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SHORT COMMUNICATION

Post-authorisation Safety Study of Pioglitazone Use and Safety Endpoints of Interest in Denmark After Direct Healthcare Professional Communication

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Abstract

Introduction A Direct Healthcare Professional Communication (DHPC) sent in Denmark on 11 August 2011 provided information on new pioglitazone labelling and guidance on monitoring treatment effectiveness. We describe pioglitazone use in Denmark after the DHPC, estimate the incidence of heart failure (HF), quantify pioglitazone cessation following a diagnosis of bladder cancer (BC) or uninvestigated macroscopic haematuria, and describe glycated haemoglobin (HbA1c) values.

Methods This was a cohort study. From Danish population-based registries, cohorts of type 2 diabetes mellitus incident or prevalent users of pioglitazone or insulin in 2011–2015 were created. Patient characteristics, treatment patterns, laboratory results (available for a regional subset of the population), and incidence rates of HF and BC were estimated.

Results There were 80 pioglitazone and 17,699 insulin incident users, 140 pioglitazone and 13,183 insulin prevalent users. There were no new BC cases among incident pioglitazone users, and < 5 new BC cases among prevalent pioglitazone users. Pioglitazone was rarely the first-line treatment. History of haematuria was documented in < 5 incident and 11 prevalent pioglitazone users. During follow-up, there were < 5 HF cases among 77 incident pioglitazone users and < 5 among 133 prevalent pioglitazone users without a history of HF. Median HbA1c at index date was 7.8% and 8.8% in incident pioglitazone and insulin cohorts, and 7.5% and 7.6% in prevalent pioglitazone and insulin cohorts, respectively. During follow-up of up to 4.4 years, 28.8% incident and 20.7% prevalent pioglitazone users discontinued pioglitazone.

Conclusions Numbers of pioglitazone users in Denmark were low and decreased over time. Risks of BC or HF were low and risk estimates imprecise.

Key Points

A drug utilisation study in Denmark was requested by the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) and conducted to assess compliance with prescribing information following pioglitazone labelling changes on haematuria, bladder cancer and guidance on monitoring treatment effectiveness approved in Europe in July 2011.

The number of pioglitazone users in Denmark was low and decreased over time.

Based on the small numbers of pioglitazone users in Denmark over a 4-year period, no inference can be made confidently on the risks of heart failure, bladder cancer or haematuria from exposure to pioglitazone treatment.

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1 Introduction

Pioglitazone is an oral drug of the thiazolidinedione class that is indicated for glycaemic control in type 2 diabetes mellitus (T2DM) [1]. Pioglitazone is usually prescribed as second-line therapy in combination with metformin [2–4].

A potential excess risk of bladder cancer (BC) associated with pioglitazone exposure was identified in patients in the PROspective pioglitAzone Clinical Trial In macrovascular Events (PROactive) trial. In PROactive, cases of BC were reported in 14 patients treated with pioglitazone ($n = 2605$) versus six on placebo ($n = 2633$) over an average observation time of 34.5 months. After blinded review, 11 cases were excluded as they could not plausibly be related to treatment (six pioglitazone vs. three placebo) [5]. The European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) confirmed in July 2011 that pioglitazone is a "valid treatment option for certain patients with T2DM", while acknowledging "that there is a small increased risk of BC in patients taking these medicines" [6]. Prescribers were advised not to use pioglitazone-containing medicines in patients with concurrent or a history of BC or with uninvestigated macroscopic haematuria, and to start elderly patients on the lowest possible dose, as they are at a higher risk of BC, as well as heart failure (HF) [7].

A Direct Healthcare Professional Communication (DHPC) was sent to Danish prescribers on 11 August 2011 providing information on updated pioglitazone labelling. According to data from Danish health registers, in 2011 there were 306,624 patients with diabetes, and 90% of them had T2DM [8, 9]. According to published statistics by the Danish Health Data Authority, in 2011 there were 310 pioglitazone users in Denmark, compared with 350, 380 and 255 in 2008, 2009 and 2010, respectively [10]. This drug utilisation study in Denmark was conducted to assess compliance with prescribing information following pioglitazone labelling changes on haematuria, BC and guidance on monitoring treatment effectiveness approved in Europe in July 2011.

This study had the following aims:

1. To describe the number of incident and prevalent users of pioglitazone in Denmark after the DHPC on 11 August 2011 and their glucose-lowering treatment patterns.
2. To quantify the number and proportion of pioglitazone users (incident and prevalent separately) who ceased pioglitazone treatment following a diagnosis of BC or following uninvestigated macroscopic haematuria.
3. To estimate the incidence rate of HF in incident and prevalent pioglitazone users who had no prior history of HF.
4. To describe glycated haemoglobin (HbA1c) results and other parameters relevant to the effectiveness of T2DM treatment and discontinuation of pioglitazone use due to therapy failure.

2 Methods

2.1 Study Design

We conducted a cohort study describing patient characteristics available at index date to assess indicators of pioglitazone utilisation, and a descriptive analysis of the patient cohort over the follow-up period to address the other objectives. Index date was the date of first dispensing of pioglitazone or insulin between 11 August 2011 and 31 December 2015 for incident users and 11 August 2011 for prevalent users. Pioglitazone and insulin are two alternative second-line therapies that can be added to metformin and lifestyle changes [11]. Results from insulin users are included to provide context for interpreting findings in pioglitazone.

2.2 Data Sources

This study was conducted using prospectively collected data from:

1. The Danish Civil Registration System, which since 1968 has provided unique identifiers for linkage, date of birth, sex and vital status [12, 13].
2. The Danish National Patient Registry, which since 1977 has included information on hospital admission and discharge dates with discharge diagnoses, and from 1995 outpatient specialist clinic visits were included (diagnoses coded using the International Classification of Diseases 10th Revision [ICD-10] from 1994 onwards) [14, 15].
3. The Danish Health Services Prescription Database, which holds information on reimbursed dispensings, including purchase date, Anatomical Therapeutic Chemical classification code and package size for every reimbursed dispensing at a community pharmacy since 2004 [16].
4. The Clinical Laboratory Information Systems research database, which contains laboratory test results of patients in North and Central Denmark Regions (approximately one-third of the population in Denmark) [17].

2.3 Study Population and Period

The source population was the entire population from Denmark (for laboratory data, it was residents of the North and Central Denmark regions). Incident users of pioglitazone were patients with a diagnosis of T2DM (ICD-10 E11) in their baseline period (from 1995 up to index date), one or

more dispensings of pioglitazone between 11 August 2011 and 31 December 2015, and no dispensing of pioglitazone in the 12 months before index date. Prevalent users of pioglitazone were patients with a diagnosis of T2DM, one or more dispensings of pioglitazone from 11 August 2011 to 31 December 2015, and at least one pioglitazone dispensing in the 12 months before 11 August 2011. Incident and prevalent insulin user cohorts were similarly defined.

Patients were excluded if they had a diagnosis of type 1 diabetes mellitus (T1DM) in their record or were diagnosed with T2DM before 40 years of age (to prevent incorrectly capturing T1DM misdiagnosed in the database). Patients in the insulin cohorts were also excluded if they had a pioglitazone dispensing recorded during the 12 months prior to their study period, and they were censored and included into the corresponding pioglitazone cohort if a pioglitazone dispensing was observed during the study period.

The follow-up period for each patient extended from index date to the earliest date of death, emigration or end of study period (31 December 2015) or first pioglitazone dispensing (for the insulin users who switched to the incident pioglitazone users group during the study period).

2.4 Study Variables

Exposure of interest to pioglitazone or insulin starts at index date and duration of exposure (dispensing length) is computed from the number of days supplied, based on the dispensed amount and the corresponding defined daily dose (DDD). Duration of exposure from subsequent dispensing is similarly computed, starting at each dispensing date. Exposure ends at the time of treatment discontinuation, switch to another glucose-lowering medication (GLM), or end of follow-up.

Treatment patterns identified in the applicable cohorts were:

1. *First-line pioglitazone treatment:* Use of pioglitazone without previous GLM in the 12 months prior or longer. First-line insulin treatment was similarly defined.
2. *Persistence:* Continued treatment for at least 12 months after index date.
3. *Discontinuation of pioglitazone therapy:* Absence of new pioglitazone dispensing for 180 days after the expiration of the DDD supplied in all pioglitazone dispensings.
4. *Overlap of dispensing drug supplies:* Two different prescriptions with days of supply overlapping.
5. *Switch of medication:* A dispensing of another GLM than the one received at index date (pioglitazone or insulin), without overlap and within 60 days after expiry of the last dispensing.
6. *Augmentation/co-medication:* A dispensing during the study period of a GLM (other than pioglitazone/insulin as applicable) with at least 1 day's overlap with the pioglitazone or insulin dispensing. First augmentation was recorded.

Co-morbidities and endpoints of interest were HF (defined as a recorded code for HF plus initiation of a loop diuretic within 90 days of diagnosis), BC, haematuria (excluding or including recurrent haematuria), and uninvestigated macroscopic haematuria (patients with a recording of haematuria, but without a subsequent laboratory urine assessment, antibiotic treatment, magnetic resonance imaging of the bladder, ultrasounds, urinary calculi, or referral to a hospital-based urologist; required to be within the prior 90 days).

Other variables of interest included patient sex, age, co-morbidities, GLM and laboratory test results data (HbA1c and lipid profile).

2.5 Statistical Analysis

Numbers of incident and prevalent pioglitazone and insulin users in the T2DM cohort were reported and their characteristics described using summary statistics. Duration of pioglitazone use after index date was described as the median and the mean (standard deviation [SD]) number of months.

The number and proportion (%) of incident pioglitazone users after 11 August 2011 with a history of BC (ever) or uninvestigated macroscopic haematuria (within the prior 90 days) were assessed. The number of patients with a new diagnosis of BC or haematuria who ceased or continued pioglitazone treatment after the DHPC on 11 August 2011 was calculated.

The number and proportion (%) of patients with HF occurring after index date (excluding patients with prior HF) were calculated. Incidence rates for HF during and after treatment with pioglitazone and co-medication with insulin were calculated. All estimates were provided with 95% confidence intervals (CIs).

For patients with available laboratory data, most recent levels in the 12 months pre-index date and over 6 months post-index date, HbA1c levels (mean [SD]) and lipid levels (LDL, HDL, plasma triglycerides, total cholesterol) were described.

Selected analyses were stratified by age (<65 and ≥ 65 years) and sex; all analyses were conducted using SAS software, version 9.2 (Cary, NC, USA).

Recent regulations from the data-source custodians in Denmark require masking counts of <5 and the corresponding relative frequencies, whether observed or computable from the remaining data, to prevent identification of individuals.

3 Results

In 2011, 2012, 2013, 2014 and 2015, the numbers of persons with at least one community pharmacy dispensing of pioglitazone were, respectively, 310, 250, 215, 155 and 100 [10]. Between 11 August 2011 and 31 December 2015, the following groups were identified: 80 incident pioglitazone users; 17,699 incident insulin users; 140 prevalent pioglitazone users and 13,183 prevalent insulin users. Demographic characteristics, co-morbidities and co-medications of the four study cohorts at index date are described (Table 1).

Median follow-up time on pioglitazone after index date was 5.3 months for incident and 26.2 months for prevalent pioglitazone users. Mean [SD] follow-up time after index date was 8.3 [9.2] months for incident and 23.5 [14.3] months for prevalent pioglitazone users. Pioglitazone was rarely the first-line GLM. During follow-up, 65.0% of incident and 65.7% of prevalent pioglitazone users switched to another GLM, and 80.0% or more in both pioglitazone cohorts had augmentation with another GLM. Among 80 incident pioglitazone users, 23 (28.8%) discontinued pioglitazone during the follow-up; among 140 prevalent pioglitazone users, 29 (20.7%) discontinued pioglitazone during follow-up (Table 2).

There was no history of BC (since 1995) or uninvestigated macroscopic haematuria (within 90 days of index date) in either of the pioglitazone cohorts. History of any haematuria (since 1995) was seen in less than five of the 80 incident and in 11 of the 140 prevalent pioglitazone users. There was no new diagnosis of BC among incident pioglitazone users during the follow-up and among prevalent pioglitazone users less than five cases were recorded, all of them after treatment with pioglitazone had been stopped. During follow-up, no cases of uninvestigated macroscopic haematuria were noticed.

There were less than five cases of HF among 77 pioglitazone incident users (incidence rate of 9/1000 person-years [95% confidence interval (CI): 2, 34]) and less than five cases of HF among 133 pioglitazone prevalent users without a history of HF (incidence rate of 2/1000 person-years [95% CI: 0, 13]).

HbA1c measurements (Table 3) preceding the index date were present in 95.0% of incident and 92.3% of prevalent

Table 1 Patient demographics, co-morbidities and co-medications at index date

	Incident pioglitazone users		Incident insulin users		Prevalent pioglitazone users		Prevalent insulin users	
	N	%	*N*	%	*N*	%	*N*	%
No. of users	80	100.0	17,699	100.0	140	100.0	13,183	100.0
< 65 years	47	58.7	7556	42.7	59	42.1	5525	41.4
≥ 65 years	33	41.2	10,143	57.3	81	57.9	7658	58.1
Men	45	56.2	10,800	61.0	87	62.1	7796	59.1
Women	35	43.7	6899	39.0	53	37.9	5387	40.9
Age (median, P25–P75, years)	62.4 (55.5–69.3)		67.2 (58.4–75.4)		66.0 (58.2–74.1)		66.8 (60.2–74.1)	
Alcohol disorders	5	6.3	975	5.5	< 5	2.x	485	3.7
Heart failure	< 5	≤ 5.0[a]	1949	11.0	7	5.0	931	7.1
Bladder cancer	0	0.0	139	0.8	0	0.0	66	0.5
Haematuria (inclusive)	< 5	≤ 5.0	1135	6.4	11	7.8	573	4.35
Uninvestigated haematuria	0	0.0	11	0.1	0	0.0	< 5	0.0
Hypertension	26	32.5	7570	44.8	58	41.4	4989	37.8
Chronic kidney disease	< 5	≤ 5.0	969	5.5	< 5	< 1.5	305	2.3
Myocardial infarction	< 5	≤ 5.0	1752	9.9	7	5.0	1043	7.9
Lipid-lowering agents	60	75.0	13,604	76.9	122	87.1	11,434	86.7
Antiplatelet agents	37	46.3	10,186	57.6	63	45.0	8318	63.1
Diuretics	38	47.5	10,111	57.1	75	53.6	7630	57.9
Beta blockers	22	27.5	7458	42.1	45	32.1	4948	37.5
Calcium channel blockers	32	40.0	7939	44.9	64	45.7	6308	47.9
ACE inhibitors	46	57.5	10,830	61.2	94	67.1	8919	67.7
AR blockers	53	66.3	13,044	73.7	120	85.7	10,785	81.8
Insulins and analogues	< 5	≤ 5.0	17,699	100.0	6	4.29	13,183	100.0

ACE angiotensin-converting enzyme, *AR* angiotensin II receptor

[a]Certain values or their proportions masked to avoid identification of individuals

pioglitazone users. Median HbA1c at index date was 8.8% and 7.6% in the incident and prevalent insulin cohorts, respectively. Considering HbA1c ≥ 7.5% as inadequate glycaemic control, 61.8% of pioglitazone users were inadequately controlled.

4 Discussion

This study reports on drug utilisation and incidence of safety endpoints of interest for patients with T2DM using pioglitazone after risk-minimisation measures were implemented by the EMA [6]. Because of the small number of observed pioglitazone users, no inference can be made regarding the incidence of endpoints of interest during follow-up in association with pioglitazone treatment. Approximately two-thirds of pioglitazone users had suboptimal glycaemic control. Since the DHPC in Denmark, the number of persons with at least one pioglitazone outpatient dispensing declined from 310 in 2011 to 100 in 2015. This is suggestive of clinicians responding to the new risk minimisation measures. Similar DHPC were issued in other European countries [18–20]. One study undertaken on several European healthcare data sources from Finland, the Netherlands, Sweden and the UK, in response to a request by EMA, reported 61,587 patients exposed to pioglitazone among 940,294 eligible patients in the period up to 2011, prior to the DHPC [21].

Over recent years multiple studies have reported results on the risk of BC on patients with diabetes exposed to pioglitazone, some of them suggesting an increased risk [22–25] and some suggesting no risk [21, 26–29]. Controversy remains [30], although the Food and Drug Administration (FDA) concluded that "Discrepant findings between studies, as well as between interim and final reports of the Kaiser Permanente Northern California and PROactive studies, combined with limitations in study design and the inherent difficulty of investigating moderate effect sizes in long latency endpoints, render the totality of evidence inconclusive" [31]. Treatment with pioglitazone is not recommended for patients with a medical history of BC or uninvestigated macroscopic haematuria. The lowest starting dose of pioglitazone is recommended for elderly patients.

The association between exposure to pioglitazone and increased incidence of HF has been described [32, 33] but not confirmed compared with other GLMs [34–36], and pioglitazone should not be used in patients with a history of HF [37] because it can cause dose-dependent fluid retention, which may exacerbate or precipitate HF [38].

Table 3 Laboratory test results among users of pioglitazone with measurements pre-index and 6 months post-index (North and Central Denmark Regions)

Median (P25–P75)	Incident pioglitazone users	Prevalent pioglitazone users
Pre-index		
HbA1c (%)	7.8 (7.5–8.9)	7.5 (6.9–8.2)
LDL (mmol/L)	2.1 (1.7–2.4)	1.9 (1.6–2.7)
HDL (mmol/L)	1.2 (0.9–1.6)	1.2 (1.0–1.4)
Plasma triglycerides (mmol/L)	2.2 (1.6–2.7)	1.8 (1.2–2.2)
Total cholesterol (mmol/L)	4.3 (3.9–4.6)	4.2 (3.5–4.7)
6 months post-index		
HbA1c (%)	7.7 (7.0–8.9)	7.4 (6.9–8.1)
LDL (mmol/L)	1.9 (1.5–2.4)	2.0 (1.5–2.9)
HDL (mmol/L)	1.2 (0.9–1.5)	1.3 (1.1–1.4)
Plasma triglycerides (mmol/L)	2.1 (1.5–2.8)	1.8 (1.3–2.6)
Total cholesterol (mmol/L)	3.9 (3.5–4.8)	4.1 (3.5–5.0)

HbA1c glycated haemoglobin, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein

Table 2 Antidiabetic treatment patterns of pioglitazone users after index date

	Incident pioglitazone users		Prevalent pioglitazone users	
	N	%	*N*	%
No. of users in study period	80	100.0	140	100.0
First-line pioglitazone	< 5[a]	≤ 5.0	14	10.0
Persistence	18	22.5	99	70.7
Discontinuation	23	28.8	29	20.7
Switching	52	65.0	92	65.7
Augmentation	64	80.0	125	89.3
Duration of pioglitazone treatment until discontinuation (median, P25–P75, in months)	4.3 (1.4–13.1)		25.0 (10.9–28.9)	
Duration of pioglitazone treatment until switching (median, P25–P75, in months)	4.6 (1.6–11.4)		26.2 (9.1–28.8)	
Duration of pioglitazone treatment until augmentation (median, P25–P75, in months)	0.3 (0.0–1.0)		0.9 (0.4–1.6)	

[a]Certain values or their portions masked to avoid identification of individuals

Observational studies from real-world settings contribute to improved understanding of the effectiveness and safety of medicines in routine clinical practice [21, 39, 40]. Results from these studies supplement data from clinical trials and contribute to informed decisions.

The most important limitation of the analysis reported here is the small number of pioglitazone users, precluding meaningful inferences and resulting in high uncertainty around point estimates. This limitation derives from the declining number of pioglitazone users over the study period. Therefore, the current study size is not as large as originally expected. Future studies with a longer inclusion period or adding data from other countries could accrue larger numbers of pioglitazone users and produce precise estimates. Nevertheless, making findings of this European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) registered study publicly available contributes to full disclosure of results and future research efforts [41, 42].

As in similar studies, there are potential sources of systematic error. Selection bias is expected to be negligible because the Danish medical registries routinely capture data representing the entire population of Denmark. We are also confident about lab test data, which were only partially available, since Danish regions generally can be considered representative of the Danish population in terms of demographic and socioeconomic characteristics as well as healthcare utilization and medication use [43]. Information bias may have resulted from relying on dispensing information and the inability to ascertain the actual drug intake and its timing. Nevertheless, T2DM is a chronic condition requiring glucose-lowering treatment, including pioglitazone; hence, we assume that there is high correlation between drug dispensing and actual use. However, the exact time of treatment initiation or discontinuation is expected to be somehow misclassified. Additionally, interpretation of results and comparisons to other studies need to take into account the treatment pattern definitions used in the current study. Data on smoking status or body mass index were not recorded in the data sources we used; obesity diagnoses based only on hospital record information are likely to result in prevalence estimates discrepant with the true prevalence of obesity in the target study population. The presence of some risk factors for BC among pioglitazone users (e.g. smoking and occupational exposures) could not be assessed.

5 Conclusions

In summary, based on the small numbers of pioglitazone users in Denmark over a 4.4-year period, risk estimates of BC or HF or haematuria from exposure to pioglitazone treatment are small and imprecise because of low occurrence.

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Compliance with Ethical Standards

Availability of data and material The data that support the findings of this study are hosted by the population-based registries in Denmark described in the *Methods* section and can be accessed through the corresponding application procedure.

Conflict of interest JCR is an employee of Evidera, a PPD business unit. DB is an employee of Takeda Pharmaceutical Company Limited. SPU and VE are salaried employees of Aarhus University/Aarhus University Hospital.

Ethics approval and consent to participate This is a registry-based study committed with European Health Authorities, which uses anonymized data from secondary data sources and requires no patient contact. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Author contributions JCR, SPU, VE and DB made substantial contributions to the conception and design of the study. VE and SPU processed the data and conducted the statistical analyses. All authors interpreted the data. JCR wrote the first draft of the manuscript. All authors critically revised the manuscript, provided final approval and agree to be accountable for all aspects of the work.

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