Pioglitazone and bladder cancer: a propensity score matched cohort study

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Pioglitazone is mainly used in combination with diet and exercise and other anti-diabetic medications to treat type 2 diabetes mellitus.
- Long term use of pioglitazone (>24 months of therapy) may be associated with an increased risk of bladder cancer.

WHAT THIS STUDY ADDS

- In this study population, pioglitazone does not appear to be significantly associated with an increased risk of bladder cancer in patients with type 2 diabetes.

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Keywords

bladder cancer, cohort study, pioglitazone

Received

5 February 2012

Accepted

8 May 2012

**Accepted Article
Published Online**

11 May 2012

AIM

To examine whether exposure to pioglitazone use is associated with increased incidence of bladder cancer in patients with type 2 diabetes mellitus.

METHOD

A cohort study was done in the General Practice Research Database (GPRD) between 2001 and 2010. Two hundred and seven thousand seven hundred and fourteen patients aged ≥ 40 years with type 2 diabetes were studied (23 548 exposed to pioglitazone and 184 166 exposed to other antidiabetic medications but not pioglitazone). The association between pioglitazone and risk of bladder cancer was assessed by a Cox regression model. A propensity score matched analysis was done in a group of patients without missing baseline characteristics data.

RESULTS

Sixty-six and 803 new cases of bladder cancer occurred in the pioglitazone and other group, respectively (rates of 80.2 (95% CI 60.8, 99.5) and 81.8 (95% CI 76.2, 87.5) per 100 000 person-years respectively). Pioglitazone did not increase the risk of bladder cancer significantly compared with the other antidiabetic drugs treatment group, (adjusted hazard ratio (HR), 1.16, 95% CI 0.83, 1.62). In a matched propensity score analysis in which both groups had similar baseline characteristics (17 249 patients in each group), the adjusted HR was 1.22 (95% CI 0.80, 1.84).

CONCLUSION

The results suggest that pioglitazone may not be significantly associated with an increased risk of bladder cancer in patients with type 2 diabetes.

Introduction

Pioglitazone, an antidiabetic drug, became available in the UK in 2000 and is mainly used in combination with a diet and exercise programme and other anti-diabetic medications to treat type 2 diabetes mellitus. A recent observa-

tional study [1] using the Kaiser Permanente Northern California diabetes registry data found that among 193 099 diabetic patients who were ≥ 40 years old, use of pioglitazone at any time ($n = 30\,173$) was not associated with risk of bladder cancer (adjusted hazard ratio (HR) 1.2 [95% CI 0.9, 1.5]). However, long term use of pioglitazone

(>24 months of therapy) was associated with an increased risk of bladder cancer (adjusted HR 1.4 [95% CI 1.03, 2.0]). More recent data from observational studies report relative risks ranging from 1.12 to 1.33 when diabetic patients receiving pioglitazone are compared with diabetic patients receiving other antidiabetic medicines but not exposed to pioglitazone [2]. We have performed a propensity score matched cohort study, the methodology of which minimizes the chance of finding a spurious result [3]. The study was performed in the General Practice Research Database (GPRD), a large, well-validated UK based primary care database established in the late 1980s [4] to examine whether pioglitazone use was associated with increased risk of bladder cancer compared with other oral anti-diabetic treatments.

Methods

A cohort study was done in the GPRD database between 2001 and 2010 [4].

Study population

The study population consisted of all type 2 diabetic patients registered with a practice during the study period.

Study subjects

All patients who were taking oral anti-diabetic drug treatment (BNF Chapter 6.1.2) (defined as at least one prescription) between January 2001 and December 2010 and who were aged 40 years or over formed the study cohort. They were divided into two groups according to pioglitazone use status during the study period: (i) pioglitazone treatment group and (ii) other oral hypoglycaemic drug treatment group. Patients in the control group were those who were never on pioglitazone treatment. Patients in the pioglitazone group were also on other oral hypoglycaemic drug treatment during the follow-up period. Patients entered the study at the date of first prescription for pioglitazone or other oral hypoglycaemic drugs during the study period and were followed up until December 2010.

Patients were excluded from the study if they had any cancer diagnosis before the entry date or had less than 90 days of follow-up time.

Study outcome

The study outcome was incident bladder cancer during the follow-up period.

Definition of bladder cancer

Bladder cancer was defined as a patient who had a record for incident bladder cancer in the GP records during the follow-up period.

Definition of first diagnosis of type 2 diabetes mellitus

The first diagnosis of type 2 diabetes mellitus was defined as the date of first record of type 2 diabetes mellitus in the GP record during the study period.

Covariates

Covariates included in the study were age, gender, duration of diabetes from the first diagnosis to the first oral antidiabetic drug treatment during the study period, smoking status and body mass index (BMI) prior to entry into the study, and insulin treatment and number and type of different oral hypoglycaemic drug classes used during the follow-up period. If smoking and BMI information was not available at baseline, but was available at follow-up then follow-up information on smoking and BMI was used as it was likely that this information reflected the baseline status. For example, if a patient was recorded as a current smoker during the follow-up then it was more likely that this patient was a smoker at baseline.

Statistical analysis

Data are summarized as means (SD) or medians (IQR) for continuous variables and numbers of subjects (%) for categorical variables. Data distributions and Cox model assumptions were checked before any statistical tests were carried out. Chi-square test and t-test or non-parametric Mann-Whitney U test were performed to determine significant differences. The Cox proportional hazard model was used to compare the risks of bladder cancer between the pioglitazone treatment group and the other oral hypoglycaemic drug treatment group. To minimize confounding by indication, where patients with more severe illness were more likely to be treated with pioglitazone, a propensity score, i.e. the likelihood that a patient would be treated with pioglitazone based on known baseline characteristics (i.e. age, gender, smoking status, BMI and duration of diabetes) was calculated for each subject. A propensity score matched cohort analysis (1:1 match) was carried out in patients who did not have any missing data for the baseline characteristics. A sensitivity analysis was carried out. We repeated the analysis using only data recorded after practices' 'up-to-standard' dates and also only those practices which could be record-linked to the Hospital Episode Statistics (HES) dataset. In this case, hospital diagnosis of diabetes mellitus and cancer were extracted from the HES dataset. Population attributable risks (PAR) for bladder cancer were calculated using the following equation: $PAR = pd[(RR-1)/RR]$, where pd is the proportion of cases exposed to pioglitazone, and RR is the adjusted relative risk [5]. Statistical analyses were carried out using SAS (Statistical Analysis System) software version 9.2 (SAS Institute, Cary, North Carolina, USA).

Scientific approval

Approval for this study was obtained from the Independent Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency (MHRA) database research.

Results

Main cohort results

There were 23 548 patients in the pioglitazone treatment group and 184 166 patients in the other oral hypoglycaemic drugs treatment group. Follow-up smoking/BMI status was used for 18 135/22632 patients in whom smoking/BMI status at the index date was not available, with the median time from the index date to the date of follow-up measurement of smoking/BMI of 93/133 days. Table 1 shows the baseline characteristics of the patients. There were significant differences for all the characteristics between the two groups.

Sixty-six new cases of bladder cancer in the pioglitazone treatment group and 803 new cases of bladder

cancer in the other oral hypoglycaemic drugs treatment group were recorded during a mean follow-up time of 3.5 (2.4) and 5.3 (3.2) years, respectively. The event rates were 80.2 (95% CI 60.8, 99.5) per 100 000 person-years for the pioglitazone treatment group and 81.8 (95% CI 76.2, 87.5) per 100 000 person-years for the other oral hypoglycaemic drugs treatment group. Table 2 shows the unadjusted and adjusted hazard ratios for incident bladder cancer. There was no significant difference in risk of new bladder cancer between the two groups. Overall, compared with other antidiabetic drugs treatment, pioglitazone did not increase the risk of bladder cancer significantly (adjusted hazard ratio (HR), 1.16, 95% CI 0.83, 1.62). Age was the main confounder to drive the unadjusted HR from 0.99 to adjusted HR of 1.16. If the point estimate of 1.16 is accurate then at least 7640 patients with diabetes would need to be treated for 5 years in order to result in harm to one individual. The population attributable risk was 1%. If we only included patients with follow-up time >12 months ($n = 100\,443$) or >24 months ($n = 85\,399$), the adjusted HR were 1.12 (95% CI 0.76, 1.64) and 1.20 (95% CI 0.74, 1.93), respectively.

Table 1

Characteristics of patients with type 2 diabetes mellitus in the main cohort and HES record-linked cohort

	Pioglitazone treatment group <i>n</i> (%) All GPRD practices	Other oral hypoglycaemic drugs treatment group <i>n</i> (%)	<i>P</i> value	Pioglitazone treatment group <i>n</i> (%) Within HES practices	Other oral hypoglycaemic drugs treatment group <i>n</i> (%)	<i>P</i> value
Number of patients	23 548	184 166	–	11 140	89 090	–
Gender						
Male	13 425 (57.0)	99 560 (54.1)	<0.01	6350 (57.0)	46 995 (54.6)	<0.01
Female	10 123 (43.0)	84 606 (45.9)		4790 (43.0)	39 095 (45.4)	
Age (years) (mean, SD)	62.9 (11.1)	64.8 (12.3)	<0.01	63.2 (11.1)	65.3 (12.3)	<0.01
Smoking history						
Current smoker	3576 (15.2)	33 089 (18.0)	<0.01	1617 (14.5)	14 907 (17.3)	<0.01
Ex-smoker	11 492 (48.8)	91 628 (49.8)		5378 (48.3)	42 561 (49.4)	
Non-smoker	8435 (35.8)	55 766 (30.3)		4130 (37.1)	27 178 (31.6)	
Missing data	45 (0.2)	3683 (2.0)		15 (0.1)	1444 (1.7)	
BMI category (kg m ⁻²)						
<18.5	142 (0.6)	1768 (1.0)	<0.01	56 (0.5)	689 (0.8)	<0.01
18.5–24.9	2596 (11.0)	26 853 (14.6)		1288 (11.6)	13 117 (15.2)	
25.0–30	7561 (32.1)	62 412 (33.9)		3606 (32.4)	29 457 (34.2)	
>30	12 750 (54.1)	81 185 (44.1)		5952 (53.4)	37 097 (43.1)	
Missing data	499 (2.1)	11 948 (6.5)		238 (2.1)	5730 (6.7)	
Average time from first diagnosis date to first oral hypoglycaemic drug treatment date (days) (median (IQR))*	1610 (835–2548)	440 (78–1119)	<0.01	1299 (612–2249)	755 (254–1350)	<0.01
Number of different oral hypoglycaemic drug classes used						
1	1066 (4.5)	93 243 (50.6)	<0.01	480 (4.3)	43 940 (51.0)	<0.01
2	8183 (34.8)	69 264 (37.6)		3884 (34.9)	32372 (37.6)	
3	10 834 (46.0)	21 659 (11.8)		5178 (46.5)	9778 (11.4)	
4	3465 (14.7)	–		1598 (14.3)	–	
Insulin treatment during the follow-up period	5331 (22.6)	34 211 (18.6)	<0.01	2450 (22.0)	16 268 (18.9)	<0.01

*There were missing data in 22% of the pioglitazone group and 49% of the other oral hypoglycaemic drugs treatment group.

Table 2

Univariable and multivariable hazard ratios for incident bladder cancer

	Univariable		Multivariable	
	HR	95% CI	HR	95% CI
Within all GPRD practices				
<i>Main analysis</i>				
Other oral hypoglycaemic drug treatment	1.00		1.00	
Pioglitazone treatment	0.99	0.77, 1.27	1.16	0.83, 1.62
<i>Propensity matched analysis</i>				
Other oral hypoglycaemic drugs treatment	1.00		1.00	
Pioglitazone treatment	1.07	0.71, 1.62	1.22	0.80, 1.84
Within HES practices				
<i>Main analysis</i>				
Other oral hypoglycaemic drug treatment	1.00		1.00	
Pioglitazone treatment	1.02	0.73, 1.43	1.12	0.50, 2.53
<i>Propensity matched analysis</i>				
Other oral hypoglycaemic drugs treatment	1.00		1.00	
Pioglitazone treatment	1.39	0.50, 3.92	1.59	0.55, 4.61

Results from a propensity score matched analysis

A total of 34 498 patients were included in the analysis (17 249 in each group). There were no differences in age, gender, smoking, BMI and duration of diabetes between the two groups after matching for the propensity score (Table 3).

Thirty-nine and 48 new cases of bladder cancer were recorded for the pioglitazone treatment group and the other hypoglycaemic drugs treatment group during mean follow-up times of 3.2 (2.7) and 4.2 (3.6) years, respectively. The event rates were 76.0 (95% CI 55.2, 99.8) per 100 000 person-years for the pioglitazone treatment group and 71.3 (95% CI 51.1, 91.5) per 100 000 person-years for the other oral hypoglycaemic drugs treatment group. There was no significant difference in risk of bladder cancer between the two groups (Table 2). The adjusted HRs were 1.22 (95% CI 0.80, 1.84) for overall and 1.20 (95% CI 0.75, 1.92) and 1.30 (95% CI 0.72, 2.36) for patients with follow-up time of >12 months or >24 months, respectively.

Table 3

Characteristics of patients with type 2 diabetes mellitus in the propensity score matched analysis

	Pioglitazone treatment group n (%) All GPRD practices	Other oral hypoglycaemic drugs treatment group n (%)	P value	Pioglitazone treatment group n (%) Within HES practices	Other oral hypoglycaemic drugs treatment group n (%)	P value
Number of patients	17 249	17 249	–	2086	2086	–
Gender						
Male	9886 (57.3)	9858 (57.2)	0.76	1156 (55.4)	1152 (55.2)	0.90
Female	7363 (42.7)	7391 (42.8)		930 (44.6)	934 (44.8)	
Age (years) (mean, SD)	62.3 (11.1)	62.3 (11.6)	0.70	65.7 (11.2)	65.8 (11.2)	0.85
Smoking history						
Current smoker	2700 (15.7)	2643 (15.3)	0.37	270 (12.9)	280 (13.4)	0.64
Ex-smoker	8249 (47.8)	8377 (48.6)		984 (47.2)	954 (45.7)	
Non-smoker	6300 (36.5)	6229 (36.1)		832 (39.9)	852 (40.8)	
Missing data	–	–		–	–	
BMI category (kg m ⁻²)						
<18.5	92 (0.5)	77 (0.5)	0.42	16 (0.8)	11 (0.5)	0.65
18.5–24.9	1792 (10.4)	1802 (10.5)		250 (12.0)	256 (12.3)	
25.0–30	5556 (32.2)	5659 (32.8)		680 (32.6)	656 (31.5)	
>30	9809 (56.9)	9711 (56.3)		1140 (54.7)	1163 (55.8)	
Missing data	–	–		–	–	
Average time from date of first diagnosis of diabetes to first oral hypoglycaemic drug treatment date (days) (median (IQR))	1539 (795–2385)	1526 (798–2417)	0.69	1292 (612–2250)	1252 (594–2233)	0.46
Number of different oral hypoglycaemic drug classes used						
1	728 (4.2)	8984 (52.1)	<0.01	121 (5.8)	1225 (58.7)	<0.01
2	6190 (35.9)	6334 (36.7)		720 (34.5)	672 (32.2)	
3	7863 (45.6)	1931 (11.2)		917 (44.0)	189 (9.1)	
4	2468 (14.3)	–		328 (15.7)	–	
Insulin treatment during follow-up period	3378 (19.6)	2821 (16.4)	<0.01	640 (30.7)	1010 (48.4)	<0.01

Results from sensitivity analysis

There were 97 230 patients (46.8%) for whom it was possible to record-link data with the HES database (11 140 patients in the pioglitazone treatment group and 86 090 patients in the other oral hypoglycaemic drugs treatment group). The distributions of baseline characteristics were similar to the main analysis (Table 1). Thirty-seven and 469 bladder cancers occurred during the follow-up period in the pioglitazone treatment group and the other oral hypoglycaemic drugs treatment groups, respectively. There was no significant increase in bladder cancer during the follow-up in the pioglitazone group. However, the propensity matched analysis in 4172 patients (2086 in each group) without missing data for the matching variables showed that there was a 59% increase in point estimate of risk of bladder cancer, but this was not significant.

Discussion

We did not find a significant association between pioglitazone use and risk of bladder cancer in a large primary care sample of patients with type 2 diabetes mellitus representative of the UK population. The main adverse effects reported with pioglitazone are weight gain, pedal oedema, bone loss and precipitation of congestive heart failure in at-risk individuals, without any increase in cardiovascular disease or all-cause mortality [6]. The pioglitazone safety issue has arisen since the publication of a study entitled 'Risk of bladder cancer among diabetic patients treated with pioglitazone' in *Diabetes Care* in April 2011 which found an association between long term pioglitazone use (defined as >2 years) and risk of bladder cancer in diabetic patients [1]. However, as the risk of cancer is also related to obesity and poor diabetic control, the findings in that study may have been due to the higher use of pioglitazone in this type of patient rather than pioglitazone itself causing bladder cancer. Although the study adjusted for a number of factors, a propensity score matched cohort study is a more appropriate design to minimize confounding in this type of study.

Our propensity score matched analysis results did not show a statistically significant increased risk of bladder cancer in pioglitazone users when compared with other oral anti-diabetic drug users. The point estimate of relative risk was similar to the other study findings. The sensitivity analysis in which we used patient data that can be linked to the HES database showed that the point estimate of risk increased from 22% to 59%. The strength of this additional analysis was the improved accuracy of the diagnosis of bladder cancer and diabetes mellitus, but the limitation was that this reduced the study sample size by more than half and the results of this analysis may therefore be underpowered since the sample size was relatively small with only a few events occurring in each group. Based on the current evidence, the European Medicines Agency (EMA),

MHRA and the US Food and Drug Administration (FDA) have issued health warnings that the use of pioglitazone may be associated with an increased risk of bladder cancer [7,8] and that healthcare professionals should take precautions when using pioglitazone. However, the population attributable fraction suggests that only 1% of bladder cancer could be due to use of pioglitazone. The number needed to harm (NNH) should conventionally be calculated only for statistically significant results [9]. However, for illustrative purposes, if the point estimate of 1.16 is accurate then at least 7640 type 2 diabetic patients would need to be treated with pioglitazone for 5 years to result in one extra case of bladder cancer. The risks and benefits of pioglitazone should both be taken into account when deciding to prescribe this therapy to patients.

Our results should be interpreted cautiously because of some limitations of this study. Firstly, the main challenges with observational studies in general, including using GPRD, are the coding for the exposure, outcome and co-variables and dealing with missing data. A sensitivity analysis linking to Cancer Registry Data would strengthen our results. However, from previous experience this may not be realistic in practice as it could take more than 1 year to obtain these data. Secondly, we did not consider treatment adherence, switching of medications and concurrent use of pioglitazone and other oral antidiabetic medications, all of which could have an impact on the outcome of interest. Thirdly, cumulative exposure was only partially addressed by the sensitivity analysis in a subgroup of patients who had at least 1 or 2 years of follow-up time. A detailed analysis of cumulative exposure to pioglitazone would help to assess any causal pathway. Fourthly, for some patients, smoking status and BMI were only available during the follow-up and in these cases we assumed the status was the same at baseline. However, there may have been a change in status during the follow-up period. Fifthly, the study is observational and all potential confounding factors cannot be fully controlled for. Although our study population was large at over 200 000, due to the low event rate, the study was still statistically underpowered to draw firm conclusions.

In conclusion, the results of the present study seem not to support an association between pioglitazone exposure and an increased risk of bladder cancer in patients with type 2 diabetes.

Competing Interests

LW and ISM have no conflicts of interest. TMM is a member of the Kaiser Permanente scientific advisory board for an epidemiological study of the relationship between pioglitazone and cancers funded by Takeda pharmaceuticals. TMM has also received honoraria from Takeda for lectures about the risk management of diabetic and non-diabetic patients.

LW designed the study, did the statistical analysis and wrote the manuscript. TMM designed the study, contributed to discussion and reviewed/edited the manuscript. ISM contributed to discussion and reviewed/edited the manuscript. LW is the guarantor. This study was unfunded.

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