no difference on cardiovascular risk with respect to thiazolidinedione versus metformin and thiazolidinedione versus sulfonylurea as initial single agents. A direct comparison between initial monotherapy with metformin

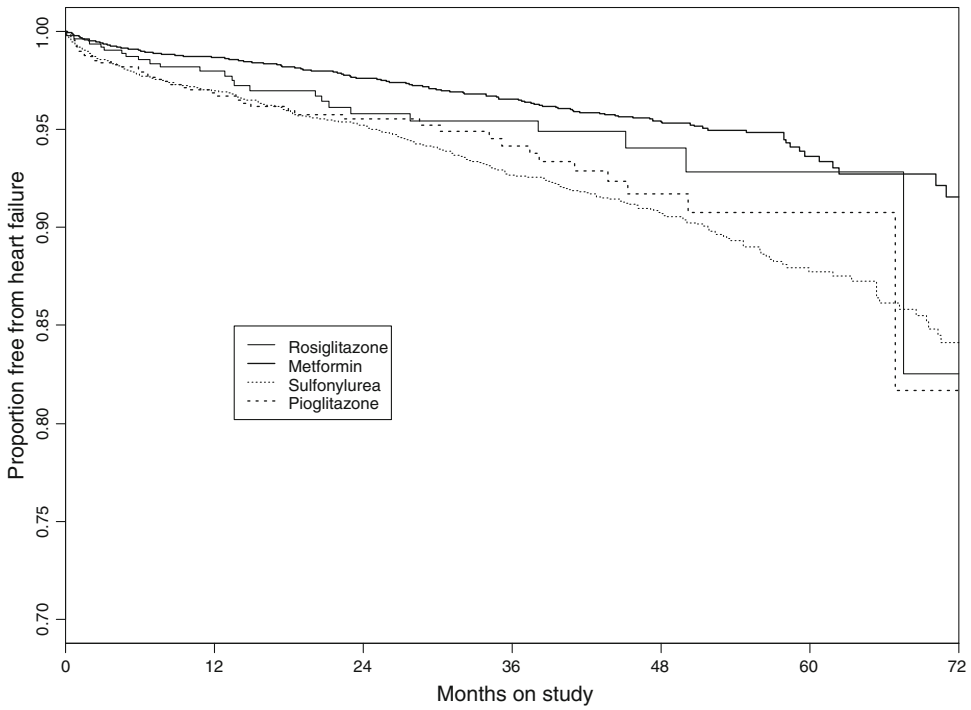

Fig. 2 CHF in the monotherapy group

Number of patients at risk for CHF

Drugs	0 Months	12 Months	24 Months	36 Months	48 Months	60 Months	72 Months
Rosiglitazone	831	436	294	186	91	18	4
Metformin	8684	5163	3546	2402	1356	346	146
Sulfonylurea	6189	3841	2807	1995	1246	400	228
Pioglitazone	1167	599	377	248	117	18	5

and sulfonylurea showed no difference with respect to the risk of CAD. Our finding that initial rosiglitazone monotherapy had a similar effect on cardiovascular risk compared to those treated initially with metformin monotherapy is in agreement with the ADOPT findings. However, our findings did not reproduce the findings in ADOPT which suggested cardiovascular events were lower in those treated with a sulfonylurea (glyburide) when compared to rosiglitzone or metformin [14]. Our results were similar to the recently published retrospective analyses of large databases derived from medical records by McAfee et al. [9] which did not support an increase in cardiovascular risk in patients taking rosiglitazone.

The risk of CAD with initial pioglitazone monotherapy, when compared to those treated initially with rosiglitazone monotherapy, was consistent with no difference between therapies. Rosiglitazone was not associated with an increase in cardiovascular risk when compared to pioglitazone, and pioglitazone was not associated with a decrease in cardiovascular risk when compared to rosiglitazone. The thiazolidinediones were not analyzed as a class because of the discrepancies in reported risk between rosiglitazone (higher risk) and pioglitazone (lower risk and reported benefit) with respect to the measured outcomes, which could have lead to false interpretations of thiazolidinediones as a medication class.

Comparison of initial monotherapy with metformin to sulfonylurea, with respect to CAD in the present study, suggests a non-significant risk reduction. The recently published retrospective analysis by McAfee et al. looking at CHD outcomes in patients receiving rosiglitazone, metformin, or sulfonylurea found metformin monotherapy resulted in a 23% risk reduction of acute myocardial infarction or coronary revascularization when compared to sulfonylurea monotherapy (HR 0.77, 95% CI 0.62–0.96) [9]. The UKPDS subset study on obese individuals showed a 39% reduction in CAD (myocardial infarction) in the metformin treatment group when compared to the conventional treatment group, but did not differ from the sulfonylurea or insulin intensively treated groups [3]. Our result, which showed no statistically significant difference in the risk of CAD when initial metformin monotherapy was compared to initial sulfonylurea monotherapy, is consistent with this UKPDS finding.

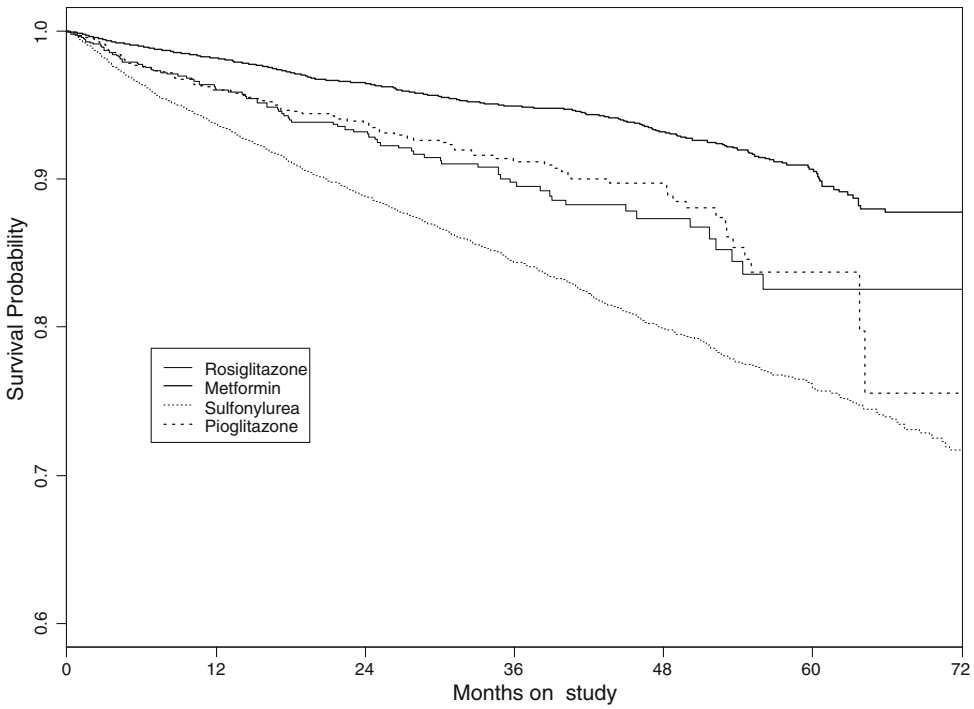

Fig. 3 Mortality in the monotherapy group

Number of patients at risk for mortality

Drugs	0 Months	12 Months	24 Months	36 Months	48 Months	60 Months	72 Months
Rosiglitazone	1079	753	517	323	161	41	11
Metformin	10436	7342	5278	3621	2057	546	228
Sulfonylurea	7427	5710	4321	3079	1896	625	338
Pioglitazone	1508	1014	686	451	221	25	10

The present study shows no difference in CHF risk when initial rosiglitazone monotherapy is compared to initial metformin monotherapy. This is consistent with the ADOPT study which also showed no difference in the risk of CHF when rosiglitazone was compared to metformin (HR 1.22, 95% CI 0.66–2.26) [14]. The present study did suggest an increased risk of CHF of borderline significance with initial pioglitazone monotherapy when compared to initial metformin monotherapy. The present study found no difference in the risk of CHF in those treated initially with rosiglitazone monotherapy (or pioglitazone) versus sulfonylurea monotherapy in contrast to the ADOPT findings which found rosiglitazone was associated with higher rate of CHF than that associated with glyburide (HR 2.20, 95% CI 1.01–4.79) [14]. Lastly, the present study found initial metformin monotherapy was associated with a 24% decrease in the risk of CHF when compared to those treated initially with sulfonylurea monotherapy (HR 0.76, 95% CI 0.64–0.91). This finding contrasts the ADOPT study which found sulfonylurea therapy (glyburide) was associated with a lower rate of CHF than metformin [14].

The results of this study were supportive of the assertion that metformin is associated with a reduction in mortality when compared to sulfonylurea therapy. These results support the findings of the retrospective cohort study by Johnson et al. which found metformin therapy was associated with a decreased all-cause mortality compared to sulfonylurea monotherapy (HR 0.60, 95% CI 0.49–0.74) [18]. However, it is unclear if the results by Johnson et al. and the results of the present study, are due to a protective effect of metformin or a deleterious effect of sulfonylurea therapy. The study by Johnson et al. could not control for level of glycemic control, BMI, or other modifiable cardiovascular risk factors (e.g. smoking). The present study was able to control for baseline glycemic control, BMI, and other modifiable cardiovascular risk factors. The results of the present study and Johnson et al. are not supported by ADOPT which had a similar all-cause mortality among the monotherapy cohorts: rosiglitazone (34 deaths/1,456 subjects), metformin (31 deaths/1,454 subjects), and sulfonylurea (31 deaths/1,441 subjects) [8, 14].

In our analysis, sulfonylureas were analyzed as a class and not as individual agents. It is possible that meaningful clinical differences could exist between the different specific sulfonylurea agents. Some research suggests that

Table 3 Hazard ratios and *P* values

Contrast	HR	95% CI		*P* value
		Lower	Upper	
CAD				
Pioglitazone versus metformin	1.11	0.91	1.34	0.32
Pioglitazone versus sulfonylurea	1.04	0.86	1.26	0.69
Rosiglitazone versus metformin	0.96	0.76	1.21	0.74
Rosiglitazone versus sulfonylurea	0.90	0.71	1.14	0.41
Metformin versus sulfonylurea	0.94	0.85	1.05	0.23
Pioglitazone versus rosiglitazone	1.15	0.87	1.53	0.32
CHF				
Pioglitazone versus metformin	1.38	1.00	1.90	0.05
Pioglitazone versus sulfonylurea	1.05	0.77	1.43	0.76
Rosiglitazone versus metformin	1.16	0.78	1.73	0.48
Rosiglitazone versus sulfonylurea	0.88	0.60	1.31	0.55
Metformin versus sulfonylurea	0.76	0.64	0.91	0.003
Pioglitazone versus rosiglitazone	1.19	0.74	1.91	0.48
Mortality				
Pioglitazone versus metformin	1.08	0.78	1.51	0.64
Pioglitazone versus sulfonylurea	0.59	0.43	0.81	<0.001
Rosiglitazone versus metformin	1.33	0.93	1.91	0.11
Rosiglitazone versus sulfonylurea	0.73	0.51	1.02	0.08
Metformin versus sulfonylurea	0.54	0.46	0.64	<0.001
Pioglitazone versus rosiglitazone	0.81	0.52	1.27	0.36

CAD model adjusted for baseline covariates: age, sex, race (Caucasian vs. noncaucasian), MDRD estimated glomerular filtration rate (GFR), albumin/urine creatinine ratio (*alb:cr*), hemoglobin A1C (*HbA1C*), body mass index (*BMI*), systolic blood pressure (*SBP*), diastolic blood pressure (*DBP*), high density lipoprotein cholesterol (*HDL*), low density lipoprotein cholesterol (*LDL*), triglycerides (*TG*), smoking status, angiotensin converting enzyme therapy (*ACE*) or angiotensin receptor blocker therapy (*ARB*), aspirin therapy (*ASA*), clopidogrel therapy, cholesterol lowering medication, new diabetes, median household income

CHF model adjusted for baseline covariates: age, GFR, HbA1C, BMI, SBP, DBP, smoking status, ACE or ARB, ASA, clopidogrel therapy, cholesterol lowering medication, median household income

Mortality model adjusted for baseline covariates: age, sex, race (Caucasian vs. noncaucasian), GFR, alb:cr, HbA1C, BMI, SBP, DBP, HDL, LDL, TG, smoking status, ACE or ARB, ASA, clopidogrel therapy, cholesterol lowering medication, new diabetes, median household income, oral hypoglycemic agent × age interaction

individual sulfonylureas may have different effects on the ischemic myocardium [19, 20], but data regarding differences in mortality with specific sulfonylureas has been conflicting [21–23]. Due to the interest of space and to avoid excessive numbers of statistical comparisons, we chose to focus this analysis on the individual thiazolidinediones.

The current study has several limitations inherent to most retrospective studies. The analysis was based on exposure to a medication based on the initial prescription entered in the EHR; however, there is no documentation of compliance with the prescribed medication. The limitations of this study are not just secondary to retrospective nature, but also because the outcomes were derived from a single institution's EHR. First, there is variable capture of CAD and CHF outcomes in our EHR based on physician and subspecialist entry (as to a more accurate capture of lab values). Secondly, we have not included events or prescriptions that occurred outside our health system and not accurately documented by providers seen in our institution (unlike claims databases used in many retrospective studies).

The prescribed medication at baseline defined which medication group the patient belonged; however, the medication exposure times after baseline are unknown. Some patients may have stopped taking the study drug, switched to another oral anti-diabetic agent (including the ones used in this study), or had another oral anti-diabetic agent, insulin, or a non-insulin injectable added to their diabetic regimen. When analyzing current clinical practice procedures, it is more likely for additional agents to be added to a baseline medication than to switch from one class of anti-diabetic agent to another. Approximately 75% of the cohort remained on a single drug (baseline medication) throughout their time in the cohort.

The medication groups in our study were not balanced with respect to baseline variables and risk factors; however, the multivariable analysis adjusted for the differences in baseline variables and risk factors that had the most relevance with respect to the risk of developing the outcomes of interest. Nonetheless, we could not adjust for differences in unmeasured baseline characteristics. Inability to control for family history or alcohol use is a recognized limitation. In addition, oral anti-diabetic class was not randomized in the present study so selection bias may be present. It is likely patients without insurance, on a budget (elderly), and those from lower socioeconomic classes were prescribed less expensive medications (metformin or sulfonylurea). However, we adjusted for socioeconomic status by including the median household income estimated from zip code data from the 2000 census in the multivariable analysis. Patients prescribed thiazolidinediones or sulfonylurea may have been those with more advanced diabetes whereas metformin may have been used in those thought to have milder disease. Patients with renal insufficiency, which is associated with an increased risk of death, were less likely to be treated with metformin (contraindication) but the multivariable analysis adjusted for differences in baseline renal function and this should not explain the differences observed. Although the study had several limitations, it did have some strengths: large cohort of patients followed up to

8 years and real world effect of the medications in a diverse patient population.

The *P* values of the statistically significant outcomes were all ≤0.003, so it is unlikely these statistically significant findings were the result of random chance due to our multiple (18) comparisons.

It is possible that we lacked sufficient power to detect small (25%) differences in CHF risk between pioglitazone and rosiglitazone (power = 0.19). However, the power to detect significant (50%) differences in CHF risk was >0.89 for all of the other comparisons. The power to detect significant (50%) differences in risk for all of the comparisons in terms of CAD or mortality was >0.99.

The results from this study demonstrate a similar incidence of CAD among the various treatment options and suggests that baseline monotherapy with metformin has the lowest risk of CHF and mortality, specifically when compared to sulfonylurea therapy. It is unclear if the results of this study are the consequence of a deleterious effect of one agent or the result of a protective effect of the agent to which it is being compared. The results suggest the choice of initial anti-diabetic agent does impart risk and influences outcomes, independent of glycemic control, and that metformin may be the preferred first line agent. A careful examination of a patient's comorbidities should be conducted, and these comorbidities should be considered when picking an oral anti-diabetic agent to control glycemia.

The current study did not observe an increased risk of CAD with rosiglitazone. These findings are in contrast to recent findings by meta-analyses, and would support continuing prospective studies to determine whether these agents have evidence of causing adverse cardiac outcomes and are associated with an increase in overall mortality.

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Appendix

See Table 4

Table 4 Definitions and ICD-9 codes for baseline and measured cardiovascular outcomes

CAD		
ICD	410.xx	Acute myocardial infarction
ICD	411.xx	Other ischemic heart disease
ICD	413.xx	Angina pectoris
ICD	414.xx	Chronic ischemic heart disease
ICD	V45.81	Aortocoronary bypass status
ICD	V45.82	Percutaneous transluminal coronary angioplasty status
ICD	V45.3	Intestinal bypass or anastomosis status
ICD	440.30; 996.03	Of unspecified graft; due to coronary bypass graft
ICD	414.04	Of artery bypass graft-internal mammary artery
CHF		
ICD	402.x1	Hypertensive heart disease with heart failure
ICD	404.x1	Hypertensive heart disease and kidney disease with heart failure
ICD	428.xx	Heart failure
Diabetes		
ICD	250.xx	Diabetes with or without mention of complication
ICD	357.2	Polyneuropathy in diabetes
ICD	362.01	Background diabetic retinopathy
ICD	362.02	Proliferative diabetic retinopathy
ICD	366.41	Diabetic cataract
ICD	648.0x	Diabetes mellitus

ICD-9 International Classification of Diseases Version 9, *CAD* coronary artery disease, *CHF* congestive heart failure

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