# Bladder cancer risk in relation to pioglitazone exposure among patients with T2DM – Pan European Multi-Database Study

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## Introduction

This Pan European cohort study was undertaken at the request of European Medicines Agency (EMA) to further assess the association between pioglitazone use and bladder cancer risk among patients with type 2 diabetes mellitus (T2DM). As the incidence of bladder cancer is very low, databases from Finland (FIN), Sweden (SWE), Netherlands (NL HOSP-PHARM and NL GP) and the UK (CPRD GOLD and CPRD GOLD-HES) were used to have adequate statistical power for investigating the association.

## Study Population and Design

Linked prescription, hospital, general practitioner, cancer and death registration records were used to construct the study database from the country specific datasets.

**Inclusion criteria:**

- Patient was treated with any oral antidiabetic drugs at any time in the available medication records.
- Patient was prescribed at least one antidiabetic drug during the study period.
- Patient's baseline anti-diabetic treatment was modified at cohort entry point to include pioglitazone (exposure group) or another antidiabetic medication (reference group).
- Patient was over 40 years of age at cohort entry.
- Patient had at least 12 months of medication database membership during baseline period prior to cohort entry.

**Exclusion criteria:**

- Patient had a diagnosis of T1DM, gestational diabetes, or secondary and other types of diabetes prior to cohort entry
- Patient with a diagnosis or history of bladder cancer
- Patient had an unacceptable registration in the database.
- Patient had a concurrent prescription with other thiazolidinediones (TZD) at cohort entry

Follow-up time per individual was split on events of treatment change and occurrence of pre-specified comorbidities. A potential cohort entry date (CED) was defined as the time of initiation of pioglitazone for the exposed and times of treatment change for the unexposed. Follow-up was from cohort entry until first incident bladder cancer, secondary malignant neoplasm of bladder, death, start of other TZDs, leaving the database, end of database coverage or 30 June 2011 whichever occurred first.

Bladder cancer diagnosis was based on cancer registries in the FIN, SWE and CPRD GOLD-HES datasets. For the NL datasets and CPRD GOLD dataset the bladder cancer diagnosis was mainly based on hospital or GP diagnoses.

To limit channelling bias, pioglitazone exposed and non-exposed individuals were matched based on treatment history and propensity scores accounting for variables affecting pioglitazone initiation at CED. Cohorts were matched at the country specific dataset level and pooled to increase the power of the study.

**Exact matching variables:** use of other TZDs prior to CED, type of antidiabetic treatment immediately prior to CED, type of modification in baseline antidiabetic therapy at CED (treatment switch or add-on).

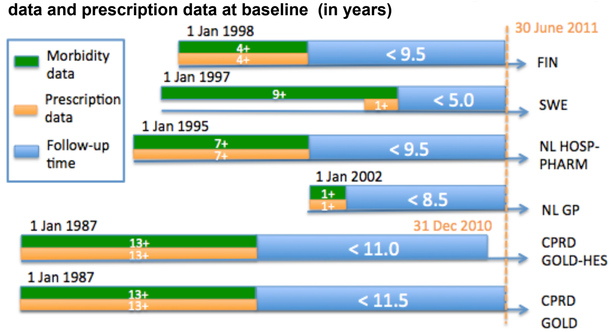
**Propensity score variables:** exact matching variables, duration of treated diabetes mellitus at CED, history of diabetic complications at CED, history of myocardial infarction or stroke at CED, history of congestive heart failure at CED, year of CED, duration of membership in medication database prior to CED, number of different antidiabetic drug classes prior to cohort entry.

## Data Summary

**Table 1: Size of population in pooled analysis**

| Dataset | FIN | SWE | NL HOSP-PHARM | NL GP | CPRD GOLD | CPRD GOLD-HES | TOTAL |
|---|---|---|---|---|---|---|---|
| Ever | 18,794 | 3,712 | 7,491 | 2,823 | 11,408 | 12,109 | 56,337 |
| Never | 18,794 | 3,712 | 7,491 | 2,823 | 11,408 | 12,109 | 56,337 |

**Figure 1: Maximum follow-up time and length of coverage for morbidity data and prescription data at baseline (in years)**




**SOURCE OF MORBIDITY AND PRESCRIPTION DATA**

**Finland and Sweden:** In FIN and SWE datasets morbidity data is based on inpatient hospitalizations and outpatient hospital visits. Both datasets contain information on prescribed medications purchased from community pharmacies. The Swedish National Diabetes Register provided detailed information on characteristics of patients (type of diabetes, smoking status, and HbA1c).

**Netherlands:** The Dutch datasets were constructed from the PHARMO Database Network, one dataset was based on linked hospital and pharmacy databases (NL-HOSP-PHARM), the other on the GP database (NL-GP). Overlap between the datasets was removed for the pooled analysis. Drug usage data was based on prescription data in the NL GP dataset and on dispensing data in the NL-HOSP-PHARM dataset.

**UK:** In CPRD GOLD-HES morbidity data is based on GP records and inpatient hospitalizations. In CPRD GOLD morbidity data is based on GP records only. Drug usage data was based on prescription data in both datasets.

## Acknowledgments

- The study was fully sponsored by Takeda Development Centre Europe Ltd
- Dr Tim Williams and Susan Eaton, both of CPRD, were involved in the study design.
- Research Ethics approval: FIN, Protocol version 2.0, Dnro 96/13/00/2013
- Research permissions for FIN data: Statistics Finland (Dnro TK/53-373-13), National Institute for Health and Welfare (Dnro THL/388/5.05.00/2013), Social Insurance Institute (Dnro Kela 25/522/2013), Population Register Centre (Dnro 726/410/13).

## Main Analysis

**Table 2: Patient characteristics and follow-up time**

| | | Ever exposed N=56 337 | Never exposed N=56 337 |
|---|---|---|---|
| Age at CED | 40-49 | 6,728 (11.94) | 5,608 (9.95) |
| | 50-59 | 14,881 (26.41) | 12,618 (22.40) |
| | 60-69 | 18,366 (32.60) | 17,262 (30.64) |
| | ≥70 | 16,362 (29.04) | 20,849 (37.01) |
| Gender | Male | 31,732 (56.33) | 30,561 (54.25) |
| | Female | 24,605 (43.67) | 25,776 (45.75) |
| Antidiabetic treatment prior to CED | insulin (only or in comb.) | 2,705 (4.80) | 2,705 (4.80) |
| | metformin and SU | 14,277 (25.34) | 14,277 (25.34) |
| | metformin only | 16,526 (29.33) | 16,526 (29.33) |
| | no treatment | 6,657 (11.82) | 6,657 (11.82) |
| | other drugs or comb. | 10,062 (17.86) | 10,062 (17.86) |
| | SU only | 6,110 (10.85) | 6,110 (10.85) |
| Follow-up time for bladder cancer | range (min, max) | (0.00, 10.52) | (0.00, 10.81) |
| | mean (+/- sd) | 2.89 (2.20) | 2.82 (2.37) |
| Number of bladder cancer events (N) | | 130 | 153 |
| Crude incidence rate per 10000 (95% CI) | | 7.97 (6.71, 9.47) | 9.62 (8.21, 11.27) |

The hazard ratios (HR) with 95% confidence intervals (CIs) were estimated using Cox's model with adjustments for relevant confounders. Stepwise variable selection was performed to evaluate potential covariates, but none met the inclusion threshold in the pooled analysis.

**Table 3: Hazard Ratios for bladder cancer incidence**

| | Adjusted Model | Trend test p-value |
|---|---|---|
| **Pioglitazone exposure** | | |
| Never | Reference | - |
| Ever | 0.99 (0.75, 1.30) | |
| **Duration of pioglitazone exposure (months)** | | |
| Never | Reference | 0.42 |
| <18 | 1.10 (0.82, 1.48) | |
| 18-48 | 0.78 (0.52, 1.19) | |
| >48 | 0.86 (0.44, 1.66) | |
| **Cumulative pioglitazone dose (mg)** | | |
| Never | Reference | 0.45 |
| 1-14,000 | 1.05 (0.77, 1.42) | |
| 14,001-40,000 | 0.99 (0.66, 1.46) | |
| >40,000 | 0.65 (0.33, 1.26) | |

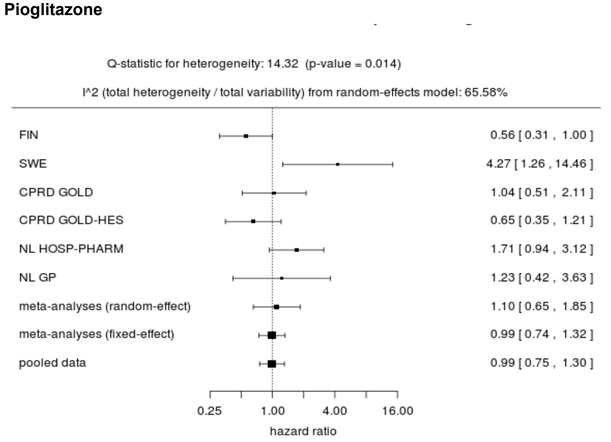
**Model was adjusted for:**

- ❑ Exact matching variables
- ❑ Propensity score variables
- ❑ Propensity score quintile
- ❑ Age at cohort entry
- ❑ Gender
- ❑ Use of metformin*
- ❑ Use of sulphonylureas*
- ❑ Use of insulin*
- ❑ Use of other noninsulin antidiabetic drugs*
- ❑ Dataset identifier

- Time updating variables

## Meta Analysis

**Figure 2: Bladder cancer risk for never vs ever exposed to Pioglitazone**




According to the $I^2$ statistic 65.6 % of the total variability of the effect size estimates was due to heterogeneity between datasets. There was significant heterogeneity in the results between the datasets ($I^2$ heterogeneity test p-value 0.014).

## Sensitivity and Stratified Analysis

Our study included an extensive examination of stratified analyses and did not identify any subgroups in which there was an increased risk of bladder cancer associated with pioglitazone exposure. Additionally, we included a large number of sensitivity analyses which confirmed the robustness of our data.

## CONCLUSIONS

Exposure to pioglitazone did not increase the risk of bladder cancer. In the analysis of the pooled dataset consisting of 6 non-overlapping datasets from FIN, SWE, NL and UK the HR of bladder cancer incidence for ever vs. never exposed to pioglitazone was 0.99 (95% CI: 0.75, 1.30) after adjusting for the design variables and all potential confounders. We did not observe any evidence of increasing risk of bladder cancer with increasing duration of pioglitazone use or with increasing cumulative dose of pioglitazone.

The size of this study, its use of datasets from multiple countries, the inclusion of long-term exposure and follow-up, controlling for channelling bias, and use of time updating covariates make this one of the most important studies to have examined the role of pioglitazone and risk of bladder cancer.

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