Abstract

Rationale and Background: A Direct Healthcare Professional Communication (DHPC) was sent to Danish prescribers on 11 August 2011 informing them of the label change for pioglitazone that was approved by the European Medicines Agency (EMA); this change included new labelling on haematuria and bladder cancer and guidance on monitoring treatment effectiveness.

Objectives: The objectives of this study were as follows : 1) Quantify the number of incident and prevalent pioglitazone users after the DHPC, including duration of use among incident users; 2) describe patterns of antidiabetic co-medication use among incident and prevalent pioglitazone users after the DHPC ; 3) quantify the number and proportion of patients who initiated pioglitazone as a first-line therapy after the DHPC; 4) estimate the cumulative incidence of heart failure (HF) by incident and prevalent pioglitazone users during the study period, overall and stratified by age and insulin co-medication; 5) quantify the number and proportion of incident pioglitazone users who initiated pioglitazone treatment after the DHPC, despite pre-existing bladder cancer or uninvestigated macroscopic haematuria; 6) quantify the number and proportion of pioglitazone users (by incident and prevalent users) after the DHPC who ceased pioglitazone treatment following a diagnosis of bladder cancer or uninvestigated macroscopic haematuria; 7) describe glycated haemoglobin (HbA1c) monitoring and other parameters relevant to the effectiveness of type 2 diabetes mellitus (T2DM) treatment and to quantify the proportion of patients (by incident and prevalent pioglitazone users) who discontinued pioglitazone due to therapy failure, overall and stratified by the HbA1c level change compared with previous measurements.

Study Design: This study was composed of four historic cohorts (incident and prevalent pioglitazone and insulin users) linking data from the Danish National Patient Register, the Danish National Health Services Prescription Database and the Clinical Laboratory Information Systems. The study inclusion period was between 11 August 2011 and 15 November 2013, with follow-up through 15 November 2013 (most recent data available to date). Lab data were available from two regions only (25%)

Results: This study identified 80 incident pioglitazone users (mean age= 63.4 years, 51.3% male); 9,130 incident insulin users (mean age = 66.2 years, 61.2% male); 149 prevalent pioglitazone users (mean age= 65.8 years, 62.4% male) and 15,007 prevalent insulin users (mean age = 66.8 years, 59.1% male). The most common treatment pattern for antidiabetic co-medication use among incident pioglitazone users was pioglitazone alone (38.8%) or treatment with biguanides (37.5%). The percentage of patients who initiated on pioglitazone as a first-line therapy was low; roughly 9.4% of prevalent patients initiated on the treatment compared to 3.8% of incident pioglitazone users following the DHPC. The number of incident cases of HF following incident pioglitazone use was low, with only one case among 93.9 person-years at risk. In addition, there were 57 HF cases among 8,290 person-years of insulin incident users, one among 267 person-years of prevalent pioglitazone users and 125 cases among 30,489 person-years of insulin prevalent users. During follow-up, there was one incident case of HF among the 77 incident users of pioglitazone and one incident case of HF among 145 prevalent users of pioglitazone. The two-year and three-month cumulative incidence of HF per 100 incident pioglitazone users was also low (1.3 overall and 2.3 in users who were <65 years old). In patients using insulin as co-medication, the cumulative incidence of HF per 100 subjects was three among prevalent and zero among incident users. Of the 80 identified incident pioglitazone users, one

patient had a recorded history of haematuria, and no subject had a previous history of bladder cancer or uninvestigated macroscopic haematuria in the 90 days leading up to initiation of pioglitazone treatment. No new cases of either bladder cancer or haematuria were recorded during the follow up period. Eighteen (22.5%) incident and 41 (27.5%) prevalent pioglitazone users had an HbA1c measurement. In the six months post--index date, incident (n=17) and prevalent pioglitazone (n=35) users had between one and three HbA1c measurements. Among pioglitazone users, 11 incident users (13.8%) and 13 prevalent users (8.7%) discontinued pioglitazone during follow-up. Of those, only one had a pre-discontinuation HbA1c measurement of ≥9.0%. The median (interquartile range) HbA1c level before cohort entry was 8.0% (7.5%–8.9%) and 8.8% (7.7%–10.3%) in the incident pioglitazone and incident insulin cohort, respectively, and 7.5% (6.9%–8.2%) and 7.6% (6.9%–8.5%) in the prevalent pioglitazone and prevalent insulin cohort, respectively.

Conclusion: This report contains results of the pioglitazone utilization and cohort analyses among pioglitazone users in Denmark. The number of pioglitazone users in Denmark has been decreasing in recent years, so the current report is based on a smaller number of pioglitazone users than originally projected, limiting the interpretation of results. The proportion of patients who initiated on pioglitazone as first-line therapy is similar to that reported by the drug utilization study conducted in the United Kingdom (UK), where only 5.4% of patients used pioglitazone as a first-line treatment. The current results do not support an increased risk of HF, haematuria or bladder cancer associated with pioglitazone use over a two-year and three-month period.