PIOGLITAZONE USE AND RISK OF BLADDER CANCER: A SYSTEMATIC LITERATURE REVIEW AND META-ANALYSIS OF OBSERVATIONAL STUDIES

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RATIONALE

Several studies investigating the possible risk of bladder cancer in type 2 diabetes (T2DM) patients treated with pioglitazone have been published with conflicting results. Most previous meta-analyses have utilized studies published prior to 2013, after which several long-term observational studies have been published, raising the need to review the accumulated real world evidence.

OBJECTIVES

To determine the association between exposure to pioglitazone and bladder cancer risk among subjects with T2DM.

METHODS

This meta-analysis was based on a systematic literature review of observational peer-reviewed studies published prior to September 30, 2016 investigating the potential association between pioglitazone use and bladder cancer. Studies were identified using a specified MEDLINE search strategy. The reference section of each included study and previous meta-analyses[1-6] were also screened to identify additional records. Combined meta-analysis hazard ratios (HRs) were derived using random effects model as the primary approach. Hierarchical Bayesian meta-analysis with country-specific effects was conducted as a sensitivity analysis.

ACKNOWLEDGMENT

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STUDY REGISTRATION

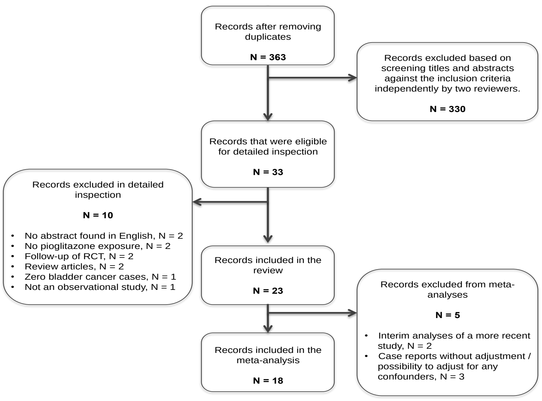
The study was registered into the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) e-register of studies (EUPAS16082).

CONFLICT OF INTEREST STATEMENT

YY was an employee of Takeda Pharmaceutical Company Limited during study start up activities. DB is an employee of Takeda Pharmaceutical Company Limited. JM, HK, FH, SC and PK are employees of a CRO and thus in continuous collaboration with pharmaceutical companies.

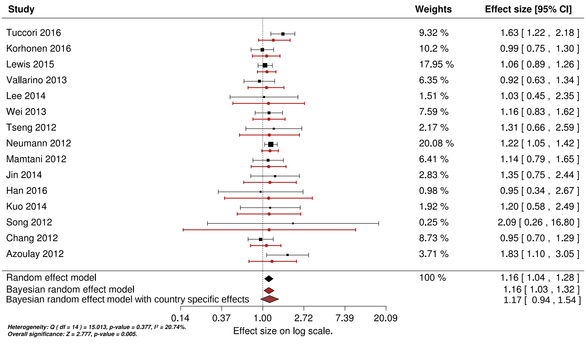
RESULTS

Figure 1. Flowchart of the electronic search, screening of studies against the inclusion criteria for eligibility and final number of included studies.



After a systematic review of 363 identified records, 18 studies were included in the meta-analyses.

Figure 2. Meta-analysis results for the association of ever exposure (vs. never) to pioglitazone and bladder cancer using a random effect model (Black) and a Bayesian random effect model (Red).



For bladder cancer outcome, the meta-analysis HR for ever use vs. never use of pioglitazone was estimated at 1.16 (95% CI: 1.04, 1.28).

Using a Bayesian random effect model the meta-analysis HR was 1.16 (95% CI: 1.03, 1.32). Using a hierarchical Bayesian meta-analysis with country-specific effects the HR was estimated at 1.17 (95% CI: 0.94, 1.54).

In a sensitivity analysis including only studies adjusted for lifestyle-related factors the meta-analysis effect size was 1.18 (95% CI, 1.00-1.40).

Table 1. Meta-analysis results for the association between cumulative dose and cumulative duration of pioglitazone exposure and bladder cancer derived using a random-effects model.

Subgroup	Effect size	Heterogeneity	
Cumulative exposure dose	**HR (CI)**	**I^2**	**P-value**
<10 500 mg	1.12 (0.98, 1.30)	2%	0.440
10 500 – 28 000 mg	1.09 (0.83, 1.42)	54 %	0.075
>28 000 mg	1.41 (1.06, 1.88)	55 %	0.066
Cumulative exposure duration			
<12 months	1.07 (0.94, 1.22)	35%	0.183
12-24 months	1.19 (1.07, 1.32)	0%	0.284
>24 months	1.38 (1.04, 1.82)	82%	0.002

CONCLUSIONS

In line with previous meta-analyses, we observed a small but statistically significant association between pioglitazone use and increased bladder cancer risk. However, causality is not established and alternative explanations cannot be ruled out. In the cumulative dose and duration analyses, highest effects were observed in the highest and longest exposure groups, but substantial heterogeneity across individual studies was present.

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