Original article

Pioglitazone and risk of bladder cancer in type 2 diabetes mellitus patients: A systematic literature review and meta-analysis of observational studies using real-world data

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ABSTRACT

Objectives: Patients with type 2 diabetes mellitus (T2DM) have a higher incidence of bladder cancer (BC); however, the evidence underlining the association between pioglitazone use and BC risk remains inconclusive. We conducted a systematic review and meta-analysis of observational studies to investigate the effect of pioglitazone on risk of BC in T2DM patients.

Methods: We searched all publications regarding risk of BC with pioglitazone use through PubMed, Web of Science and Cochrane library databases from inception to March, 2017. Pooled hazard ratio (HR) and 95% confidence interval (CI) were calculated using a random-effect, generic inverse variance method. **Results:** Total 15 observational (9 cohort and 6 case-control) studies were meta-analyzed. The pooled results showed a significant association between risk of BC and pioglitazone use (HR 1.20, 95%CI 1.09–1.31; $P < 0.0001$; $I^2 = 4\%$). In subgroup analysis, cumulative dose of pioglitazone ($-$ and $>$ mg) showed a significant association with risk of BC (HR 1.27; 95%CI 1.05–1.54; $P = 0.01$; $I^2 = 0\%$ and HR 1.68, 95%CI 1.36–2.08; $P < 0.0001$; $I^2 = 0\%$ respectively). In addition, a significant association was seen with risk of BC and pioglitazone treatment duration (12–24 months and $>$ 24 months) (HR 1.43; 95%CI 1.19–1.71; $P = 0.0001$; $I^2 = 0\%$ and HR 1.58; 95%CI 1.27–1.97; $P < 0.0001$; $I^2 = 29\%$ respectively). Meta-analysis of pioglitazone vs. rosiglitazone use, showed a significant association (HR 1.34; 95%CI 1.05–1.71; $P = 0.02$; $I^2 = 0\%$) with BC risk and pioglitazone use.

Conclusion: Pioglitazone use is associated with risk of BC in T2DM patients. Risk of bladder cancer appears to be associated with higher dose and longer duration of pioglitazone use.

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1. Introduction

Thiazolidinediones (TZDs), pioglitazone and rosiglitazone are oral hypoglycaemic drugs used for the management of type 2 diabetes mellitus (T2DM). TZDs are insulin sensitizers, widely used for the management of T2DM. Pioglitazone belongs to the TZD group, target PPAR- γ protein, a key transcription factor for adipogenesis and glucose homeostasis.¹ On the other hand, patients with diabetes mellitus have a higher incidence of bladder cancer,² but the association between TZD use and bladder cancer still a matter of debate.^{3,4} According to American Cancer Society, new cases of bladder cancer and deaths from bladder cancer are

expected in 2016 in the United States (US).⁵ Incidence of bladder cancer first time observed in a PROactive study, where 14 cases of bladder cancer were found in the pioglitazone treatment arm compared with 5 cases in the placebo group.⁶ Preclinical studies reported that pioglitazone and rosiglitazone treatment could develop bladder cancer in diabetic rats.^{7,8} It has been also found that pioglitazone exposure caused bladder cancer in male rats, while not observed in mice of either sex. However, mechanism behind the pioglitazone-induced urinary bladder cancer might not be due to PPAR- γ interactions because of differential variation in PPAR- γ expression subsist between the species and sex.⁹ Results from a 2 year nonclinical carcinogenicity studies suggested that monotherapy of rosiglitazone were not associated with the bladder cancer.¹⁰ Conversely, another study reveals that rosiglitazone remarkably prop up the bladder neoplasm occurrence in rats pre-treated with hydroxybutyl (butyl) nitrosamine.⁷ An independent re-analysis of the RECORD trial data confirmed the original

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results,¹¹ that rosiglitazone did not increase cardiovascular risk compared to a combination of metformin and sulfonylurea⁴; this has prompted the United States Food Drug Administration (US FDA) to ease some restrictions on rosiglitazone use. An interim report of longitudinal cohort study reviewed by FDA, which showed that short-term use of pioglitazone was not associated with risk of bladder cancer, whereas >2 years use of pioglitazone found to be linked with the bladder cancer in diabetic patients.¹² Additionally, US FDA in 2011 also updated the drug labels of pioglitazone containing medicines and recommended healthcare professionals to avoid prescribing pioglitazone in patient with active bladder cancer and prescribe it with caution in patient having prior history of bladder cancer.¹³ Similarly, results of a retrospective cohort study performed in France also reported risk of bladder cancer in pioglitazone users among diabetic patients,¹⁴ and French Medicines Agency (Afssaps) decided to suspend the use of pioglitazone in diabetic patients.¹⁵ Conversely, a recent retrospective cohort study conducted in India documented that pioglitazone was not associated with the bladder cancer in the T2DM patients.¹⁶ Drug Technical Advisory Board (DTAB) of India in 2013 recommended deferment of pioglitazone or manufacture and sale of pioglitazone containing formulation be withdrawn and allowed to be marketed with special caution.¹⁷ Limited real world data regarding safety concern of pioglitazone use and risk of bladder cancer are equivocal and unknown. Information about pioglitazone safety would be important for indemnity and decision making when these drugs are being considered. We therefore performed a systematic literature review and meta-analysis of observational studies to provide more robust evidence regarding the risk of bladder cancer in T2DM patients with pioglitazone use.

2. Materials and methods

2.1. Protocol and registration

Our study protocol is registered on PROSPERO, the international prospective register of systematic reviews.¹⁸ The current systematic review and meta-analysis was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guideline.¹⁹

2.2. Search strategies

We performed a comprehensive literature search by using electronic databases PubMed, Web of Science and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception through March, 2017 to identify relevant studies that investigated the association between pioglitazone and risk of bladder cancer in patients with diabetes mellitus. The PubMed search strategy used the following text words or Medical Subject Headings (Mesh): “diabetes mellitus”, “diabetes”, “bladder cancer”, “urinary bladder neoplasms”, “pioglitazone”, “glitazone”, and “thiazolidinediones”. Manual searches were also performed on Google Scholar and bibliographies of included studies and previous reviews were also examined to identify additional relevant publications. The literature search was performed with no time-frame restrictions. Language other than English was not included in analysis.

2.3. Study selection

Study selection was based on an initial screen of identified titles and abstracts and a second screen of full-text articles. Studies were considered eligible if they met the following criteria: (1) the study design was an observational study (Cohort, nested case-control or case control); (2) the exposure of interest was pioglitazone (3) the outcome of interest was bladder cancer incidence or effect of

pioglitazone on bladder cancer; (4) patients with T2DM; (5) reported unadjusted or adjusted estimates [hazard ratio (HR) or odds ratio (OR)] of the association between exposure and outcome, and the corresponding 95% confidence interval (CI), or sufficient raw data to allow their calculation.

2.4. Data extraction

Three independent reviewers (MA, RK and SV) extracted the abstract judiciously according to inclusion criteria. Any discrepancies were arbitrated by the third senior reviewers (AK, PG, and MS) until consent is achieved on every issue. A standard data extraction format was used to collect study information including: name of the first author, year of the publication, age, percentage of male, settings, country, database used, study population, exposure and outcome ascertainment, number of cases/control, exposure vs. comparison, duration of follow up, dose and duration of pioglitazone therapy, unadjusted and fully adjusted HR or OR and their 95% CI, and adjusted variables.

2.5. Quality assessment

Two reviewers (MA and RK) independently assessed the quality of each study by using Newcastle-Ottawa Scale (NOS), as recommended by the Cochrane Non-Randomized Studies Methods Working Group.²⁰ The NOS consists of three parameters of quality: selection, comparability, and exposure (case-control studies) or outcome (cohort studies). The NOS based on star system (with a maximum of nine stars) assigns a maximum of four stars for selection, two for comparability, and three for exposure/outcome. We considered studies with a score of 6 or greater as high quality.

2.6. Statistical analysis

The adjusted effect estimates (HR, or OR) and associated 95% CI for the bladder cancer outcomes and use of pioglitazone were extracted. All analyses were conducted on the natural log scale and standard errors (SE) derived from the formula: $[\log(95\%CI, \text{upper limit}) - \log(95\%CI, \text{lower limit})] / 3.92$.²¹ The OR was considered as equivalent to HR when the disease of interest is not common.²² We used HR as the common measure of association across studies. Because of the clinical heterogeneity inherent in our data, we used random effects models (DerSimonian and Laird) for meta-analyses of extracted log HR and their SE.²³ Generic inverse variance outcome type was used to pool HR with 95% CI of included studies. Statistical heterogeneity was assessed using the I^2 statistic, with results ranging from 0 to 100% and values of 25, 50 and 75% representing low, moderate and high levels of heterogeneity, respectively.²⁴ Primary analysis focused on assessing the risk of bladder cancer among pioglitazone users. Predefined subgroup meta-analysis was performed for the effect of pioglitazone cumulative dose and duration on risk of bladder cancer. A sensitivity analysis was conducted to assess the influence of individual studies on the pooled result, by excluding each study one by one and recalculating the combined HR on the remaining studies analysis. We also excluded those studies which mentioned only unadjusted estimates and poor quality (score <6) of study according to NOS. The potential publication bias was performed by using a funnel plot for asymmetry and was examined by using the Begg's adjusted rank correlation test and Egger's linear regression test, if >10 studies were included in the analysis of the primary outcomes.^{25,26} All the statistical analysis was conducted with Review Manager 5.3 (Nordic Cochrane Centre, Cochrane Collaboration, 2014) and R software, version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria), using the packages

“meta”.²⁷ All *p* values were considered statistically significant when <0.05 .

3. Results

3.1. Literature search and study inclusion

The PRISMA flow diagram summarizing the process of study selection is shown in Fig. 1. The electronic search identified 677 potentially relevant records, of which 620 were excluded after screening the title and abstract. The remaining 57 full-text articles were assessed for eligibility, and 41 were further excluded due no information on pioglitazone use, bladder cancer, study design, and duplicates. Total 16 articles were include for the systematic literature review and further excluded 1 study because of absence of adjusted estimate for the association between risk of bladder cancer and pioglitazone use. Finally, 15 studies were included in the meta-analysis.

3.2. Study characteristics and quality assessment

Of 16 observational studies, 10 studies^{12,14,28–35} were cohort and 6 studies^{36–41} were case-control, with 5 of these being case-control studies nested within cohorts.^{36–40} The general characteristics of each study are reported in Table 1. Among the 16 studies, 2 were conducted in USA,^{12,34} 5 in Taiwan^{29,32,37–39}, 3 in Korea^{33,40,41}, 1 in Japan,³¹ 4 in UK^{28,30,35,36}, and 1 in France.¹⁴ 2 studies reported two drugs pairs, pioglitazone vs. no pioglitazone use and pioglitazone vs. rosiglitazone use.^{35,36} Mamtani and colleagues²⁸ reported data on pioglitazone vs. rosiglitazone use, total 15 studies,^{12,14,29–41} reported data on pioglitazone vs. no pioglitazone use. More comprehensive study characteristics are provided in the Appendix Tables A1 and A2.

The quality assessment of the included studies is shown in Appendix Table A3. The NOS results showed that the average score was 7.7 (range 4–9) for cohort studies and 7.6 (range 6–8) for case-control studies. From 16 observational studies, 1 cohort study³¹ did not report adjusted estimates for the risk of bladder cancer and low

quality study according to NOS excluded from the meta-analysis. Summary of meta-analyses of included studies shown in Table 2.

3.3. Pioglitazone use and risk of bladder cancer

We identified 14 eligible observational studies, among these, 8 were cohort^{12,14,29,30,32–35} and 6 were case-control studies^{36–41} included total 24,70397 patients with bladder cancer cases. Fig. 2 represents the pooled HR of the association between pioglitazone use and risk of bladder cancer. Results from the forest plot showed a significant association between risk of bladder cancer and pioglitazone users vs. non users (HR = 1.20; 95% CI 1.09–1.31; $P < 0.0001$; $I^2 = 4\%$). When restricting the analysis only to cohort studies, the risk estimate was almost similar (HR = 1.19; 95% CI 1.09–1.31; $P = 0.0001$; $I^2 = 0\%$), whereas results from case-control analysis showed a non-significant association between risk of bladder cancer and pioglitazone users vs. non users (HR = 1.25; 95% CI 0.93–1.68; $P = 0.14$; $I^2 = 28\%$).

3.4. Risk of bladder cancer with increasing cumulative pioglitazone dose

Total 8 studies^{12,14,29,32,35–37,39} reported data regarding cumulative dose of pioglitazone user vs. non users. Only 6 studies^{12,14,29,32,35,36} were eligible for the meta-analysis. Patients who received a cumulative dose of pioglitazone ranged from $< \text{mg}$ and $> \text{mg}$ showed a significant association with risk of bladder cancer (HR = 1.27; 95% CI 1.05–1.54; $P = 0.01$; $I^2 = 0\%$ and HR = 1.68; 95% CI 1.36–2.08; $P < 0$ $I^2 = 0\%$ respectively), whereas no association (HR = 1.13; 95% CI 0.95–1.35; $P = 0.16$; $I^2 = 0\%$) was found in patients who received a cumulative dose of pioglitazone $< \text{mg}$ (Fig. 3).

3.5. Risk of bladder cancer with increasing cumulative pioglitazone duration

Of 10 observational studies^{12,14,29,30,32,35–38,40} reporting data regarding cumulative duration of pioglitazone users vs. non users, only 9 studies^{12,14,29,32,35–38,40} were eligible for the meta-analysis. 2

Fig. 1. PRISMA flow diagram of study selection process.

Table 1
Characteristics of included studies.

Author, year	Study design	Data source	Country	Study period	No.of participants	Male (%)	Age, (year)	Follow-up (years)	Drug comparison	BC cases	Adjusted estimates (95% CI) ¹
Lewis, 2011 ¹²	Longitudinal cohort	KPNC	USA	1997–2008	193099	53	≥40	Pio: Median-9.3 No Pio: Median-6.2	Pio vs. no Pio	881	1.20 (0.90–1.50)
Mamtani, 2012 ²⁸	Retrospective cohort	THIN	UK	2000–2010	88369	56	Pio: Median-62 Rosi: Median-63	Pio: Median-2.4 Rosi: Median-4.4	Pio vs. Rosi	127	1.14 (0.79–1.66)
Neumann, 2012 ¹⁴	Population-based cohort	PMSI, SNIIRAM	France	2006–2009	1491060	53	Range: 40–79	Mean 3.1	Pio vs. no Pio	2016	1.22 (1.05–1.43)
Tseng, 2012 ²⁹	Population-based cohort	NHI	Taiwan	2006–2009	54928	NR	NR	Max-4	Pio vs. no Pio	165	1.30 (0.66–2.58)
Wei, 2013 ³⁰	Population-based cohort	GPRD	UK	2001–2010	207714	57	Mean: 63	Pio: Mean-3.5 No Pio: Mean-5.3	Pio vs. no Pio	869	1.16 (0.83–1.62)
Fujimoto, 2013 ³¹	Retrospective cohort	Kitano Hospital	Japan	2000–2011	21335	NR	NR	NR	Pio vs. no Pio	170	NR
Lee, 2014 ³²	Population-based cohort	NHI	Taiwan	2003–2009	34970	47	NR	4	Pio vs. no Pio	84	1.03 (0.45–2.35)
Jin, 2014 ³³	Population-based retrospective cohort	Tertiary referral hospitals*	Korea	2005–2011	113193	52	Mean: 63	NR	Pio vs. no Pio	267	1.13 (0.77–1.67)
Lewis, 2015 ³⁴	Population-based cohort	KPNC	USA	1997–2012	193099	53	≥40	Pio: Median-6.1 No Pio: Median-7.2	Pio vs. no Pio	1261	1.06 (0.89–1.26)
Tuccori, 2016 ³⁵	Population-based cohort	CPRD	UK	2000–2013	145806	57	Mean: 64	Mean: 4.7	Pio vs. no TZD Pio vs. Rosi	551 110	1.63 (1.22–2.19) 1.48 (1.01–2.16)
Azouzlay, 2012 ³⁶	Nested-case control within cohort	GPRD	UK	1988–2009	115727	81	Mean: 69	Pio: Mean-4.8 Rosi: Mean-4.8	Pio vs. no TZD	376/ 6699	1.83 (1.1–3.05)
Chang, 2012 ³⁷	Nested-case control within cohort	NHI	Taiwan	2000–2007	606583	64	Mean: 71	Median: 7.9	Pio vs. Rosi	55/842	1.60 (0.88–2.90)
Hsiao, 2013 ³⁸	Nested-case control within cohort	NHI	Taiwan	1997–2008	NR	68	Mean: 66	Mean: 3.6	Pio vs. no Pio	1583/ 6308	0.95 (0.7–1.29)
Kuo, 2014 ³⁹	Nested-case control within cohort	NHI	Taiwan	2002–2009	64745	62	Mean: 69	NR	Pio vs. no Pio	3412/ 17060	1.62 (0.92–2.85)
Han, 2016 ⁴⁰	Nested-case control within cohort	NHIS-NSC	Korea	2003–2013	47738	69	≥40	Median: 7.9	Pio vs. no Pio	259/ 1036	1.20 (0.58–2.49)
Song, 2012 ⁴¹	Retrospective, matched case- control	Severance Hospital	Korea	2005–2011	NR	84	Mean: 69	NR	Pio vs. no Pio	85/850 329/ 658	0.75 (0.26–2.15) 2.09 (0.26–16.81)

Abbreviations: BC, bladder cancer; CI, confidence interval; Pio, pioglitazone; Rosi, rosiglitazone; TZD, thiazolidinedione; NR, not reported; NHI, National Health Insurance; KPNC, Kaiser Permanente Northern California; THIN, The Health Improvement Network; PMSI, Programme De Médicalisation Des Systèmes d'Information; SNIIRAM, Système National D'information Inter-Régimes De L'assurance Maladie; GPRD, General Practice Research Database; CPRD, Clinical Practice Research Datalink; NHISNSC, National Health Insurance Service-National Sample Cohort.

¹ Risk estimates are as follows: hazard ratio [12,14,28–36], odd ratio [37–41].

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⁵ Adjusted data calculated from pooling current/recent/past users estimates.

studies required to pool their estimates into one estimate by using inverse variance method, i) 2–3 years and ≥3 years³⁷; ii) ≤3 months and 3–12 months.⁴⁰ Results from the summary of meta-analysis showed a significant association with risk of bladder cancer and pioglitazone treatment ranged from 12 to 24 months and >24 months (HR = 1.43; 95% CI 1.19–1.71; $P = 0.0001$; $I^2 = 0\%$ and HR = 1.58; 95% CI 1.27–1.97; $P < 0.0001$; $I^2 = 29\%$ respectively), whereas pioglitazone treatment for <12 months showed no

association with risk of bladder cancer and pioglitazone treatment (HR = 1.11; 95% CI 0.90–1.37; $P = 0.31$; $I^2 = 42\%$) (Fig. 4).

3.6. Pioglitazone use vs. rosiglitazone use and risk of bladder cancer

Among 3 studies, 2 were cohort^{28,35} and 1 case-control³⁶ studies included patients and 292 bladder cancer cases. After pooling data, an increased risk of bladder cancer with pioglitazone

Table 2
Summary of the meta-analysis.

	No. of studies	Total no. of BC cases	Total no. of patients	Heterogeneity		Model	Pooled estimates		
				I^2 (%)	P value		HR	95% CI	P
Pio vs. no Pio	14	12,138	24,70397	4	0.41	Random effect	1.20	1.09–1.31	<0.0001
Pio cumulative dose (mg)	–	–	–						
<10,500	6			0	0.84	Random effect	1.13	0.95–1.35	0.16
10,501–28,000	4			0	0.66	Random effect	1.27	1.05–1.54	0.01
>28,000	4			0	0.61	Random effect	1.68	1.36–2.08	<0.0001
Pio cumulative duration (months)	–	–	–						
<12	9			42	0.09	Random effect	1.11	0.90–1.37	0.31
12–24	6			0	0.83	Random effect	1.43	1.19–1.71	0.0001
>24	6			29	0.22	Random effect	1.58	1.27–1.97	<0.0001
Pio vs. Rosi	3	292		0	0.51	Random effect	1.34	1.05–1.71	0.02

Abbreviations: BC, bladder cancer; HR, hazard ratio; CI, confidence interval; Pio, pioglitazone; Rosi, rosiglitazone.

Fig. 2. Forest plot of the association between use of pioglitazone and risk of bladder cancer. Red squares and horizontal lines represent study-specific estimates and 95% CI. The size of the square is proportional to the weights of the individual studies. Black diamond represents pooled estimates (center) and 95% CI (width). Abbreviation: SE: standard error, IV: inverse variance, BC: bladder cancer.

use was found. Association between risk of bladder cancer and pioglitazone use was significant (HR=1.34; 95% CI 1.05–1.71; $P=0.02$; $I^2=0\%$) (Appendix Fig. A1).

3.7. Sensitive analysis and publication bias

In the “leave-one-out” sensitive analysis when omitting one study,³⁵ resulted in loss of statistical significance of the pooled estimates (HR=1.25; 95% CI 0.91–1.72; $P=0.16$; $I^2=0\%$) (Appendix Fig. A1). Otherwise, we did not find any major changes in direction or magnitude of the summary estimates and P values of heterogeneity in the other analyses. Only pioglitazone use vs. no pioglitazone use subgroup analysis was eligible for an asymmetry test for publication bias because there were <10 studies in any other particular meta-analysis. The shape of the funnel plots for included studies seemed asymmetrical. Begg’s adjusted rank correlation and Egger’s linear regression tests showed no significant evidence of publication bias (Begg’s test $P=0.87$; Egger’s test $P=0.49$) (Appendix Fig. A2).

4. Discussion

This systematic review and meta-analysis analyses the effect of pioglitazone on the risk of bladder cancer in patients with T2DM. The summary results from the studies indicated that pioglitazone

use was significantly associated with increased risk of bladder cancer.

TZD activates the PPAR- γ nuclear receptors and improves insulin sensitivity. Results from the laboratory studies suggested that PPAR- γ agonist might have anti-cancer properties, such as cell-cycle arrest, induction of apoptosis and inhibition of cell invasion.⁴² In contrast, preclinical studies indicate that PPAR- γ agonists can potentiate tumorigenesis.⁴³ Few animal studies also have examined pioglitazone exposure in relation to development of bladder tumor.⁸ However, mechanisms underlying carcinogenic effect of pioglitazone yet not completely explored.

Few unmeasured confounders such as smoking, duration of diabetes, COPD, kidney disease, urinary tract disease may be linked with the TZD use and risk of bladder cancer. An increased bladder cancer risk has been consistently associated with smoking and renal transplant population.^{44,45} Data from the cohort included in 8-year interim to the FDA suggested that proteinuria test results were positively associated (HR=2.45, 95%CI 2.12–2.82) with bladder cancer risk. Proteinuria testing may be a potential confounder in studies of the association between pioglitazone use and risk of bladder cancer.⁴⁶ However, growing body of evidences reported no risk of bladder cancer development in the diabetic patients who are treated with pioglitazone use.^{32,34} In contrast, several clinical studies have suggested significant association of pioglitazone use with risk of bladder cancer.^{14,35} When we examined the association between bladder cancer risk

Fig. 3. Forest plot of the association between dose of pioglitazone use and risk of bladder cancer. Red squares and horizontal lines represent study-specific estimates and 95% CI. The size of the square is proportional to the weights of the individual studies. Black diamond represents pooled estimates (center) and 95% CI (width). Abbreviation: SE: standard error, IV: inverse variance, BC: bladder cancer.

and increasing levels of pioglitazone exposure, the risk of bladder cancer increased with increasing duration and cumulative dose of pioglitazone use. Dose <mg and duration <12 months are not associated with risk of bladder cancer, whereas dose =mg and >mg as well as duration 12–24 and >24 months of pioglitazone exposure are associated with risk of bladder cancer. In line with our findings, few studies also suggested that dose <mg and duration <12 months of pioglitazone was not associated with risk of bladder cancer in T2DM patients.³² On the other hand, increasing cumulative dose and duration of pioglitazone use are strongly associated with risk of bladder cancer. These findings are congruence with our current results. Furthermore, recently Korhonen and colleagues⁴⁷ conducted a retrospective cohort study in T2DM patients using datasets from four European countries to evaluate the association between pioglitazone use and risk of bladder cancer. Results from this cohort study showed a non-significant association between risk of bladder cancer and pioglitazone use vs. use (HR = 0.99, 95%CI 0.75–1.30) and (HR = 1.00, 95%CI 0.83–1.21) in the nearest and multiple match cohorts, respectively. Similarly, increase in cumulative dose (>mg) and duration (>48 months) of pioglitazone exposure was also not significantly associated with risk of bladder cancer (HR = 0.65, 95% CI 0.33–1.26 and HR = 0.86, 95% CI 0.44–1.66, respectively) in the nearest match cohort.

Clinically, TZDs may be a risk factor for bladder cancer in patients with diabetes, but findings from clinical and epidemiological studies are inconsistent. For instances, analysis from a population-based retrospective cohort study of 11,3193 patients with diagnosis of T2DM, TZD exposure seems to reduce the risk of overall cancer including bladder cancer (in a dose dependent manner).⁴⁸

Additionally, in the subgroup analysis stratified by head to head comparison between the pioglitazone use vs. rosiglitazone use and risk of bladder cancer, our summary effect estimates showed

significant trends towards the increased risk of bladder cancer among diabetic patients using pioglitazone compared with the risk in those using rosiglitazone. However, a previous meta-analysis conducted in 2 observational studies showed non-significant effect when compared pioglitazone use vs. rosiglitazone and risk of bladder cancer.⁴⁹ This finding reflects the importance of extensive real world evidence as the results became discernable after the inclusion of study conducted by Tuccori and colleagues.³⁵

Considering an increased risk of bladder cancer with pioglitazone, the U.S. Food and Drug Administration (FDA) recommends that healthcare professionals should not prescribe pioglitazone in patients with active bladder cancer. Moreover, the benefits of glycemic control vs. unknown risks for cancer recurrence with pioglitazone should be considered in patients with a prior history of bladder cancer.

This systematic review and meta-analysis has several strengths. We included in the meta-analysis only studies with a clear definition of the exposure and outcomes. Of included studies, we conducted separate meta-analysis for pioglitazone use vs. no use, to achieve robust results. Several studies provide cumulative dose and duration of the pioglitazone exposure to find out the possible association with risk of bladder cancer.

Our systematic review and meta-analysis has several limitations. First, there was potential heterogeneity across the studies in the main analysis of bladder cancer. Heterogeneity may be due to study design and lack of certain variables known to be associated with bladder cancer, such as smoking, occupational exposure, duration of diabetes, nephropathy, COPD, and urinary tract disease. Second, possible overlapping of the studies such as 6 studies^{29,32,37–40} uses NHI database (Taiwan), 2 studies^{12,34} uses KPNC database (USA), 2 studies^{30,36} uses GPRD database (UK). Although, the duration of study, follow up, study design, patient population, definition of exposure, inclusion/exclusion criteria was different, so we included these studies for the meta-analysis for the pooled

Fig. 4. Forest plot of the association between duration of pioglitazone use and risk of bladder cancer. Red squares and horizontal lines represent study-specific estimates and 95% CI. The size of the square is proportional to the weights of the individual studies. Black diamond represents pooled estimates (center) and 95% CI (width). Abbreviation: SE: standard error, IV: inverse variance, BC: bladder cancer.

estimates as these studies qualified for the inclusion in the analysis.

Our results could significantly influence the current clinical practice guideline in long term T2DM patients. However, to engrain the findings of our meta-analysis into clinical practice, high quality studies (randomized controlled trials/real world registries) with longer duration of follow up (especially designed to assess the effect of pioglitazone on bladder cancer in T2DM patients) is warranted. While we await further studies, clinicians should ensure that pioglitazone is judiciously prescribed especially patient subgroups with possible contraindications.

5. Conclusion

In conclusion, our study suggests that pioglitazone treatment was significantly associated with the risk of bladder cancer. Risk of bladder cancer appears to be associated with higher dose and longer duration of pioglitazone use. Literature is punctuated with evidence underlining association of bladder cancer with substantial morbidity and mortality. Because of inconsistent results risk-benefit analysis of pioglitazone use should be evaluated.

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Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.cegh.2017.08.002>.

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