

Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database

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ABSTRACT

Objective To investigate the risk of incident myocardial infarction, congestive heart failure, and all cause mortality associated with prescription of oral antidiabetes drugs.

Design Retrospective cohort study.

Setting UK general practice research database, 1990-2005.

Participants 91 521 people with diabetes.

Main outcome measures Incident myocardial infarction, congestive heart failure, and all cause mortality. Person time intervals for drug treatment were categorised by drug class, excluding non-drug intervals and intervals for insulin.

Results 3588 incident cases of myocardial infarction, 6900 of congestive heart failure, and 18 548 deaths occurred. Compared with metformin, monotherapy with first or second generation sulphonylureas was associated with a significant 24% to 61% excess risk for all cause mortality ($P < 0.001$) and second generation sulphonylureas with an 18% to 30% excess risk for congestive heart failure ($P = 0.01$ and $P < 0.001$). The thiazolidinediones were not associated with risk of myocardial infarction; pioglitazone was associated with a significant 31% to 39% lower risk of all cause mortality ($P = 0.02$ to $P < 0.001$) compared with metformin. Among the thiazolidinediones, rosiglitazone was associated with a 34% to 41% higher risk of all cause mortality ($P = 0.14$ to $P = 0.01$) compared with pioglitazone. A large number of potential confounders were accounted for in the study; however, the possibility of residual confounding or confounding by indication (differences in prognostic factors between drug groups) cannot be excluded.

Conclusions Our findings suggest a relatively unfavourable risk profile of sulphonylureas compared with metformin for all outcomes examined. Pioglitazone was associated with reduced all cause mortality compared with metformin. Pioglitazone also had a favourable risk profile compared with rosiglitazone;

although this requires replication in other studies, it may have implications for prescribing within this class of drugs.

INTRODUCTION

More than 180 million people worldwide have type 2 diabetes, a disease associated with at least double the risk of death, mainly from cardiovascular disease.¹ Oral antidiabetes drugs are commonly used to improve glycaemic control, but there are concerns that some may increase the risk of cardiovascular events.²⁻¹¹ Thiazolidinediones, for example, were initially approved as glucose lowering agents with a beneficial effect on insulin sensitivity and a potential beneficial effect on risk of cardiovascular disease. The initial enthusiasm for this class of drugs was, however, soon tempered by the observation in several clinical trials that rosiglitazone and pioglitazone were associated with an increased incidence of congestive heart failure, resulting in a black box warning against the use of these drugs in patients with pre-existing congestive heart failure.² A meta-analysis of data from clinical trials then found an increased risk of myocardial infarction and death from cardiovascular causes in relation to use of rosiglitazone, although a further meta-analysis and other studies failed to replicate this result.³⁻⁵ The mortality associated with these drugs and their net benefit on cardiovascular events is still highly debated. This debate is set against a background of uncertainty about the cardiovascular safety of another class of oral antidiabetes drugs—sulphonylureas—with some studies suggesting an adverse effect and others no effect.¹²

Given the common and increasing use of antidiabetes drugs, it is essential to determine their relative benefits and disadvantages to cardiovascular health. Analyses of observational data examining risks associated with use of antidiabetes drugs among patients attending general practice are limited,¹³⁻¹⁶ but such “phase IV” studies are an important additional step in

drug surveillance.¹⁷ Phase III randomised controlled trials are often too small and of too short a duration to detect small or cumulative adverse effects and are necessarily prescriptive in their choice of patients for entry into trials. In contrast, surveillance data through general practice are able to capture information on drugs and events routinely on a wide range of patients as they present for clinical care. This is an important strength that cannot be captured in other ways.

We investigated the risk of myocardial infarction, congestive heart failure, and all cause mortality associated with prescription of different classes of oral anti-diabetes drugs among men and women with diabetes included in the general practice research database in the United Kingdom. A previous analysis of the database based on a much smaller patient population focused on risk of congestive heart failure among users of older oral antidiabetes drugs and insulin.¹⁶ We aimed to expand these data by studying a much larger patient population ($n=91\,521$) and a range of cardiovascular and other outcomes, and to examine the risks associated with the thiazolidinediones rosiglitazone and pioglitazone.

METHODS

The general practice research database comprises clinical and prescribing data from anonymised patient based clinical records of about five million people.^{17,18} We obtained data on patients aged 35-90 years with an episode of care between 1 January 1990 and 31 December 2005 and a diagnostic (Read) code associated with a clinical or referral event for diabetes. We excluded those records with multiple or missing date of death (see web extra appendix).

Definition of events and drug treatments

Primary events were first occurrence of incident myocardial infarction, congestive heart failure, and all cause mortality. Events were identified by Read codes (see web extra appendix tables 1-3). Validation studies within the general practice research database have confirmed about 83-90% of diagnoses for myocardial infarction and congestive heart failure.^{16,19} We included fractures (non-hip) as a positive control because of the known association between thiazolidinedione use and risk of fractures.²⁰ We identified oral antidiabetes treatments of individual patients from prescription records: rosiglitazone monotherapy, rosiglitazone combination therapy (with other antidiabetes drugs), pioglitazone monotherapy, pioglitazone combination therapy, metformin monotherapy, monotherapy with first generation sulphonylureas (acetohexamide, chlorpropamide, tolbutamide, or tolazamide), monotherapy with second generation sulphonylureas (glipizide, gliquidone, gliclazine, glibenclamide, or gliclazide), other oral antidiabetes drugs (for example, acarbose, nateglinide, repaglinide), and combination therapies excluding thiazolidinediones and insulin. As the pioglitazone monotherapy group was small, we analysed it jointly with the pioglitazone combination group. We excluded

untreated patients, without prescriptions for anti-diabetes treatment, from further analyses.

Data analysis

We used an interval of drug treatment as the unit of observation, defined as the period from onset of a drug treatment to onset of the next drug treatment, or until censored or until occurrence of the event of interest. For example, a patient prescribed monotherapy with sulphonylureas at entry to the cohort then prescribed a combination of sulphonylurea and metformin and remaining on that combination therapy until a myocardial infarction occurred, or until censored, was considered to have contributed a total of two intervals. Similarly, if a patient was prescribed monotherapy with sulphonylureas at entry to the cohort and then continued taking sulphonylurea but was also prescribed aspirin, a new drug interval was calculated. In total there were 2 843 007 intervals of oral antidiabetes treatments among 91 521 patients with diabetes. We excluded periods when patients received insulin therapy, and events throughout these periods.

We used Cox regression stratified by age at diagnosis (quartiles) and calendar year of prescription to account for secular trends in events under study. Alternative models stratifying by either age at diagnosis (continuous) or duration of diabetes or adjusting for age at diagnosis (continuous) resulted in similar risk estimates. Censoring was at the end of each period of constant prescription (or the end of the study). As metformin is advocated as first line pharmacotherapy for type 2 diabetes we compared the risk associated with each drug or drug class with that of metformin monotherapy.^{21,22} We also compared risks among the thiazolidinediones. Analyses were further adjusted, sequentially, for sex and duration of diabetes (model 1); plus previous complications from diabetes, previous peripheral artery disease, previous cardiovascular disease, and coprescribed drugs (model 2); plus body mass index, cholesterol concentration, systolic blood pressure, HbA_{1c} level, creatinine concentration, albumin concentration, and smoking status (model 3). Covariates were reascertained at the onset of each interval except for sex and smoking, which were ascertained only at baseline. Data on model 2 were missing for 503 to 169 103 intervals. For model 3 we included the first non-missing measurement during the prescription interval. If this was not available, we used the most recent preceding measurement if available, dating back to baseline (909 367 to 948 800 intervals). Overall, 28 812 patients had missing values of at least one covariate used in model 3 and therefore were excluded from that analysis.

Sensitivity analyses included an analysis of prescriptions for second generation sulphonylureas only (a similar analysis was not feasible for first generation sulphonylureas owing to small numbers), adjustment for cumulative past prescriptions of antidiabetes drugs prescribed from the start of the study period until the beginning of each drug interval, only drug prescriptions after introduction of thiazolidinediones (≥ 2000) into the

market, patients aged more than 65 or 65 or less at prescription for oral antidiabetes drug, sex specific analyses, and subgroup analyses by thirds of duration of diabetes before drug treatment. To explore possible interactions we fitted interaction terms (model 2) separately for each drug or drug class by age (>65 or ≤65), sex, aspirin use, and statin or fibrate use.

Statistical analysis was done by IT and MPL using SAS v9.0 and SPSS v15.0. A two sided P value of 0.05 was used to denote significance. We found no evidence for violation of the proportional hazard assumption, assessed by testing for a non-zero slope of the scaled Schoenfeld residuals on functions of time.

RESULTS

The mean (SD) age of the 91 521 people receiving oral antidiabetes agents was 65.0 (11.9) years. The median follow-up period was 24 days (interquartile range 13-42 days) per interval and the mean follow-up per individual was 7.1 years. During the study period there were 3588 first events of myocardial infarction, 6900 first events of congestive heart failure, 18 548 deaths, and 2123 fractures. Among all drug treatments, metformin monotherapy was most commonly prescribed (74.5% of patients), followed by monotherapy with second generation sulphonylureas (63.5%;

table 1). Table 1 shows the patients' characteristics according to drug prescriptions.

Myocardial infarction

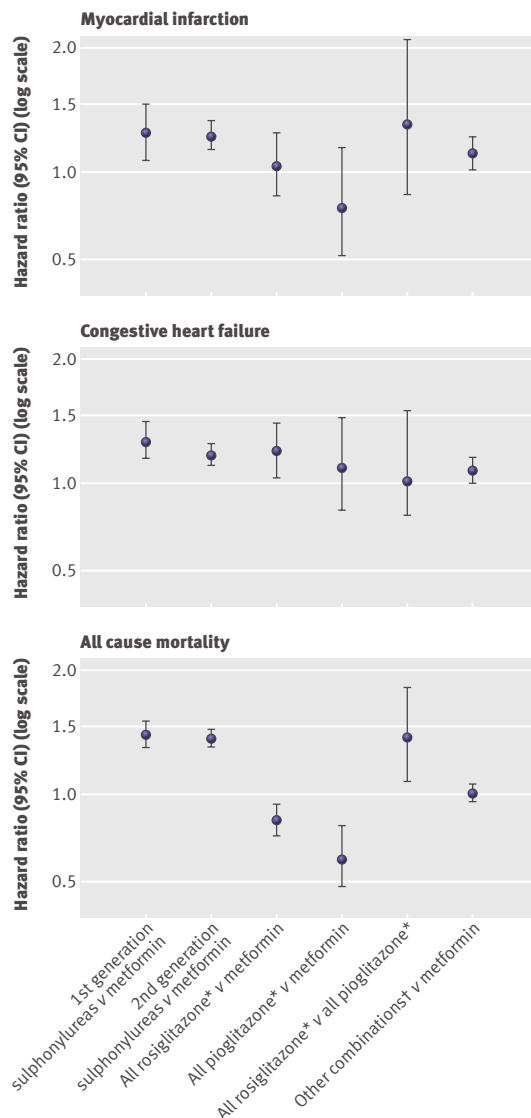
First and second generation sulphonylureas were associated with a significant excess risk of a first episode of myocardial infarction compared with metformin monotherapy in models 1 and 2: the adjusted hazard ratio ranged from 1.37 (95% confidence interval 1.15 to 1.62) to 1.27 (1.07 to 1.50) for first generation sulphonylureas and from 1.31 (1.21 to 1.43) to 1.25 (1.15 to 1.36) for second generation sulphonylureas (table 2, figure). The excess risk associated with sulphonylureas was observed for all subclasses of second generation drugs (see web extra appendix table 4). In the fully adjusted model (model 3), based on 30% of intervals, point estimates for risk of myocardial infarction for both first and second generation drug groups were still above 1, although these hazard ratios were no longer statistically significant. (In evaluating the effects of additional adjustment for confounders in model 3 compared with models 1 and 2, the much reduced sample size consequent on use of model 3 should be considered in interpreting these non-significant results).

Rosiglitazone, either alone or in combination, showed no significant association with incidence of

Table 1 | Characteristics of drug treatment intervals at onset of each interval. Values are means (standard deviations) unless stated otherwise

Variables	Drug treatment intervals						
	First generation sulphonylureas	Second generation sulphonylureas	Rosiglitazone	Rosiglitazone combination	Pioglitazone monotherapy or combination	Other drugs or combinations	Metformin
No of intervals	85 156	988 356	47 695	92 387	45 807	533 897	1 049 709
No of patients	6053	58 095	8442	9640	3816	37 253	68 181
Men (%)	48.6	52.6	50.5	53.6	54.3	53.6	50.6
Age at prescription (years)	73.2 (10.3)	70.4 (10.7)	65.7 (10.9)	64.5 (10.8)	64.8 (10.6)	67.4 (10.5)	66.3 (10.8)
Age at diagnosis of diabetes (years)	64.5 (11.4)	63.5 (11.2)	58.6 (10.8)	57.0 (10.4)	57.7 (10.4)	58.3 (10.5)	60.4 (11.0)
Duration of diabetes at prescription (years)	8.5 (7.4)	6.6 (6.4)	6.7 (6.0)	7.1 (6.1)	6.7 (5.8)	8.8 (6.7)	5.59 (6.1)
Previous prescription:							
Metformin monotherapy (%)	11.8	19.6	44.1	40.2	40.8	42.2	—
First generation sulphonylureas (%)	—	1.9	2.7	2.6	1.6	5.1	1.9
Second generation sulphonylureas (%)	7.7	—	33.3	30.5	32.1	42.2	19.2
Thiazolidinediones (%)	0.6	2.0	—	—	—	1.8	2.4
Body mass index (kg/m ²)	27.8 (4.9)	28.5 (5.2)	31.7 (6.6)	31.8 (6.5)	31.9 (6.3)	30.1 (5.7)	31.47 (6.0)
Systolic blood pressure (mm Hg)	151.3 (23.1)	147.0 (21.7)	143.2 (19.4)	142.1 (18.8)	141.6 (18.4)	146.5 (20.8)	144.7 (19.8)
Cholesterol concentration (mmol/l)	5.7 (1.3)	5.4 (1.3)	5.3 (1.34)	5.2 (1.3)	5.2 (1.3)	5.3 (1.3)	5.24 (1.3)
Creatinine concentration (µmol/l)	104.4 (30.8)	100.0 (29.8)	94.1 (27.7)	91.5 (24.6)	93.9 (25.8)	93.7 (24.1)	91.77 (22.5)
HbA _{1c} level (%)	8.1 (2.1)	8.2 (2.0)	8.4 (1.8)	8.5 (1.8)	8.4 (1.8)	8.4 (2.0)	8.13 (1.8)
Current smoker (%)	10.2	12.5	11.5	13.1	14.1	12.7	13.8
Aspirin (%)	16.6	17.7	14.5	29.8	24.9	23.8	20.1
Statin or fibrate (%)	8.8	18.2	28.5	50.9	40.8	28.4	29.2
ACE inhibitors or angiotensin II receptor blockers (%)	18.4	24.5	26.4	45.0	38.0	33.6	30.3
NSAIDs (%)	25.2	24.5	18.7	36.2	30.7	31.2	26.6
Clinical history:							
Diabetes complications (%)	10.2	14.5	25.3	25.3	25.2	19.7	15.1
Cardiovascular disease (%)	15.0	16.5	15.5	14.5	15.4	17.6	13.4
Peripheral arterial disease (%)	3.5	2.8	3.0	2.9	2.5	3.4	2.1

ACE=angiotensin converting enzyme; NSAIDs=non-steroidal anti-inflammatory drugs.



Risk of myocardial infarction, congestive heart failure, and all cause mortality for different comparisons of drug groups. Analysis is stratified by year of prescription and quartiles of age at treatment, and adjusted for sex, duration of diabetes, previous peripheral arterial disease, previous cardiovascular disease, aspirin, statin or fibrate, diuretics, calcium channel blockers, spironolactone, β adrenergic antagonists, angiotensin converting enzyme inhibitors or angiotensin II receptor blockers, nitrates, steroids, non-steroidal anti-inflammatory drugs, digoxin, and any previous complications from diabetes (model 2). *Any therapy (monotherapy and combinations). †Other drugs and combinations of any oral antidiabetes drugs excluding rosiglitazone and pioglitazone

myocardial infarction when compared with metformin monotherapy in all models; hazard ratios ranged from 0.79 (0.41 to 1.53) in the fully adjusted model 3 to 0.94 (0.62 to 1.43) in the minimally adjusted model 1 for monotherapy and 0.82 (0.56 to 1.20) to 1.08 (0.86 to 1.36) for combination therapy, respectively. Pioglitazone was associated with a non-significant reduced risk of myocardial infarction, which ranged from 22% in both model 1 and model 2 to 29% in the fully

adjusted model 3 (table 2 and figure). When compared with pioglitazone (either monotherapy or in combination with other oral antidiabetes drugs) rosiglitazone was associated with 34% (model 1) to 14% (model 3) non-significant higher risks of myocardial infarction (figure, and see web extra appendix figures 1a and 2a). Other drugs and combination therapies excluding thiazolidinediones were associated with an excess risk of myocardial infarction compared with metformin, although this was not the case in the fully adjusted model 3 (table 2 and figure, and see web extra appendix figures 1a and 2a).

Congestive heart failure

Compared with metformin monotherapy, first generation sulphonylureas were associated with a significant excess risk of a first episode of congestive heart failure in models 1 and 2; hazard ratios ranged from 1.29 (1.17 to 1.44) to 1.46 (1.32 to 1.63; table 3 and figure). In the fully adjusted model 3, however, associations became non-significant, possibly reflecting the reduced sample size and small numbers of events in this analysis. Second generation sulphonylureas were associated with a significant excess risk of congestive heart failure in all models, with hazard ratios ranging from 1.18 (1.04 to 1.34) in model 3 to 1.30 (1.22 to 1.38) in model 1. The subclasses of second generation sulphonylureas were associated with an excess risk of congestive heart failure in most analyses (see web extra appendix tables 4-6). Individuals prescribed rosiglitazone combination therapy had a significant excess risk of developing congestive heart failure compared with those prescribed metformin monotherapy in models 1 and 2; hazard ratios ranged from 1.27 (1.06 to 1.53) in model 2 to 1.31 (1.09 to 1.58) in model 1 (table 3 and figure). The association, however, lost statistical significance in the fully adjusted model 3. Pioglitazone monotherapy or combination therapy was associated with a non-significant excess risk of heart failure, ranging from 1.17 (0.77 to 1.77) in model 3 to 1.18 (0.88 to 1.57) in model 1.

All cause mortality

Sulphonylureas, either first or second generation, were associated with an increased risk of mortality compared with metformin alone in all models examined. Hazard ratios for first generation sulphonylureas were higher than for second generation sulphonylureas and ranged from 1.37 (1.11 to 1.71) for the fully adjusted model 3 to 1.61 (1.49 to 1.74) adjusted for age, sex, year, and duration of diabetes in model 1 (table 4, figure). Risks were higher at younger compared with older ages (see web extra appendix tables 7 and 8). Rosiglitazone combination therapy was associated with a reduced risk of all cause mortality compared with metformin, as was pioglitazone alone and combined. Hazard ratios for pioglitazone attained statistical significance in all models and ranged from 0.69 (0.49 to 0.98, $P=0.024$) in model 3 to 0.61 (0.47 to 0.80, $P=0.0003$) in model 1. Among the thiazolidinediones, rosiglitazone was associated with a higher risk of all cause mortality than pioglitazone;

hazard ratios ranged from 1.41 (1.09 to 1.83) in model 1 to 1.34 (0.90 to 1.97) in model 3 (figure and see web extra appendix figures 1 and 2).

Findings were similar when analyses were limited to drug prescriptions from 2000 onwards after introduction of thiazolidinediones and when analyses were adjusted for the cumulative dose of all other previous prescriptions of oral antidiabetes drugs (see web extra appendix tables 9 and 10). Sensitivity analyses for men and women, for different duration of disease before treatment, and for inclusion of recurrent events are presented in web extra appendix tables 11-16, and tests of interaction in web extra appendix table 17.

Fractures

Thiazolidinediones were associated with an excess risk of non-hip fractures compared with metformin alone. After adjustment for confounders, there was a 53% excess risk for rosiglitazone combination therapy compared with metformin alone (hazard ratio 1.53, 1.25 to 1.88, $P < 0.001$; see web extra appendix table 18). Pioglitazone was associated with a non-significant excess risk (hazard ratio 1.28, 0.93 to 1.77; $P = 0.127$).

DISCUSSION

Our study presents observational data from large numbers of patients with type 2 diabetes attending for routine clinical care in general practice in the UK. We

report important differences in risk associated with different classes of oral antidiabetes drugs. Compared with metformin, monotherapy with either first or second generation sulphonylureas was associated with a significant excess risk of all cause mortality, and second generation sulphonylureas with an excess risk of congestive heart failure. The thiazolidinediones were not associated with risk of myocardial infarction; there was a significantly lower risk of all cause mortality associated with pioglitazone use compared with metformin. Among the thiazolidinediones, a higher risk of all cause mortality was observed for rosiglitazone compared with pioglitazone; however, risk was not significant in the fully adjusted model.

Strengths and weaknesses of the study

Our study of observational data in general practice allows assessment of the relative benefits and hazards of use of oral antidiabetes drugs in a “real world” clinical setting.

A diagnosis of cardiovascular disease in the general practice research database has been shown to have high validity.^{16,19} Our analyses of the database involved about three million intervals of drug treatments, with ascertainment of drug co-prescriptions and covariates at the beginning of each interval. This enabled us to account for switching of drugs and timing of treatments, make extensive adjustments for covariates, and provide prognostic information associated with different drug therapies. We used metformin monotherapy as a common reference group, in contrast with the meta-analyses of data from clinical trials that pooled results across studies with varying drug and non-drug reference groups, introducing possible heterogeneity into those analyses.

We assumed that a drug prescription interval equates to the patient taking the drug, whereas it is well known that there is variable adherence with prescribed treatments.²³ Also, we assumed that patients were prescribed more than one oral antidiabetes treatment if more than one drug was prescribed on the same date. In a few cases the second drug might have been prescribed some days later. On the basis that these assumptions lead to non-systematic misclassification errors, they may result in underestimation of true effects, although overestimation is also possible since, for example, specific groups of patients (with varying morbidities) may be more or less likely to comply with prescribed treatments.²³

As with any observational study, the possibility of residual confounding or confounding by indication (differences in prognostic factors between different drug groups) cannot be excluded. This may result in spurious associations of drug with events. We guarded against this possibility by careful sequential building of models, including a large number of potential confounders in our analyses, and we included fractures as a positive control because of the well known association with thiazolidinediones. We presented models both adjusted and unadjusted for potential confounders as some factors, such as body mass index, may be considered

Table 2 | Risk of a first episode of myocardial infarction among patients receiving rosiglitazone, pioglitazone, sulphonylureas, and other drugs and combinations compared with patients receiving metformin alone

Models and treatments	No of events	Hazard ratio (95% CI)	P value
Model 1 (2 761 889 intervals):			
First generation sulphonylureas	170	1.37 (1.15 to 1.62)	0.0003
Second generation sulphonylureas	1575	1.31 (1.21 to 1.43)	<0.001
Rosiglitazone	23	0.94 (0.62 to 1.43)	0.783
Rosiglitazone combination	83	1.08 (0.86 to 1.35)	0.524
Pioglitazone alone and combined	24	0.78 (0.52 to 1.17)	0.230
Other drugs and combinations	793	1.19 (1.08 to 1.31)	0.0007
Model 2 (2 761 889 intervals):			
First generation sulphonylureas	170	1.27 (1.07 to 1.50)	0.007
Second generation sulphonylureas	1575	1.25 (1.15 to 1.36)	<0.001
Rosiglitazone	23	0.97 (0.64 to 1.48)	0.902
Rosiglitazone combination	83	1.06 (0.84 to 1.33)	0.610
Pioglitazone alone and combined	24	0.78 (0.52 to 1.17)	0.224
Other drugs and combination	793	1.13 (1.02 to 1.25)	0.016
Model 3 (925 790 intervals):			
First generation sulphonylureas	27	1.36 (0.91 to 2.02)	0.130
Second generation sulphonylureas	365	1.09 (0.94 to 1.27)	0.266
Rosiglitazone	9	0.79 (0.41 to 1.53)	0.485
Rosiglitazone combination	29	0.82 (0.56 to 1.20)	0.310
Pioglitazone alone and combined	11	0.71 (0.39 to 1.30)	0.272
Other drugs and combinations	173	0.95 (0.79 to 1.15)	0.625

Model 1: adjusted for sex and duration of diabetes, stratified by year and quartiles of age at treatment. Model 2: model 1 plus previous peripheral arterial disease, previous cardiovascular disease, previous heart failure, aspirin, statin or fibrate, diuretics, calcium channel blockers, spironolactone, β adrenergic antagonists, angiotensin converting enzyme inhibitors or angiotensin II receptor blockers, nitrates, steroids, non-steroidal anti-inflammatory drugs, digoxin, and any previous complications from diabetes. Model 3: model 2 plus cholesterol concentration, body mass index, HbA_{1c} level, creatinine concentration, albumin concentration, systolic blood pressure, and smoking.

Table 3 | Risk of a first episode of congestive heart failure among patients receiving rosiglitazone, pioglitazone, sulphonylureas, and other drugs and combinations compared with patients receiving metformin alone

Models and treatments	No of events	Hazard ratio (95% CI)	P value
Model 1 (2 673 904 intervals):			
First generation sulphonylureas	520	1.46 (1.32 to 1.63)	<0.001
Second generation sulphonylureas	3276	1.30 (1.22 to 1.38)	<0.001
Rosiglitazone	38	1.00 (0.72 to 1.38)	0.990
Rosiglitazone combination	125	1.31 (1.09 to 1.58)	0.004
Pioglitazone alone and combined	48	1.18 (0.88 to 1.57)	0.270
Other drugs and combinations	1345	1.16 (1.08 to 1.26)	<0.001
Model 2 (2 673 904 intervals):			
First generation sulphonylureas	520	1.29 (1.17 to 1.44)	<0.001
Second generation sulphonylureas	3276	1.19 (1.12 to 1.27)	<0.001
Rosiglitazone	38	1.07 (0.77 to 1.48)	0.688
Rosiglitazone combination	125	1.27 (1.06 to 1.53)	0.011
Pioglitazone alone and combined	48	1.10 (0.83 to 1.47)	0.512
Other drugs and combinations	1345	1.08 (1.00 to 1.17)	0.043
Model 3 (909 367 intervals):			
First generation sulphonylureas	29	1.01 (0.70 to 1.47)	0.941
Second generation sulphonylureas	557	1.18 (1.04 to 1.34)	0.011
Rosiglitazone	10	0.61 (0.33 to 1.15)	0.128
Rosiglitazone combination	51	1.21 (0.91 to 1.63)	0.194
Pioglitazone alone and combined	24	1.17 (0.77 to 1.77)	0.456
Other drugs and combinations	227	1.06 (0.90 to 1.24)	0.505

Model 1: adjusted for sex and duration of diabetes, stratified by year and quartiles of age at treatment. Model 2: model 1 plus previous peripheral arterial disease, previous cardiovascular disease, previous heart failure, aspirin, statin or fibrate, diuretics, calcium channel blockers, spironolactone, β adrenergic antagonists, angiotensin converting enzyme inhibitors or angiotensin II receptor blockers, nitrates, steroids, non-steroidal anti-inflammatory drugs, digoxin, and any previous complications from diabetes. Model 3: model 2 plus cholesterol concentration, body mass index, HbA_{1c} level, creatinine concentration, albumin concentration, systolic blood pressure, and smoking.

intermediate factors and not confounders. False negative results were also possible owing to the reduction in sample size in the analyses adjusted for multiple covariates (model 3) where large numbers with missing data were excluded. Missing values in model 3 are assumed to be missing at random, since similar patient characteristics were shown in intervals with missing and non-missing values. Intervals missing not at random might affect the validity of results presented for model 3,²⁴ and thus these analyses need to be interpreted with caution.

A further issue is that during the period of the study noticeable falls in cardiovascular disease rates took place in the UK. This should not affect comparisons of sulphonylurea treatment with metformin, as both were routinely prescribed antidiabetes treatments in the UK throughout the period, nor of rosiglitazone with pioglitazone; however, it may affect comparisons of the thiazolidinediones with metformin, since the thiazolidinediones were not introduced into the UK until 2000. We addressed this concern by both stratifying by calendar year in all our analyses and restricting analyses to 2000 onwards; this did not materially affect our findings.

Results in context

Sulphonylureas

Monotherapy with either first or second generation sulphonylureas was associated with an excess risk of

mortality. Concerns about the safety of sulphonylureas were first raised by the University Group Diabetes Study, which showed increased numbers of deaths from cardiovascular disease among users of tolbutamide.²⁵ More recently, increased risk of all cause mortality by 43% and cardiovascular disease mortality by 70% have been reported among users of sulphonylureas compared with metformin,⁸ consistent with other observational studies.^{26,27} These findings contrast with results of the United Kingdom Prospective Diabetes Study, where there was no increase in cardiovascular events or death with sulphonylurea use compared with a conventional diet group among non-obese people (despite greater weight gain and higher insulin plasma concentrations with sulphonylurea therapy).²⁸ However, among a subgroup of obese participants randomised to metformin, sulphonylureas, insulin, or conventional therapy in the United Kingdom Prospective Diabetes Study, metformin was associated with a significantly lower all cause mortality than in the groups assigned intensive therapy with sulphonylureas ($P=0.021$).²⁹ Although A Diabetes Outcome Progression Trial (ADOPT) did not find a difference in cardiovascular event rates between groups treated with glibenclamide or metformin, the comparison had low power as it was not part of the study design.³⁰ Our study extends the evidence, suggesting higher mortality with sulphonylurea use than metformin use, among unselected patients attending general practice.

The mechanism by which commonly prescribed sulphonylureas (such as glibenclamide) may adversely affect cardiovascular risk and mortality is speculative, but a previously reported dose-response relation suggests a direct drug action.³¹ Sulphonylureas bind to a regulatory subunit of the inward rectifier potassium (K_{ATP}) channel, leading to an increase in intracellular potassium ion concentrations, the opening of voltage gated calcium channels, and an influx of calcium ions. In pancreatic β cells this promotes insulin secretion, but inhibition of K_{ATP} channels in cardiac myocytes and vascular smooth muscle cells impairs ischaemic preconditioning, a mechanism for protecting the myocardium from ischaemic injury.³²

Thiazolidinediones

We did not find evidence of an excess risk of myocardial infarction associated with rosiglitazone compared with metformin use. A meta-analysis of small clinical trials reported a significant 43% increased risk of myocardial infarction among rosiglitazone users compared with other drug groups,³ although reanalysis of these data yielded non-significant results.⁵ Although another meta-analysis reported a 31% increased risk in ischaemic heart disease, the risk for a cardiovascular composite end point was not significantly increased.³³ Both meta-analyses had limitations, including short follow-up, low event rates, no time to event data, incomplete outcome ascertainment, and heterogeneity of effects between the combined studies, and concerns have been raised about the ability of such meta-

analyses to detect rare cardiovascular events.³⁴ RECORD (Rosiglitazone Evaluated for Cardiovascular outcomes in Oral agent combination therapy for type 2 Diabetes) is an ongoing trial among 4447 patients with type 2 diabetes, designed to compare the effects of rosiglitazone in combination with metformin or sulphonylurea use compared with metformin and sulphonylureas in relation to cardiovascular disease. In a recent analysis by these researchers, over 5.5 years of follow-up, risks between the two groups were similar for the primary end point of death from cardiovascular causes or admission to hospital for a cardiovascular event (hazard ratio 0.99, 0.85 to 1.16).⁴ In the same analysis, findings were inconclusive for myocardial infarction, for which a non-significant increase for the rosiglitazone group was reported (1.14, 0.80 to 1.63). A further meta-analysis including the results from an interim analysis by RECORD, the ADOPT and DREAM (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication) clinical trials, and all small trials included in the previous meta-analysis,³ again suggested rosiglitazone was associated with an increased risk of myocardial infarction (odds ratio 1.33, 95% confidence interval 1.02 to 1.72).³⁵ Previous observational data are also conflicting; a significant 80% excess risk of myocardial infarction was reported among elderly patients associated with rosiglitazone use compared with other

oral hypoglycaemic agent combination therapies,⁷ whereas two other studies in patients with diabetes did not show an increased risk.^{13,14} Overall, to date there is no clear or consistent evidence on the possible cardiovascular benefits or harms of rosiglitazone therapy, and results of clinical trials are awaited.

The observed excess risk of congestive heart failure associated with rosiglitazone or pioglitazone use compared with metformin alone accords with previous evidence from clinical trials and observational studies.^{2,4,36} In the present study, pioglitazone was associated with lower mortality than metformin. Our results for pioglitazone are in good agreement with those from the PROspective PioglitAzone Clinical Trial In MacroVascular Events Study (PROACTIVE) trial, the largest randomised clinical trial of pioglitazone on cardiovascular disease reported to date.³⁷ Their findings showed that pioglitazone non-significantly reduced the risk of the composite primary end point of all macrovascular events and significantly reduced the risk of the predefined secondary end point of all cause mortality, myocardial infarction, or stroke (hazard ratio 0.84, 95% confidence interval 0.72 to 0.98).³⁷ Overall, the trial data suggest a possible cardiovascular protective effect of pioglitazone despite the increased risk of heart failure.⁶

In our study, mortality associated with pioglitazone was significantly lower than with rosiglitazone. Although both drugs are approved as “highly selective” peroxisome proliferator activated receptor γ agonists, recent studies suggest that pioglitazone represses key endothelial and hepatic inflammatory responses through peroxisome proliferator activated receptor α , an effect not apparently shared by rosiglitazone.³⁸ Furthermore, the molecular mechanisms underlying peroxisome proliferator activated receptor γ activation are complex, involving heterodimerisation, corepressors, and coactivators; minor differences in the ligand structure of peroxisome proliferator activated receptor γ could result in significant differences in target gene response.³⁹ Such pharmacological differences may translate into a differential effect on cardiovascular protection.⁴⁰⁻⁴³ It is already reported that pioglitazone has a more favourable effect on triglycerides and high density lipoprotein cholesterol concentrations than rosiglitazone.⁴⁴ Pioglitazone has been shown to decrease the rate of progression of carotid intima media thickness and of coronary atherosclerosis,^{45,46} suggesting a possible role in slowing the development of atherosclerotic plaque.

Conclusions and clinical implications

The sulphonylureas, along with metformin, have long been considered the mainstay of drug treatment for type 2 diabetes. Our findings suggest a relatively unfavourable risk profile of sulphonylureas compared with metformin. This is consistent with the recommendations of the American Diabetes Association and International Diabetes Federation that favour metformin as the initial treatment for type 2 diabetes.^{21,22} Within class differences in risk among the sulphonylureas

Table 4 | Risk for all cause mortality among patients receiving rosiglitazone, pioglitazone, sulphonylureas, and other drugs and combinations compared with patients receiving metformin alone

Models and treatments	No of events	Hazard ratio (95% CI)	P value
Model 1 (2 842 504 intervals):			
First generation sulphonylureas	1341	1.61 (1.49 to 1.74)	<0.001
Second generation sulphonylureas	9606	1.55 (1.48 to 1.62)	<0.001
Rosiglitazone	83	1.00 (0.78 to 1.28)	0.990
Rosiglitazone combination	244	0.80 (0.70 to 0.93)	0.003
Pioglitazone alone and combined	71	0.61 (0.47 to 0.80)	0.0003
Other drugs and combinations	3291	1.03 (0.98 to 1.09)	0.271
Model 2 (2 842 504 intervals):			
First generation sulphonylureas	1341	1.43 (1.33 to 1.54)	<0.001
Second generation sulphonylureas	9606	1.40 (1.34 to 1.47)	<0.001
Rosiglitazone	83	0.92 (0.72 to 1.17)	0.489
Rosiglitazone combination	244	0.88 (0.76 to 1.02)	0.078
Pioglitazone alone and combined	71	0.62 (0.48 to 0.81)	0.0004
Other drugs and combinations	3291	1.01 (0.96 to 1.07)	0.664
Model 3 (928 702 intervals):			
First generation sulphonylureas	101	1.37 (1.11 to 1.71)	0.0003
Second generation sulphonylureas	1379	1.24 (1.14 to 1.35)	<0.001
Rosiglitazone	34	1.07 (0.77 to 1.49)	0.740
Rosiglitazone combination	89	0.88 (0.71 to 1.09)	0.070
Pioglitazone alone and combined	31	0.69 (0.49 to 0.98)	0.024
Other drugs and combinations	539	0.99 (0.89 to 1.11)	0.927

Model 1: adjusted for sex and duration of diabetes, stratified by year and quartiles of age at treatment. Model 2: model 1 plus previous peripheral arterial disease, previous cardiovascular disease, previous heart failure, aspirin, statin or fibrate, diuretics, calcium channel blockers, spironolactone, β adrenergic antagonists, angiotensin converting enzyme inhibitors or angiotensin II receptor blockers, nitrates, steroids, non-steroidal anti-inflammatory drugs, digoxin, and any previous complications from diabetes. Model 3: model 2 plus cholesterol concentration, body mass index, HbA_{1c} level, creatinine concentration, albumin concentration, systolic blood pressure, and smoking.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Oral antidiabetes drugs are commonly used for glycaemic control; however, concerns are that some may increase cardiovascular risk

Their relative benefits and disadvantages to cardiovascular health are not well established

Analyses of observational data examining risks associated with antidiabetes drugs among patients in primary care are limited

WHAT THIS STUDY ADDS

Our findings suggest a relatively unfavourable risk profile of sulphonylureas compared with metformin

The findings support recommendations of the American Diabetes Association and International Diabetes Federation that favour metformin as the initial treatment for type 2 diabetes

Pioglitazone was associated with reduced all cause mortality compared with metformin and it had a favourable risk profile compared with rosiglitazone

were not observed. We do not confirm previous reports of an excess risk of myocardial infarction associated with rosiglitazone compared with metformin. Pioglitazone was associated with reduced all cause mortality compared with metformin, and it had a favourable risk profile compared with rosiglitazone, which requires replication in other studies. This may have implications for prescribing within this class of drugs.

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Ethical approval: The GPRD Group has obtained ethical approval from a multicentre research ethics committee for all purely observational research using anonymised records from the general practice research database. This study was approved by the general practice research database Independent Scientific Advisory Committee.

Data sharing: The technical appendix and statistical code (through permission of the general practice research database) are available from the corresponding author.

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