Pioglitazone use and bladder cancer risk: a population-based cohort study

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Pioglitazone use and bladder cancer risk: a population-based cohort study

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ABSTRACT

OBJECTIVE: To determine whether the use of pioglitazone, when compared with the use of other antidiabetic drugs, is associated with an increased risk of bladder cancer in patients with type 2 diabetes.

DESIGN: Population-based cohort study.

SETTING: General practices contributing data to the United Kingdom Clinical Practice Research Datalink.

PARTICIPANTS: A cohort of 145,806 patients newly-treated with antidiabetic drugs between January 1, 2000 and July 31, 2013, with follow-up until July 31, 2014.

MAIN OUTCOME MEASURES: The use of pioglitazone was treated as a time-varying variable, with exposure lagged by one year for latency purposes. Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) of incident bladder cancer associated with the use of pioglitazone overall, by cumulative duration of use, and by cumulative dose. Similar analyses were conducted for rosiglitazone, a thiazolidinedione not previously associated with an increased risk of bladder cancer.

RESULTS: The cohort generated 689,616 person-years of follow-up, during which 622 patients were newly-diagnosed with bladder cancer (crude incidence rate: 90.2 per 100,000 person-years). Compared with the use of other antidiabetic drugs, the use of pioglitazone was associated with an increased risk of bladder cancer (121.0 vs 88.9 per 100,000 person-years; HR: 1.63, 95% CI: 1.22 to 2.19). Conversely, the use of rosiglitazone was not associated with an increased risk of bladder cancer (88.9 vs 86.2 per 100,000 person-years; HR: 1.10; 95% CI: 0.83 to 1.47). Duration- and dose-response relationships were observed for pioglitazone, but not for rosiglitazone.

CONCLUSIONS: The results of this large population-based study indicate that the use of pioglitazone is associated with an increased risk of bladder cancer. The absence of an association with rosiglitazone suggests that the increased risk is drug-specific and not a class effect.

INTRODUCTION

Pioglitazone, an antidiabetic drug belonging to the thiazolidinedione (TZD) class, has been shown to improve glycaemic levels in patients with type 2 diabetes.[1] However, in 2005, the PROactive randomized controlled trial (RCT) unexpectedly showed an imbalance in the number of bladder cancer cases with pioglitazone compared to placebo.[2] In contrast, this imbalance was never observed in RCTs of rosiglitazone, the other drug belonging to the TZD class.[1 3]

The findings of the PROactive trial were subsequently corroborated in some,[4-10] but not in all observational studies.[11-19] Indeed, in the interim analysis of a large observational study using the Kaiser Permanente Northern California (KPNC) database,[4] the use of pioglitazone for ≥ 24 months was associated with an increased risk of bladder cancer (hazard ratio [HR]: 1.4, 95% confidence interval [CI]: 1.03 to 2.0). However, in the final analysis of the KPNC study, which used the same cohort[4] but with an extended follow-up, the use of pioglitazone was no longer significantly associated with an increased risk of bladder cancer in a duration-response fashion.[20] These null findings are also consistent with those of another large multi-cohort study.[19] The apparent heterogeneity among these studies may be due to methodological limitations, such as the inclusion of prevalent users,[5 6 10-14 18] time-lag bias,[15] immortal time bias,[10 14 18] and no consideration of disease latency.[8 10 12 17 18]

Given these discrepant findings and continued uncertainty regarding the safety of pioglitazone, additional studies are needed to further investigate the association between this drug and bladder cancer. Thus, the objective of this large, population-based study was to assess the association between the use of pioglitazone and bladder cancer in patients with type 2 diabetes.

METHODS

Data source

This study was conducted using the United Kingdom (UK) Clinical Practice Research Datalink (CPRD). This database contains the complete primary care medical record of over 13 million individuals.[21] The Read code classification is used to record medical diagnoses and procedures, and a coded drug dictionary based on the UK Prescription Pricing Authority Dictionary is used to record prescriptions. The CPRD collects information on anthropometric variables, such as body mass index (BMI), and lifestyle variables such as smoking and alcohol use. Data collected in the CPRD have been previously validated and demonstrated to be of high quality.[22 23] Furthermore, cancer records have been shown to be highly consistent with those recorded in the UK National Cancer Data Repository.[24]

The study protocol, which was made available to the journal reviewers, was approved by the Independent Scientific Advisory Committee of the CPRD (protocol 11_099A) and by the Research Ethics Board of the Jewish General Hospital, Montreal, Canada.

Study population

Base cohort

We assembled a base cohort composed of all patients newly-treated for type 2 diabetes, defined as receiving a first-ever prescription for a non-insulin antidiabetic drug (metformin, sulfonylureas, prandial glucose regulators, TZDs, acarbose, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide (GLP-1) agonists, sodium-glucose co-transporter-2 (SGLT2) inhibitors) between January 1, 1988 and July 31, 2013. All patients were required to be at least 40 years of age, and have at least one year of CPRD medical history before that first prescription. We excluded patients prescribed insulin any time before their first non-insulin antidiabetic

prescription (as these likely represent those with an advanced form of type 2 diabetes), and patients diagnosed with gestational diabetes and polycystic ovary syndrome (as these are other indications for metformin).

Study cohort

Using the base cohort defined above, we identified all patients who initiated a new antidiabetic drug class on or after January 1, 2000 (the year pioglitazone and rosiglitazone entered in the UK market) until July 31, 2013. These patients included those newly-treated with an antidiabetic drug class, as well as those who switched to or added-on an antidiabetic drug class not previously used in their treatment history. Cohort entry was defined by the date of this new prescription. We excluded all patients diagnosed with bladder cancer (including malignant, in situ, and benign lesions) at any time before cohort entry, as well as those with less than one year of follow-up after cohort entry. The latter was necessary for latency considerations, as short term exposures are unlikely to be associated with incident bladder cancer.

All patients were followed starting the year after cohort entry until a first-ever diagnosis of bladder cancer (malignant and in situ), or censored upon death from any cause, end of registration with the general practice, or end of the study period (July 31, 2014), whichever occurred first.

Exposure to thiazolidinediones

The use of TZDs was entered as a time-varying variable in the models, and classified according to one of the following four mutually-exclusive categories: pioglitazone use, rosiglitazone use, pioglitazone and rosiglitazone use (mainly switchers), and no TZD use.

Patients were considered unexposed to TZDs until the time of the first TZD prescription and considered exposed thereafter, after accounting for a one-year lag period. This lag period was necessary to take into account a latency time window and minimize possible detection bias around the time of treatment initiation. This was considered the primary exposure definition.

In secondary analyses, we determined whether there was a duration- and dose-response relationship between the use of pioglitazone and bladder cancer incidence. The duration-response relationship was assessed in terms of cumulative duration of use, which was defined, in a time-dependent fashion, as the total number of years of use, calculated by summing the durations of all prescriptions received between cohort entry and the time of the event. This variable was then classified using the same categories used in the interim analysis of KPNC study[4]: <1 year, 1 to 2 years, and >2 years of use. Cumulative duration was also assessed on a continuous scale using a restricted cubic spline model with five knots.[25] Dose-response was assessed in terms of cumulative-dose, which was calculated, in a time-dependent fashion, as the sum of all doses received up until the date of the event. This variable was also categorized using the same cut-offs used in previous studies[4 5]: ≤ 10,500 mg, 10,501-28,000 mg, and > 28,000 mg. Linear trend for cumulative duration of use and dose were assessed by considering these variables as continuous in the models.

For comparison purposes, we also assessed whether there was a duration- and dose-response relationship with the use of rosiglitazone, in terms of cumulative duration of use (categorically [< 1 year, 1 to 2 years, and >2 years] and continuously using restricted cubic spline modelling) and cumulative dose (categorized on the basis of the tertile distribution of use in the cohort).

Potential confounders

All models were adjusted for the following variables measured at cohort entry: age, sex, year of cohort entry, BMI, smoking status, alcohol-related disorders (based on diagnoses for alcoholism, alcoholic cirrhosis of the liver, alcoholic hepatitis and failure, and other related disorders), haemoglobin A1c (last recorded value before cohort entry), duration of treated diabetes (defined as the time between the first-ever non-insulin prescription and cohort entry), prior bladder conditions (such as cystitis and bladder stones), history of cancer (other than non-melanoma skin cancer), presence of at least one urine protein test in the year before cohort entry, and Charlson comorbidity score[26] (adapted not to include previous cancer to avoid duplicate adjustments).

Statistical analysis

Descriptive statistics were used to summarize the characteristics of pioglitazone users, rosiglitazone users, and non-TZD users at cohort entry. We calculated crude incidence rates of bladder cancer, with 95% CIs based on the Poisson distribution for each exposure category.

Time-dependent Cox proportional hazards models were used to estimate adjusted HRs and 95% CIs for bladder cancer associated with the use of pioglitazone compared with no TZD use. We also conducted two secondary analyses to assess whether there were duration- and dose-response relationships with the use of pioglitazone and bladder cancer risk in terms of cumulative duration of use and cumulative dose (as defined above). Identical analyses were conducted for rosiglitazone. All models accounted for competing risks due to death from any cause using the model proposed by Fine and Gray.[27]

Sensitivity analyses

We conducted five sensitivity analyses to assess the robustness of our findings. First, given uncertainties related to the latency time window, we repeated the primary analysis with lag periods of 0 and 2 years. Second, the primary analysis was repeated after additionally censoring upon a new diagnosis of benign bladder lesions, in situ bladder cancer, liver failure and heart failure (the latter two were also additional exclusion criteria). Indeed, TZDs are contraindicated or not recommended for the two latter conditions, the presence of which may lead to TZD discontinuation or may influence treatment decisions. Third, in 2011, several regulatory actions were issued as a consequence of the potential association between pioglitazone and bladder cancer.[28] We performed a sensitivity analysis censoring follow-up to December 31, 2010, as it is possible that patients initiating or continuing pioglitazone after that date may have been more carefully screened for bladder cancer. Fourth, the models were additionally adjusted for the time-dependent use of other anti-diabetic drugs (metformin, sulfonylureas, incretin-based drugs, insulin, and other oral hypoglycaemic drugs) during follow-up, lagged by one year for latency considerations. Finally, we assessed the strength of an unmeasured confounder needed to move the estimated HR to the null using the "Rule Out" method proposed by Schneeweiss.[29]

Head-to-head comparison of pioglitazone versus rosiglitazone

To further assess whether an association between pioglitazone and bladder cancer is a drug-specific versus a class effect, we conducted two additional analyses that directly compared pioglitazone with rosiglitazone. In the first approach, the use of pioglitazone was contrasted with the use of rosiglitazone by setting the latter as the reference category in the model. In the second approach, we used the study cohort to assemble a sub-cohort of patients initiating pioglitazone or

rosiglitazone between January 1, 2000 and July 31, 2013, with follow-up until July 31, 2014. As with the primary analysis, all patients were required to have at least one year of follow-up after their first TZD prescription. Consequently, cohort entry was set as the year after the first TZD prescription during the study period. All patients were followed until a first-ever diagnosis of bladder cancer, or censored upon death from any cause, switching to another TZD, end of registration with the general practice, or end of the study period, whichever occurred first. The model was adjusted for high-dimensional propensity scores (HDPS),[30] which included the pre-specified variables listed above along with another 500 empirically-defined variables measured at the time of the first TZD prescription. All analyses were conducted with SAS version 9.4 (SAS Institute, Cary, NC).

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in the design and implementation of the study. There are no plans to involve patients in the dissemination of results.

RESULTS

A total of 145,806 patients met the study inclusion criteria (Supplementary Figure 1). Overall, the cohort was followed for a mean (standard deviation) of 4.7 (3.4) years, generating 689,616 person-years of follow-up. A total of 622 patients were diagnosed with bladder cancer during follow-up, yielding a crude incidence rate of 90.2 (95% CI: 83.2 to 97.6) per 100,000 person-years.

Table 1 presents the characteristics of the cohort overall and stratified by pioglitazone users versus non TZD users at baseline. Compared with non TZD users, pioglitazone users were less likely to be obese, but more likely to have elevated haemoglobin A1c levels, to have undergone urine protein testing before cohort entry, had a longer duration of treated diabetes, and were more likely to have prior bladder conditions. Pioglitazone users were also more likely to have been exposed to sulfonylureas and less likely to have received metformin compared with non-users of TZDs. The baseline characteristics of rosiglitazone users are similar and shown in Supplementary Table 1.

Table 2 shows the results of the primary and secondary analyses for pioglitazone. Overall, compared with no TZD use, the use of pioglitazone was associated with an increased risk of incident bladder cancer (121.0 vs 88.9 per 100,000 person-years; adjusted HR: 1.63; 95% CI: 1.22 to 2.19). A duration-response relationship was observed (p-trend=0.0009) with use of pioglitazone for >2 years associated with an increased risk of bladder cancer (adjusted HR: 1.78; 95% CI: 1.21 to 2.64). In the restricted cubic spline analysis, the risk of bladder cancer was increased risk after 1.8 years of use, and continued to increase with longer durations of use, although this did not achieve statistical significance due to relatively small number of events among patients with longer duration of use (Figure 1). A dose-response relationship was also

present (p-trend=0.01) with cumulative doses below 10,500 mg (adjusted HR: 1.63; 95% CI: 1.02 to 2.60) and above 28,000 mg (adjusted HR: 1.70; 95% CI: 1.04 to 2.78) being associated with an increased risk of bladder cancer.

Overall, the use of rosiglitazone was not associated with an increased risk of incident bladder cancer (88.9 vs 86.2 per 100,000 person-years, adjusted HR: 1.10; 95% CI: 0.83 to 1.47; Supplementary Table 2). Similarly, there was no evidence of a duration-response relationship in terms of cumulative duration of use when it was classified as a categorical variable (p-trend=0.69; Supplementary Table 2) or when it was considered as a continuous variable (Supplementary Figure 2). Finally, there was no evidence of a dose-response relationship in terms of cumulative dose (p-trend=0.72; Supplementary Table 2)

Sensitivity analyses

The results of the sensitivity analyses are summarized in Figure 2 and presented in Supplementary Tables 3 and 4. In all sensitivity analyses, the use of pioglitazone was consistently associated with an increased risk of bladder cancer, with adjusted HRs ranging between 1.49 and 1.73. In contrast, the use of rosiglitazone was not associated with an increased risk of bladder cancer, with adjusted HRs ranging between 1.02 and 1.16 and all estimates accompanied by 95% CIs that include unity. Supplementary Figure 3 shows all the exposure-confounder and confounder-disease associations (right of the curve) necessary to bring down the observed HR of 1.63 down to the null.

Head-to-head comparison of pioglitazone versus rosiglitazone

Table 3 presents the results of the pioglitazone versus rosiglitazone comparisons. In the first of these analyses (main model), the use of pioglitazone was associated with increased risk of bladder cancer when compared with rosiglitazone (adjusted HR: 1.48; 95% CI: 1.01 to 2.16). Similar findings were observed in the second analysis conducted within the TZD sub-cohort (HDPS-adjusted HR: 1.46; 95% CI: 0.94 to 2.27; Supplementary Figure 4 and Supplementary Table 5 for cohort description).

DISCUSSION

Principal findings

In this large population-based cohort study with up to 15 years of follow-up, the use of pioglitazone was associated with an overall 63% increased risk of incident bladder cancer. There was also evidence of a duration- and dose-response relationship. In contrast, the use of rosiglitazone was not associated with an increased risk of bladder cancer either overall or by cumulative duration of use and dose. Overall, our findings remained consistent in several sensitivity analyses.

Strengths and weaknesses of our study

This study has a number of strengths. First, we assembled a large population-based cohort of patients newly-treated with antidiabetic drugs, followed for up to 15 years, thus enabling the identification of a substantial number of bladder cancer cases. Second, the inclusion of new users eliminated biases related to prevalent users.[31] Third, we considered a lag period to account for a minimum latency between exposure to TZDs and the development of bladder cancer. Fourth, exposure was defined in a time-dependent fashion, thereby eliminating immortal time bias.[32] Fifth, all analyses took into account competing risks due to deaths from any cause, an important consideration given the cardiovascular risk reported for TZDs in previous studies.[1] Finally, the results remained consistent in several sensitivity analyses, thus confirming the robustness of our findings.

This study has some limitations. First, residual confounding due to unmeasured variables (e.g. diet, physical activity, family history of cancer, and race/ethnicity) is possible. However, the "Rule Out" method[29] shows that a hypothetical unmeasured confounder would need to be strongly associated with both the exposure (OR>3.7) and the outcome (OR>5.0) to move the

point estimate down to the null. As the aforementioned variables are modestly associated with the outcome and it is unclear if they are associated with the exposure, we do not believe that such possible residual confounding is a likely explanation for the observed association. Second, exposure misclassification is possible, since the CPRD records prescriptions written by general practitioners, and not those filled or taken by patients. Such non-differential misclassification between the exposure groups would lead to an underestimation of the association. Finally, although cancer has been shown to be well recorded in the CPRD,[24] misclassification is possible. However, we expect this potential misclassification to be non-differential between patients exposed to the different antidiabetic drugs included in the study.

Comparison with other studies

Several observational studies have investigated the association between pioglitazone and bladder cancer.[4-19] Overall, these studies have generated conflicting findings, with seven studies reporting statistically significant increased risks[4-10] (ranging from 20% to 225%), versus nine reporting null associations.[11-19] The discrepancy between these studies is likely due to certain methodological shortcomings. Indeed, in three studies,[10 14 18] the exposure definition likely introduced immortal time bias which may have led to a spurious underestimate of the association. In another study,[15] time-lag bias was introduced by comparing pioglitazone with insulin, the latter being an exposure typically used at a more advanced stage of the disease where the risk of cancer, including bladder cancer, may be higher. Prevalent users of antidiabetic drugs were included in 11 studies,[4-6 10-14 18-20] which can be problematic in this context given the relatively rapid onset of bladder cancer after pioglitazone initiation. Finally, in five studies,[8 10 12 17 18] a minimum time between the initiation of pioglitazone and the diagnosis of bladder cancer

was not considered in the analyses, an important consideration given the latency of bladder cancer.

Biological plausibility and implications

The biological plausibility of a rapid development of bladder cancer after pioglitazone initiation has been debated, since many events observed in the PROactive trial occurred within one year of treatment initiation.[33] It is possible that these were prevalent cases and not attributable to the use of pioglitazone,[33] or promoted by pioglitazone in patients susceptible to developing bladder cancer.[34] In our study, the use of a one-year lag period ensured that all bladder cancer events had to occur at least one year after treatment initiation. However, in sensitivity analyses, removing the lag period attenuated the HR (HR: 1.49; 95% CI: 1.13 to 1.97) while applying a two-year lag period increased the HR (HR: 1.73; 95% CI: 1.26 to 2.39). Moreover, when assessed in restricted cubic spline model, the risk tended to increase with longer durations of use. Taken together, our findings do not rule out a tumour promoting effect, but also suggest that the risk may increase with longer use.

An important finding of our study is the absence of an association between rosiglitazone and bladder cancer. It is important to note that both pioglitazone and rosiglitazone entered the UK market the same year (2000) and both were intended for the same target population.[35] Given their similarities, it is unlikely that confounding by indication or detection bias can explain the association observed with pioglitazone. In the head-to-head comparison, pioglitazone was associated with close to a 50% increased risk of bladder cancer when compared with rosiglitazone. Of note, although the biological mechanism for pioglitazone-induced bladder cancer is not clear, this imbalance in the risk of bladder cancer between these two TZDs could

likely be explained by pharmacological differences. Indeed, unlike rosiglitazone, which is selective for the peroxisome proliferator activated receptor (PPAR) γ, pioglitazone has a dual PPARα/γ activity.[36 37] This is particularly important, as PPARα/γ activation in rat models has shown to increase the expression of carcinogenic biomarkers in the bladder, which has not been observed with the selective activation of PPARγ.[38-40] While differences in PPAR activity is a possible explanation for the observed association, additional studies are needed to better understand the biological mechanism behind the possible pioglitazone-specific effect on the bladder.

Conclusions

In conclusion, the findings of this population-based study indicate that the use of pioglitazone is associated with an increased risk of bladder cancer, which varies in a duration- and dose-dependent fashion. In contrast, rosiglitazone was not associated with an increased risk of bladder cancer in any analysis, suggesting the risk is drug-specific and not a class effect.

What is already known on this subject

- The association between the use of pioglitazone and bladder cancer is controversial, with studies reporting contradictory findings
- Additional observational studies are needed to assess whether this drug is associated with an increased risk of bladder cancer

What this study adds

- In this large population-based study, the use of pioglitazone was associated with an overall 63% increased risk of bladder, with evidence of duration- and dose-dependent relationships
- In contrast, the use of rosiglitazone was not associated with an increased risk, whether overall, or by duration or dose
- These findings suggest that the association observed with pioglitazone is likely to be a drug-specific and not a class effect

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COMPETING INTEREST STATEMENT

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that none of the authors have conflicts of interest to disclose.

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LA is the guarantor.

DETAILS OF ETHICAL APPROVAL

The study protocol was approved by the Independent Scientific Advisory Committee of the CPRD (protocol 11_099A) and by the Research Ethics Board of the Jewish General Hospital, Montreal, Canada.

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TRANSPARENCY DECLARATION

The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

*The manuscript's guarantor.

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FIGURES LEGENDS

Figure 1: Smooth restricted spline curve of the adjusted hazard ratio of bladder cancer (solid line) and 95% confidence limits (dashed lines) as a function of the cumulative duration of use of pioglitazone

Figure 2: Forest plot for primary and sensitivity analyses displaying adjusted HRs for the association between pioglitazone use and rosiglitazone use and the risk of bladder cancer.

*Benign bladder lesions, in situ bladder cancer, heart failure, and liver failure.

Table 1: Baseline characteristics of the cohort overall, and stratified by users and non-users of pioglitazone

Characteristics	Entire cohort (n=145,806)	Pioglitazone [a] (n=921)	No TZD use [b] (n=142,758)
Male, n (%)	82,824 (56.8)	543 (59.0)	81,114 (56.8)
Age (years), mean (SD)	63.7 (11.7)	64.6 (10.6)	63.7 (11.7)
Year of cohort entry, n (%)			
2000	8167 (5.6)	S*	7970 (5.6)
2001	9445 (6.5)	126 (13.7)	8938 (6.3)
2002	9604 (6.6)	120 (13.0)	9224 (6.5)
2003	10,393 (7.1)	114 (12.4)	10,040 (7.0)
2004	12,141 (8.3)	138 (15.0)	11,624 (8.1)
2005	11,683 (8.0)	106 (11.5)	11,273 (7.9)
2006	11,126 (7.6)	84 (9.1)	10,810 (7.6)
2007	11,657 (8.0)	64 (7.0)	11,477 (8.0)
2008	11,731 (8.1)	53 (5.8)	11,664 (8.2)
2009	12,445 (8.5)	50 (5.4)	12,391 (8.7)
2010	12,035 (8.3)	36 (3.9)	11,995 (8.4)
2011	10,659 (7.3)	14 (1.5)	10,645 (7.5)
2012	10,110 (6.9)	9 (1.0)	10,101 (7.1)
2013	4610 (3.2)	S*	4606 (3.2)
Body mass index, n (%)			
<30 kg/m^2	67,621 (46.4)	479 (52.0)	66,152 (46.3)
≥30 kg/m^2	76,627 (52.6)	433 (47.0)	75,076 (52.6)
Unknown	1558 (1.1)	9 (1.0)	1530 (1.1)
Smoking, n (%)			
Ever	85,032 (58.3)	523 (56.8)	83,342 (58.4)
Never	57,283 (39.3)	384 (41.7)	55,982 (39.2)
Unknown	3491 (2.4)	14 (1.5)	3434 (2.4)
Alcohol-related disorders, n (%)	15,491 (10.6)	80 (8.7)	15,240 (10.7)
Haemoglobin A1c, n (%)			
≤7.4 %	27,209 (18.7)	148 (16.1)	26,793 (18.8)
>7.4 %	68,309 (46.9)	537 (58.3)	66,485 (46.6)
Unknown	50,288 (34.5)	236 (25.6)	49,480 (34.7)
Duration of treated diabetes (years), mean (SD)	0.3 (1.6)	4.2 (4.6)	0.3 (1.3)
Prior bladder conditions, n (%)	13,755 (9.4)	113 (12.3)	13,415 (9.4)
Cancer, n (%)	13,908 (9.5)	76 (8.3)	13,646 (9.6)
Urine protein test, n (%)	62,729 (43.0)	491 (53.3)	61,072 (42.8)
Charlson comorbidity score [c], mean (SD)	2.0 (1.3)	2.2 (1.4)	2.0 (1.3)
Previous antidiabetic drug use, n (%) [d]			
Metformin	122,843 (84.3)	497 (54.0)	120,765 (84.6)
Sulfonylureas	31,825 (21.8)	433 (47.0)	30,217 (21.2)
Pioglitazone	921 (0.6)	921 (100.0)	0 (0.0)
Rosiglitazone	2127 (1.5)	0 (0.0)	0 (0.0)
Incretin-based drugs	375 (0.3)	0 (0.0)	375 (0.3)
Insulins	1467 (1.0)	14 (1.5)	1435 (1.0)
Others	1406 (1.0)	45 (4.9)	1217 (0.9)

Abbreviations: S: suppressed SD: standard deviation; TZDs: thiazolidinediones

* Numbers less than 5 are not displayed, as per the confidentiality policies of the Clinical Practice Research Datalink.

[a] Pioglitazone only users at cohort entry

[b] No use of any TZD at cohort entry

[c] Including myocardial infarction, congestive heart failure, peripheral vascular disease, chronic pulmonary disease, cerebrovascular disease, dementia, peptic ulcer disease, diabetes-related chronic complications, connective tissue disease, mild liver disease, hemiplegia or paraplegia, renal disease, moderate to severe liver disease, acquired immuno-deficiency syndrome (AIDS). Adapted to exclude cancer.

[d] Non-mutually exclusive categories; antidiabetic drugs received ever before and including cohort entry.

Table 2: Hazard ratios for the association between pioglitazone use and the risk of bladder cancer

Exposure [a]	Events	Person-years	Incidence rate (95% CI) [b]	Age-and-sex-adjusted HR (95% CI)	Fully adjusted HR (95% CI) [c]
Primary analysis					
No TZD use [d]	497	558,924	88.9 (81.3 to 97.1)	1.00 [Reference]	1.00 [Reference]
Pioglitazone	54	44,618	121.0 (90.9 to 157.9)	1.68 (1.26 to 2.24)	1.63 (1.22 to 2.19)
Cumulative duration					
≤ 1 year	11	12,031	91.4 (45.6 to 163.6)	1.35 (0.74 to 2.46)	1.33 (0.73 to 2.40)
1-2 years	14	11,583	120.9 (66.1 to 202.8)	1.70 (1.00 to 2.91)	1.66 (0.97 to 2.84)
> 2 years	29	21,004	138.1 (92.5 to 198.3)	1.84 (1.25 to 2.71)	1.78 (1.21 to 2.64)
p-trend				0.0004	0.0009
Cumulative dose					
≤10,500 mg	18	15,646	115.0 (68.2 to 181.8)	1.66 (1.04 to 2.67)	1.63 (1.02 to 2.60)
10,500-28,000 mg	18	15,356	117.2 (69.5 to 185.3)	1.62 (1.01 to 2.61)	1.58 (0.98 to 2.55)
>28,000 mg	18	13,616	132.2 (78.3 to 208.9)	1.76 (1.08 to 2.87)	1.70 (1.04 to 2.78)
p-trend				0.0004	0.001

Abbreviations: CI, confidence interval, HR, hazard ratio, TZD: Thiazolidinediones

[a] Users of rosiglitazone and combination of pioglitazone and rosiglitazone are not displayed in the table, but were considered in the regression model for proper estimation of treatment effects.

[b] Per 100,000 person-years.

[c] Adjusted for age, year of cohort entry, sex, alcohol-related disorders, smoking status, obesity, haemoglobin A1c, previous cancer, bladder conditions, Charlson comorbidity score, duration of treated diabetes, urine protein test.

[d] No use of pioglitazone or rosiglitazone.

Table 3: Hazard ratios for the association between pioglitazone use and the risk of bladder cancer compared with rosiglitazone use

Exposure	Patients [a]	Events	Person-years	Incidence rate (95% CI) [b]	Adjusted HR (95% CI)
Main model [c, d]					
Rosiglitazone	-	56	64,990	86.2 (65.1 to 111.9)	1.00 [Reference]
Pioglitazone	-	54	44,618	121.0 (90.9 to 157.9)	1.48 (1.01 to 2.16)
Thiazolidinedione sub to cohort analysis [e,f]					
Rosiglitazone	13,946	56	64,942	86.2 (65.1 to 112.0)	1.00 [Reference]
Pioglitazone	10,591	52	44,080	118.0 (88.1 to 154.7)	1.46 (0.94 to 2.27)

Abbreviations: CI: confidence interval; HR: hazard ratio

[a] The number of patients in the main analysis is not displayed as the exposure was defined in a time-dependent fashion.

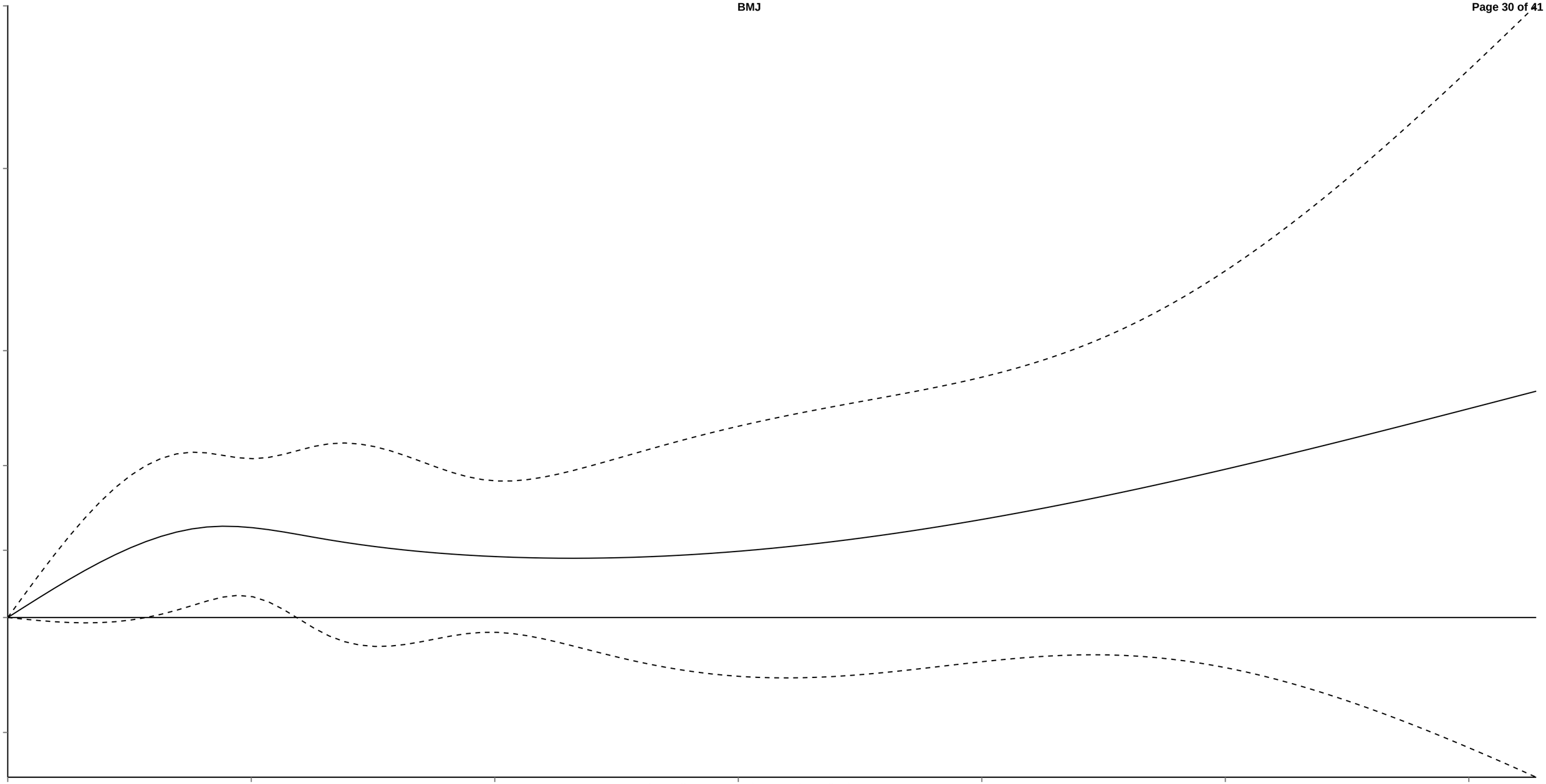
[b] Per 100,000 person to years.

[c] Users of pioglitazone to rosiglitazone combinations and no TZD users are not displayed in the table, but were considered in the regression model for proper estimation of treatment effects

[d] Adjusted for age, year of cohort entry, sex, alcohol to related disorders, smoking status, obesity, haemoglobin A1c, previous cancer, bladder conditions, Charlson comorbidity score, duration of treated diabetes, and urine protein testing.

[e] Two bladder cancer events were excluded from the pioglitazone group due to trimming related to non to overlapping propensity score distributions.

[f] Adjusted for high-dimensional propensity score quintiles.


40.0
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8
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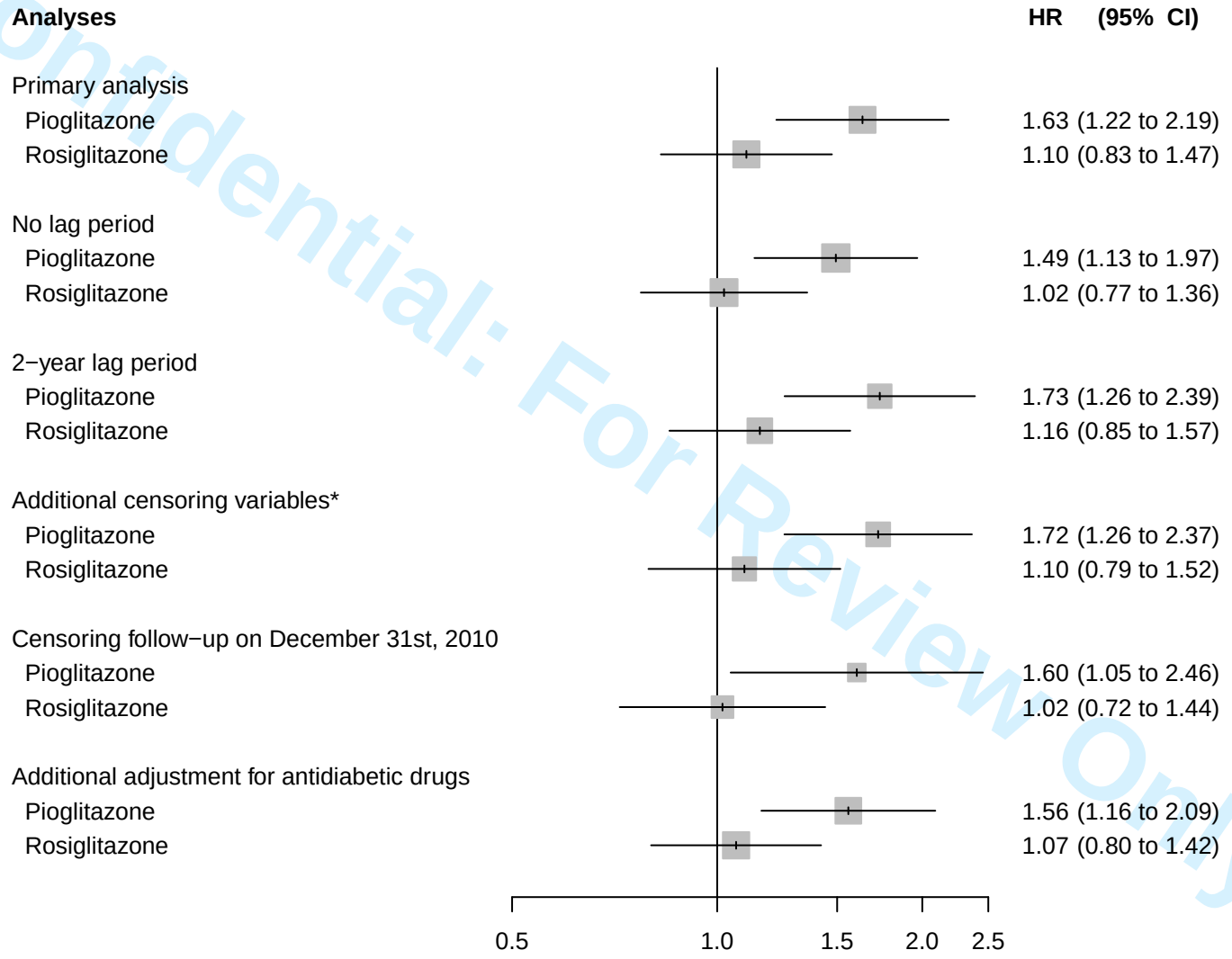
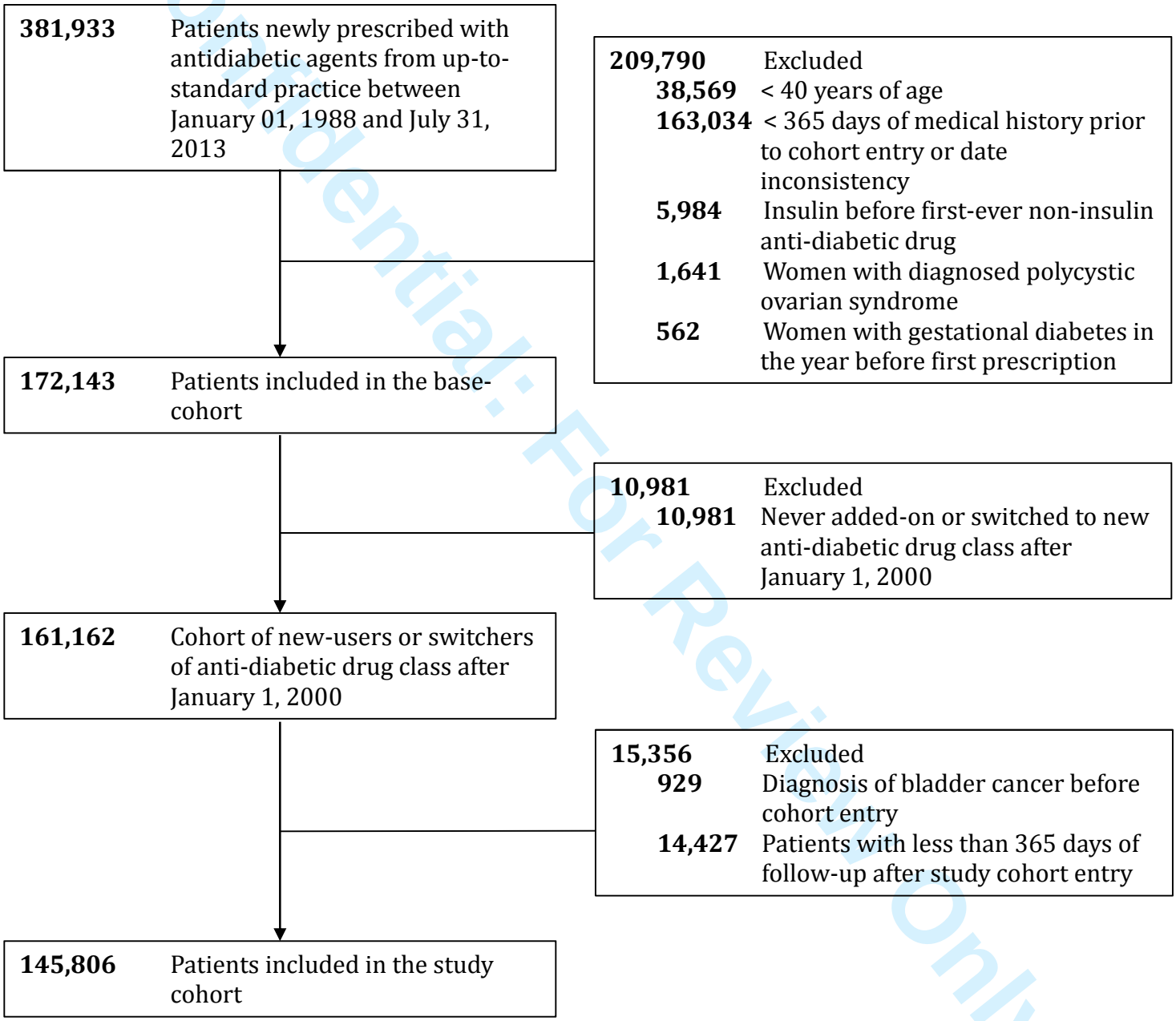
12
Cumulative duration of use of pioglitazone (years)



Pioglitazone use and bladder cancer risk: a population-based cohort study

Online supplementary material

Supplementary Figure 1: Study flow chart of patients initiating an antidiabetic between January 1, 1988 and July 31, 2013



Supplementary Table 1. Baseline characteristics of the cohort overall, and stratified by users and non-users of rosiglitazone

Characteristics	Entire cohort (n=145,806)	Rosiglitazone [a] (n=2127)	No TZD use [b] (n=142,758)
Male, n (%)	82,824 (56.8)	1167 (54.9)	81,114 (56.8)
Age (years), mean (SD)	63.7 (11.7)	64.3 (10.4)	63.7 (11.7)
Year of cohort entry, n (%)			
2000	8167 (5.6)	194 (9.1)	7970 (5.6)
2001	9445 (6.5)	381 (17.9)	8938 (6.3)
2002	9604 (6.6)	260 (12.2)	9224 (6.5)
2003	10,393 (7.1)	239 (11.2)	10,040 (7.0)
2004	12,141 (8.3)	379 (17.8)	11,624 (8.1)
2005	11,683 (8.0)	304 (14.3)	11,273 (7.9)
2006	11,126 (7.6)	232 (10.9)	10,810 (7.6)
2007	11,657 (8.0)	116 (5.5)	11,477 (8.0)
2008	11,731 (8.1)	14 (0.7)	11,664 (8.2)
2009	12,445 (8.5)	S*	12,391 (8.7)
2010	12,035 (8.3)	S*	11,995 (8.4)
2011	10,659 (7.3)	0 (0.0)	10,645 (7.5)
2012	10,110 (6.9)	0 (0.0)	10,101 (7.1)
2013	4610 (3.2)	0 (0.0)	4606 (3.2)
Body mass index, n (%)			
<30 kg/m^2	67,621 (46.4)	990 (46.5)	66,152 (46.3)
≥30 kg/m^2	76,627 (52.6)	1118 (52.6)	75,076 (52.6)
Unknown	1558 (1.1)	19 (0.9)	1530 (1.1)
Smoking, n (%)			
Ever	85,032 (58.3)	1167 (54.9)	83,342 (58.4)
Never	57,283 (39.3)	917 (43.1)	55,982 (39.2)
Unknown	3491 (2.4)	43 (2.0)	3434 (2.4)
Alcohol-related disorders, n (%)	15,491 (10.6)	171 (8.0)	15,240 (10.7)
Haemoglobin A1c, n (%)			
≤7.4 %	27,209 (18.7)	268 (12.6)	26,793 (18.8)
>7.4 %	68,309 (46.9)	1287 (60.5)	66,485 (46.6)
Unknown	50,288 (34.5)	572 (26.9)	49,480 (34.7)
Duration of treated diabetes (years), mean (SD)	0.3 (1.6)	4.4 (3.8)	0.3 (1.3)
Prior bladder conditions, n (%)	13,755 (9.4)	227 (10.7)	13,415 (9.4)
Cancer, n (%)	13,908 (9.5)	186 (8.7)	13,646 (9.6)
Urine protein test, n (%)	62,729 (43.0)	1166 (54.8)	61,072 (42.8)
Charlson comorbidity score [c], mean (SD)	2.0 (1.3)	2.0 (1.3)	2.0 (1.3)
Previous antidiabetic drug use, n (%) [d]			
Metformin	122,843 (84.3)	1581 (74.3)	120,765 (84.6)
Sulfonylureas	31,825 (21.8)	1175 (55.2)	30,217 (21.2)
Pioglitazone	921 (0.6)	0 (0.0)	0 (0.0)
Rosiglitazone	2127 (1.5)	2127 (100.0)	0 (0.0)
Incretin-based drugs	375 (0.3)	0 (0.0)	375 (0.3)
Insulins	1467 (1.0)	18 (0.9)	1435 (1.0)
Others	1406 (1.0)	144 (6.8)	1217 (0.9)

Abbreviations: S: suppressed; SD: standard deviation; TZDs: thiazolidinediones

*Numbers less than 5 are not displayed, as per the confidentiality policies of the Clinical Practice Research Datalink.

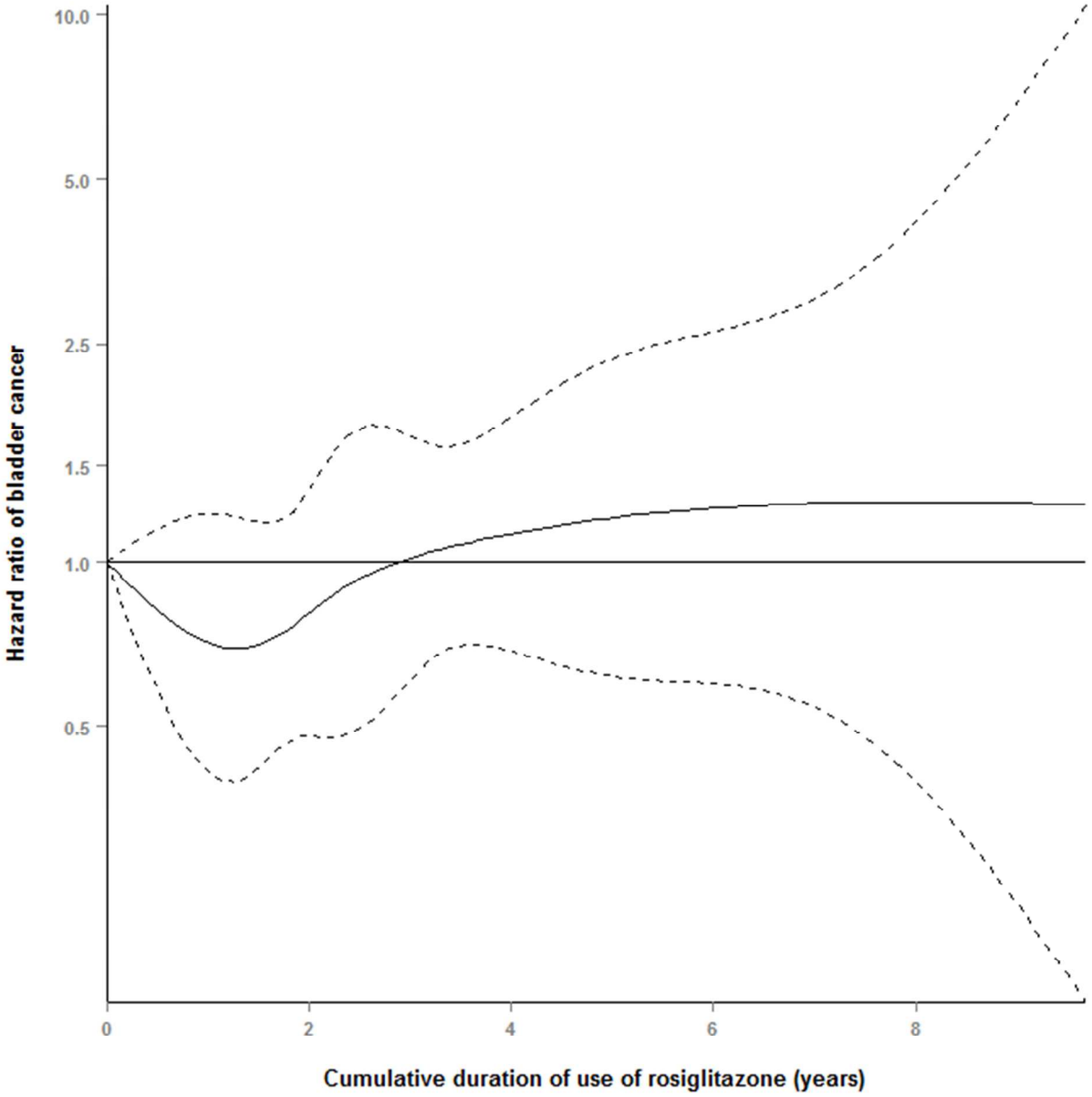
[a] Rosiglitazone only users at cohort entry

[b] No use of any TZD at cohort entry

[c] Including myocardial infarction, congestive heart failure, peripheral vascular disease, chronic pulmonary disease, cerebrovascular disease, dementia, peptic ulcer disease, diabetes-related chronic complications, connective tissue disease, mild liver disease, hemiplegia or paraplegia, renal disease, moderate to severe liver disease, acquired immuno-deficiency syndrome (AIDS). Adapted to exclude cancer.

[d] Non-mutually exclusive categories; antidiabetic drugs received ever before and including cohort entry.

Supplementary Figure 2. Smooth restricted cubic spline curve of the adjusted hazard ratio of bladder cancer (solid line) and 95% confidence limits (dashed lines) as a function of the cumulative duration of use of rosiglitazone



Supplementary Table 2. Hazard ratios for the association between rosiglitazone use and the risk of bladder cancer

Exposure [a]	Events	Person-years	Incidence rate (95% CI) [b]	Age-and-sex-adjusted HR (95% CI)	Fully Adjusted HR (95% CI) [c]
Primary analysis					
No TZD use [d]	497	558,924	88.9 (81.3 to 97.1)	1.00 [Reference]	1.00 [Reference]
Rosiglitazone	56	64,990	86.2 (65.1 to 111.9)	1.19 (0.90 to 1.58)	1.10 (0.83 to 1.47)
Cumulative duration					
≤ 1 year	17	18,142	93.7 (54.6 to 150.0)	1.34 (0.82 to 2.18)	1.23 (0.75 to 2.02)
1-2 years	10	17,718	56.4 (27.1 to 103.8)	0.78 (0.42 to 1.47)	0.71 (0.38 to 1.34)
> 2 years	29	29,130	99.6 (66.7 to 143.0)	1.36 (0.93 to 1.99)	1.27 (0.86 to 1.87)
p-trend				0.32	0.69
Cumulative dose					
≤ 2008 mg	21	21,456	97.9 (60.6 to 149.6)	1.37 (0.89 to 2.13)	1.26 (0.81 to 1.98)
2008-4960 mg	18	22,087	81.5 (48.3 to 128.8)	1.12 (0.70 to 1.80)	1.03 (0.64 to 1.66)
> 4960 mg	17	21,446	79.3 (46.2 to 126.9)	1.09 (0.67 to 1.78)	1.02 (0.62 to 1.67)
p-trend				0.34	0.72

Abbreviations: CI: confidence interval; HR: hazard ratio; TZDs: thiazolidinediones.

[a] Users of pioglitazone and combination of pioglitazone and rosiglitazone are not displayed in the table, but were considered in the regression model for proper estimation of treatment effects.

[b] Per 100,000 person-years.

[c] Adjusted for age, year of cohort entry, sex, alcohol-related disorders, smoking status, obesity, haemoglobin A1c, previous cancer, bladder conditions, Charlson comorbidity score, duration of treated diabetes, urine protein test.

[d] No use of pioglitazone or rosiglitazone.

Supplementary Table 3. Sensitivity analyses for the association between pioglitazone use and bladder cancer

Exposure [a]	Events	Person-years	Incidence rate [b] (95% CI)	Age-and-sex-adjusted HR (95% CI)	Fully Adjusted HR (95% CI)[c]
No lag period					
No TZD use	606	689,797	87.9 (81.7 to 95.1)	1.00 [Reference]	1.00 [Reference]
Pioglitazone	59	55,859	105.6 (80.4 to 136.2)	1.54 (1.17 to 2.03)	1.49 (1.13 to 1.97)
2-year lag period					
Non TZD use	412	447,751	92.0 (83.3 to 101.3)	1.00 [Reference]	1.00 [Reference]
Pioglitazone	44	34,481	127.6 (92.7 to 171.3)	1.77 (1.28 to 2.44)	1.73 (1.26 to 2.39)
Additional censoring variables [d]					
No TZD use	415	527,957	78.6 (71.2 to 86.5)	1.00 [Reference]	1.00 [Reference]
Pioglitazone	46	42,695	107.7 (78.9 to 143.7)	1.77 (1.29 to 2.43)	1.72 (1.26 to 2.37)
Censoring follow-up on December 31, 2010					
No TZD use	300	332,524	90.2 (80.3 to 101.0)	1.00 [Reference]	1.00 [Reference]
Pioglitazone	24	20,237	118.6 (76.0 to 176.5)	1.66 (1.08 to 2.53)	1.60 (1.05 to 2.46)
Additional adjustment for antidiabetic drugs					
No TZD use	497	558,924	88.9 (81.3 to 97.1)	1.00 [Reference]	1.00 [Reference]
Pioglitazone	54	44,618	121.0 (90.9 to 157.9)	1.68 (1.26 to 2.24)	1.56 (1.16 to 2.09)

Abbreviations: CI: confidence interval; HR: hazard ratio; TZDs: Thiazolidinediones.

[a] Users of rosiglitazone and combination of pioglitazone and rosiglitazone are not displayed in the table, but were considered in the regression model for proper estimation of treatment effects.

[b] Per 100,000 person-years.

[c] Adjusted for age, sex, year of cohort entry, alcohol-related disorders, smoking status, obesity, haemoglobin A1c, previous cancer, bladder conditions, Charlson comorbidity score, duration of treated diabetes, urine protein test.

[d] Benign bladder lesions, in situ bladder cancer, heart failure, liver failure.

Supplementary Table 4: Sensitivity analyses for the association between rosiglitazone use and bladder cancer

Exposure [a]	Events	Person-years	Incidence rate [b] (95% CI)	Age-and-sex-adjusted HR (95% CI)	Fully Adjusted HR (95% CI) [c]
No lag period					
No TZD use	606	689,797	87.9 (81.0 to 95.1)	1.00 [Reference]	1.00 [Reference]
Rosiglitazone	57	73,552	77.5 (58.7 to 100.4)	1.10 (0.84 to 1.45)	1.02 (0.77 to 1.36)
2-year lag period					
No TZD use	412	447,751	92.0 (83.3 to 101.3)	1.00 [Reference]	1.00 [Reference]
Rosiglitazone	52	56,743	91.6 (68.4 to 120.2)	1.27 (0.95 to 1.71)	1.16 (0.85 to 1.57)
Additional censoring variables [d]					
No TZD use	415	527,957	78.6 (71.2 to 86.5)	1.00 [Reference]	1.00 [Reference]
Rosiglitazone	45	61,310	73.4 (53.5 to 98.2)	1.19 (0.87 to 1.63)	1.10 (0.79 to 1.52)
Censoring follow-up on December 31, 2010					
No TZD use	300	332,524	90.2 (80.3 to 101.0)	1.00 [Reference]	1.00 [Reference]
Rosiglitazone	38	49,736	76.4 (54.1 to 104.9)	1.08 (0.77 to 1.53)	1.02 (0.72 to 1.44)
Additional adjustment for antidiabetic drugs					
No TZD use	497	558,924	88.9 (81.3 to 97.1)	1.00 [Reference]	1.00 [Reference]
Rosiglitazone	56	64,990	86.2 (65.1 to 111.9)	1.19 (0.90 to 1.58)	1.07 (0.80 to 1.42)

Abbreviations: CI: confidence interval; HR: hazard ratio; TZDs: Thiazolidinediones

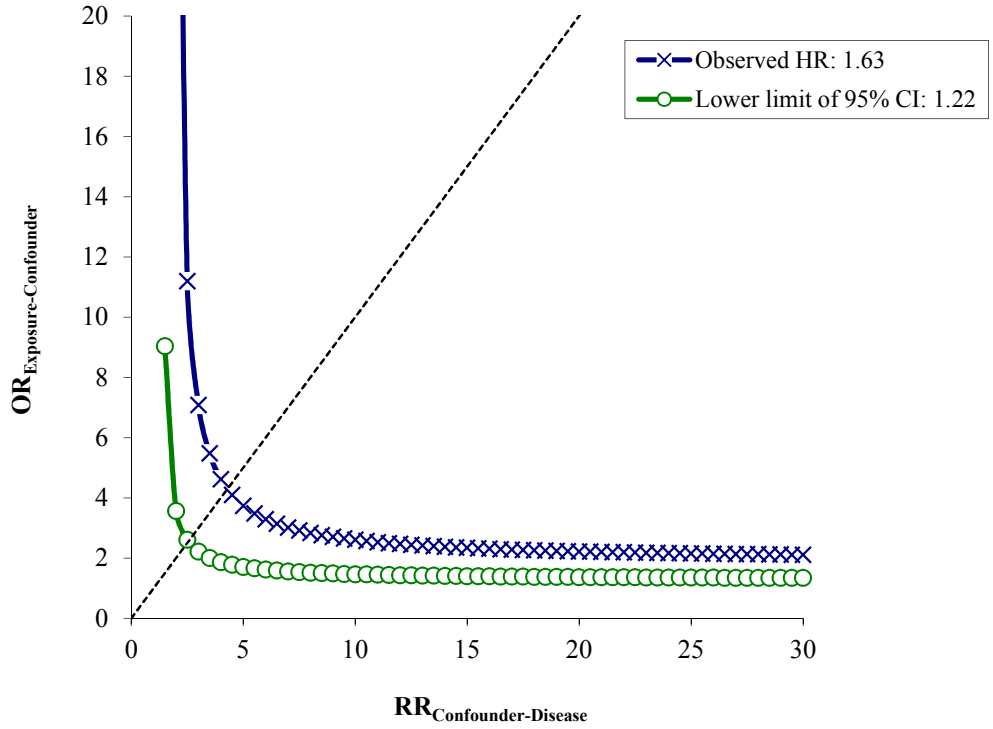
[a] Users of pioglitazone and combination of pioglitazone and rosiglitazone are not displayed in the table, but were considered in the regression model for proper estimation of treatment effects.

[b] Per 100,000 person-years.

[c] Adjusted for age, sex, year of cohort entry, alcohol-related disorders, smoking status, obesity, haemoglobin A1c, previous cancer, bladder conditions, Charlson comorbidity score, duration of treated diabetes, urine protein test.

[d] Benign bladder lesions, in situ bladder cancer, heart failure, liver failure.

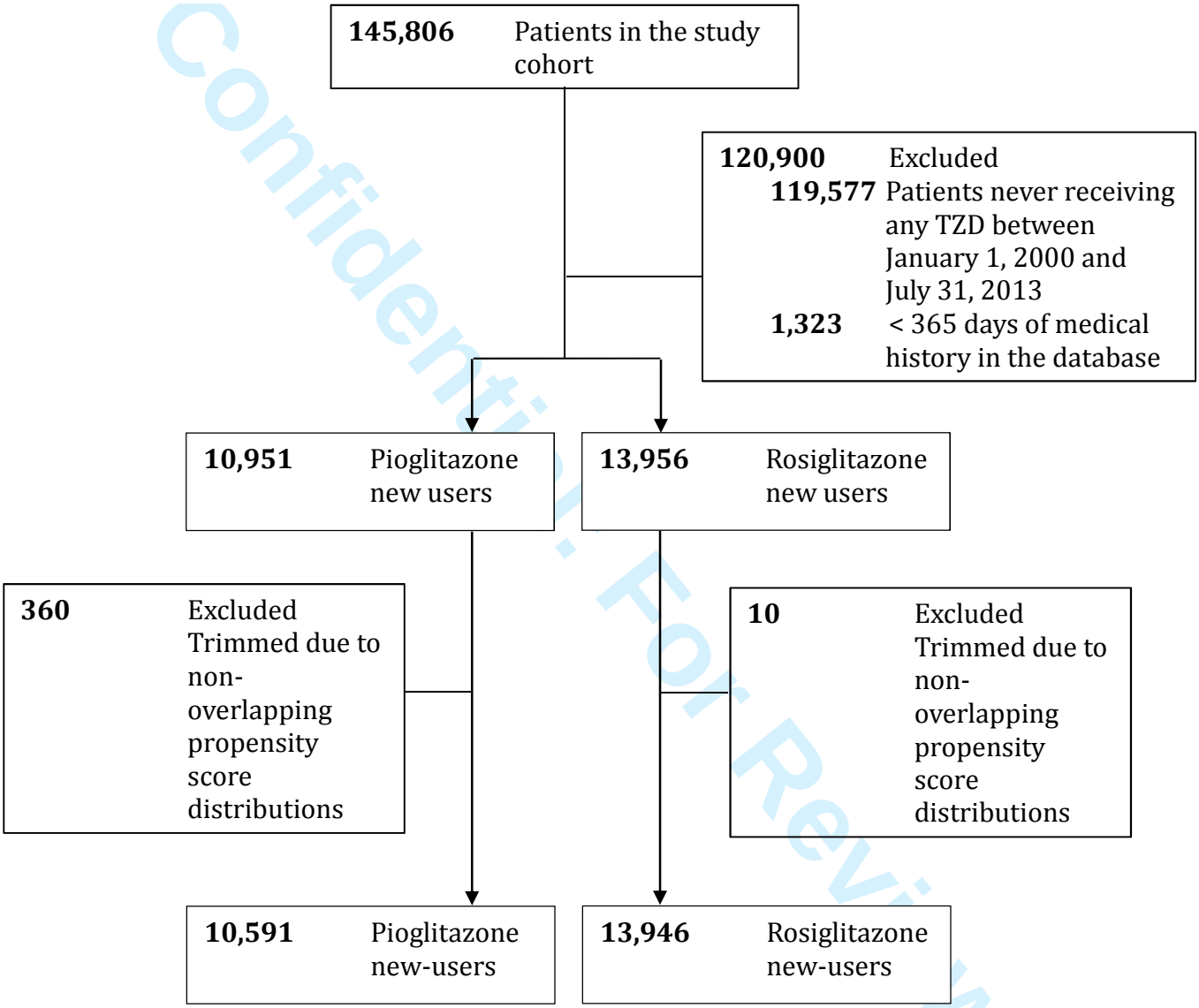
Supplementary Figure 3: Sensitivity analysis, strength of an unmeasured confounder needed to move the HR to the null.



Based on an observed HR of 1.63, a pioglitazone exposure prevalence of 7.3%, and a confounder prevalence of 20%. Blue line: observed hazard ratio (HR); Green line: lower bound of the confidence intervals. $OR_{Exposure\text{-}Confounder}$: odds ratio for the exposure-confounder association; $RR_{Confounder\text{-}Disease}$: relative risk for the confounder-disease association.

All exposure-confounder and confounder-disease associations to the right of the curves would be necessary to bring the association down to the null.

Supplementary Figure 4: Flowchart for the pioglitazone and rosiglitazone head-to-head comparison



Supplementary Table 5: Characteristics of patients initiating pioglitazone versus rosiglitazone

Characteristics	Pioglitazone[a] (n=10,591)	Rosiglitazone [b] (n=13,946)
Male, n (%)	6246 (59.0)	7838 (56.2)
Age (years), mean (SD)	62.6 (10.5)	62.6 (10.6)
Year of cohort entry, n (%)		
2000	S*	282 (2.0)
2001	S*	751 (5.4)
2002	377 (3.6)	905 (6.5)
2003	485 (4.6)	1333 (9.6)
2004	750 (7.1)	2312 (16.6)
2005	794 (7.5)	2794 (20.0)
2006	854 (8.1)	3099 (22.2)
2007	1102 (10.4)	1859 (13.3)
2008	1456 (13.8)	315 (2.3)
2009	1604 (15.1)	211 (1.5)
2010	1470 (13.9)	85 (0.6)
2011	958 (9.1)	0 (0.0)
2012	369 (3.5)	0 (0.0)
2013	125 (1.2)	0 (0.0)
Body mass index, n (%)		
<30 kg/m^2	4662 (44.0)	6189 (44.4)
≥30 kg/m^2	5907 (55.8)	7711 (55.3)
Unknown	22 (0.2)	46 (0.3)
Smoking, n (%)		
Ever	6152 (58.1)	7635 (54.8)
Never	4186 (39.5)	5723 (44.4)
Unknown	253 (2.4)	588 (4.2)
Alcohol-related disorders, n (%)	844 (8.0)	955 (6.9)
Haemoglobin A1c, n (%)		
≤7.4 %	1208 (11.4)	1318 (9.5)
>7.4 %	5814 (54.9)	7283 (52.2)
Unknown	3569 (33.7)	5345 (38.3)
Duration of treated diabetes (years), mean (SD)	3.5 (3.0)	2.9 (2.7)
Prior bladder conditions, n (%)	918 (8.7)	1200(8.6)
Cancer, n (%)	806 (7.6)	1064 (7.6)
Urine protein test, n (%)	4862 (45.9)	6258 (44.9)
Charlson co-morbidity score [c], mean (SD)	1.7 (1.0)	1.6 (1.0)

Abbreviation: S: suppressed; SD: standard deviation

* Numbers less than 5 are not displayed, as per the confidentiality policies of the Clinical Practice Research Datalink.

[a] Pioglitazone users at cohort entry.

[b] Rosiglitazone users at cohort entry.

[c] Including myocardial infarction, congestive heart failure, peripheral vascular disease, chronic pulmonary disease, cerebrovascular disease, dementia, peptic ulcer disease, diabetes-related chronic complications, connective tissue disease, mild liver disease, hemiplegia or paraplegia, renal disease, moderate to severe liver disease, acquired immuno-deficiency syndrome (AIDS). Adapted to exclude cancer.