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EMA Scientific manager	Madalena Arriegas (madalena.arriegas@ema.europa.eu)		

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Authors (participants)	Vera Ehrenstein (AUH-AS), Susan Jick (BCDSP), Lin Li (BCDSP), Sinna Pilgaard Ulrichsen (AUH-AS), Jørgen Rungby (AUH-AS), A. Ingrid Leal Anguiano (EMC), Miriam Sturkenboom (EMC), Henrik Toft Sørensen (AUH-AS), Peter R. Rijnbeek (EMC), Daniel M. Weibel (EMC), Ángel Honrado (SYNAPSE, Inc.)		
Responsible Author	Vera Ehrenstein	**Email**	ve@dce.au.dk

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DEFINITIONS

- Participants in this tender are referred to herein according to the following codes:

  - **AUH-AS** Aarhus University Hospital (Denmark).Contractor
  - **BCDSP** Boston Collaborative Drug Surveillance Program (USA). Subcontractor
  - **EMC** Erasmus University Medical Center (Netherlands). Subcontractor
  - **SYNAPSE** Synapse Research Management Partners S.L. (Spain). Subcontractor

- **Contract**: Legal document signed between the Contractor and the European Medicines Agency for the undertaking of the tender.
- **Contractor**: A tenderer to which a framework contract has been awarded and signed with the EMA. It is responsible before the EMA of the right execution of the tender and of the delivery of the results in due time and form according to the Contract.
- **EMA:** European Medicines Agency.
- **Subcontractor**: Organisation supporting the Contractor in the fulfilment of the tender objectives and technical execution.
- **Technical specifications**: Official document generated by the EMA for the tender that includes a detailed description of all technical requirements, contractual arrangements, and price, that enables the EMA to specify and acquire services provided by resources not employed directly by the EMA.
- **Tender**: Public (or restrictive) offer made by the EMA to specific providers to enter into the contract of transaction of services at certain specified cost.
- **Work plan**: Schedule of tasks, deliverables, efforts, dates and responsibilities corresponding to the work to be carried out, as specified in the Contract.

1. EXECUTIVE SUMMARY

Pioglitazone belongs to the drug class thiazolidinediones and is used as a second-line therapy in patients with type 2 diabetes mellitus. Observational studies suggested that the drug is associated with a slightly increased risk of bladder cancer. To minimise the risks, the Committee for Medicinal Products for Human Use recommended restricting use of the drug to patients without known risk factors for bladder cancer, including a history of bladder cancer, uninvestigated macroscopic haematuria, advanced age, or smoking. The risk minimisation measure was the "Dear Health Professional Communication" (DHPC), issued by the marketing authorization holder in July-August of 2011. The aim of this investigation was to evaluate the impact of risk minimisation in the form of DHPC among users of pioglitazone. The impact was measured by population-level changes in utilisation of pioglitazone-containing products before and after DHPC and by patient-level changes in objective parameters of disease. In Denmark, the entire population was covered, while the Netherlands and the United Kingdom databases covered representative samples of respective populations. We used Aarhus University (AU) Research Database in Denmark; the Integrated Primary Care Information (IPCI) database in the Netherlands, and the Clinical Practice Research Datalink (CPRD) in the United Kingdom.

The study population consisted of users of pioglitazone-containing products identified through prescription records identifiable in the three databases. The study period was 2004-2011 in Denmark; 2007-2011 in the Netherlands; and 2000-mid-2012 in the United Kingdom. First, changes over calendar time in the numbers of new users, prevalent users and prescriptions of pioglitazone-containing products were examined. Second, baseline characteristics of new users of pioglitazone before and after DHPC were described. Third, concomitant use of pioglitazone with other glucose-lowering drugs was evaluated. Fourth, initiation and termination of pioglitazone-containing products in by persons with potential contraindications and risk factors for bladder cancer were described. Furthermore, we evaluated risks of potential adverse events (deaths, cardiovascular outcomes, diabetes-related adverse events) and changes in objective parameters of disease, including concentrations of glycated haemoglobin and fasting plasma glucose in relation to DHPC. Finally, we evaluated whether periodic treatment reviews among pioglitazone users took place after DHPC.

During the study period, overall there were 897 new users of pioglitazone identified in AU, 667 in the IPCI, and 33308 in the CPRD. After DHPC, there were 35 new users in AU, 39 in IPCI, and 1291 in the CPRD. In all three databases the number of new users of pioglitazone-containing products peaked in late 2010, whereupon it decreased or plateaued. The number of prevalent users has decreased, particularly in the second half of 2011. Based on CPRD data, 0.4% of new users of pioglitazone before DHPC had a history of bladder cancer; among new users after DHPC, 0.2% had a history of bladder cancer. Corresponding data were sparse for post-DHPC new users in AU or IPCI. In all three countries, majority of the pioglitazone users were concomitantly using metformin. There was evidence, from all three databases, of patients with history of bladder cancer, haematuria and patients older than 80 years being taken off pioglitazone in the months following DHPC. Risks of adverse events were low in pioglitazone users on/after DHPC. There was evidence, on patient level, of slight net mean increase in concentrations of glycated haemoglobin and fasting plasma glucose at 6 to 12 months following DHPC. Most pioglitazone users had a record of at least one glycated haemoglobin measurement taken after DHPC in all three databases.

The present document is an interim statistical analysis report addressing the impact of DHPC on utilisation of pioglitazone-containing products and on patient outcomes among pioglitazone

users in three European Union Member States. These interim results indicate decrease of pioglitazone use in Denmark, the Netherlands and in the United Kingdom, which started before DHPC and continued thereafter. Furthermore, there is an indication of stopping the drug at least in some patients with a history of bladder cancer. The available data do not allow distinguishing whether haematuria was micro- or macroscopic or whether it was investigated. Before fully interpreting the data, the interim results will be subjected to a number of sensitivity analyses to test definitions of new use and termination of pioglitazone.

2. INTRODUCTION

Pioglitazone belongs to the drug class thiazolidinediones and is used as a second-line therapy in patients with type 2 diabetes mellitus.[1] Pioglitazone was approved for use in the European Union in 2000.[2] The drug controls type 2 diabetes in certain patients in whom traditional glucose-lowering drugs are not effective. Observational evidence suggests that the drug is associated with a slightly increased risk of bladder cancer.[3] Based on that evidence, on 21 July 2011, the EMA's Committee for Medicinal Products for Human Use (CHMP), concluded that 'although there is a small risk of bladder cancer with pioglitazone, its benefits continue to outweigh its risks in a limited population of type 2 diabetes patients'.[2] The Committee recommended discontinuation of pioglitazone in patients with bladder cancer or uninvestigated macroscopic haematuria, and in patients not deriving sufficient therapeutic benefit from pioglitazone. There was also a recommendation for consideration of patients' risk factors for bladder cancer, such as age and smoking, before initiating pioglitazone treatment; and for prescribing the lowest possible dose to elderly patients. Following the CHMP recommendation, Takeda UK Ltd., the marketing authorization holder for pioglitazone, issued a "Dear Health Professional" communication (DHPC), detailing the labelling amendments.

This study was commissioned by the EMA. EMA wishes to assess, in at least two European Union Member States, changes in pioglitazone utilisation and patient-level outcomes following the DHPC, including size and composition of the treated patient population. On the patient level, EMA wishes to assess diabetes control among patients who remained on or discontinued pioglitazone drug after the DHPC.

3. OBJECTIVES

The current interim report provides data to address the following specific objectives:

- **Objective 1**: To provide observational data on drug utilisation patterns of pioglitazone-containing products in the European Union (EU) and to study associations between changes in drug utilisation patterns and the regulatory decisions in the form of DHPC.
- **Objective 2a**: To analyse events in patients discontinuing pioglitazone after the DHPC, including adverse drug events, alterations in glycaemic control, and modification of other objective parameters of disease.
- **Objective 2b**: To analyse contraindications and events in patients continuing or starting pioglitazone, including adverse drug events, alterations in glycaemic control, and modification of other objective parameters of disease.

4. METHODS

4.1 SOURCE POPULATION AND STUDY POPULATION

The source population for this study consisted of residents of Denmark, Netherlands, and United Kingdom covered by relevant medical databases. In Denmark, the source population for the analysis of utilisation included the entire Danish population; for the analysis of laboratory data, the sample was restricted to residents of the North and the Central Denmark regions, represented by the Aarhus University Research Database (AU), in which data on laboratory tests are available.[4 5] In the Netherlands, the source population was residents treated by general practitioners participating in the Integrated Primary Care Information (IPCI) database.[6 7] In the United Kingdom, the source population consisted of patients treated by general practitioners participating in the Clinical Practice Research Datalink (CPRD), formerly known as the General Practice Research Database (GPRD).[8] For CPRD, only patients with at least one year of recorded data in the database before the initiation of pioglitazone use (as defined in current protocol, below) were included in the study. In AU and IPCI this criterion will be applied in the final analyses; in the current analyses, AU and IPCI require a minimum of 180-day record length.

The study population were members of the source population with an identifiable record of use of pioglitazone-containing products. Hereafter 'pioglitazone use' refers to use of any pioglitazone-containing product, unless stated otherwise.

4.2 STUDY DESIGN AND STUDY PERIOD

For Objective 1, we examined utilisation of pioglitazone over time, and changes in utilisation patterns in relation to DHPC. For Objectives 2a and 2b, we used the historical cohort design to provide descriptive analysis of the occurrence of potential adverse events and changes in objective parameters of disease among pioglitazone users.

The study period began on 1.1.2000 in CPRD, on 1.1.2004 in AU, and on 1.1.2007 in IPCI, reflecting availability of prescription data and the most recent update. The end of observation was 31.12.2011 in AU, 02.02.2012 in IPCI and 30.06.2012 in CPRD. For the drug utilisation analysis IPCI data were truncated on 31.12.2011 since currently not all practices have updated their data for 2012.

4.3 EXPOSURE

4.3.1 Initiation, use, and termination of pioglitazone-containing products

DHPC baseline (or DHPC) is the calendar date of the "Dear Health Professional" communication **(DHPC)**. This date was used as the baseline date of utilisation patterns among prevalent users of pioglitazone at the time of DHPC. The country-specific **DHPC** baselines are:

DENMARK	11 August 2011
NETHERLANDS	05 August 2011
UNITED KINGDOM	29 July 2011

These dates were communicated in an email from 20 February 2012 by the following official:

Sarah Harding
Medical Director, Pharmacovigilance
Takeda Global R & D Centre (Europe) Ltd.,
61 Aldwych, London WC2B 4AE
Email: s.harding@tgrd.com
Phone: +44 (0)20 3116 8325
Fax: +44 (0)20 7242 1820

New user of pioglitazone was defined as a person with the first recorded prescription for a pioglitazone-containing product in the absence of such prescriptions at least 180 days before the date of the first pioglitazone prescription within the study period. The date of the first-recorded pioglitazone prescription was the date of the initiation of pioglitazone. This date was used as baseline for ascertaining baseline characteristics among new users of pioglitazone.

Prevalent user of pioglitazone was a pioglitazone user who had initiated pioglitazone before a given date and continued to be on the drug, as evidenced by the date of the most recent prescription and the estimated prescription length.

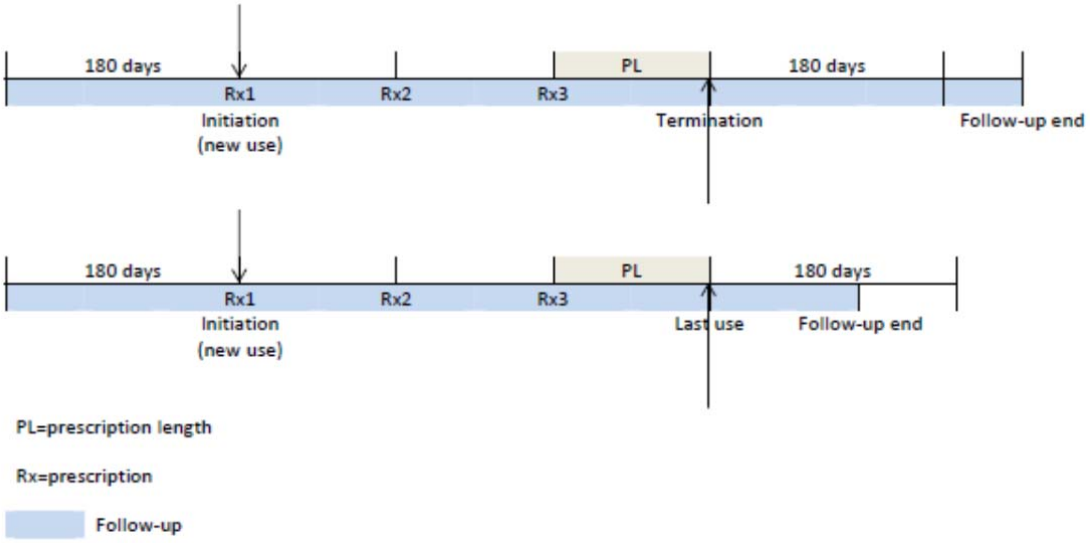
Prescription length was defined separately in each database, based on prescribing practices and the best available data. In the AU database, the prescription length was the number of days supplied based on the number of defined daily doses (DDD) in a dispensed prescription. In the IPCI database, recorded prescription length was used whenever available; if unavailable, median of prescription length was used. In the CPRD, prescription length for pioglitazone, based on recommendation and actual use.

Last prescription for pioglitazone was defined as the prescription for a pioglitazone product followed by absence of a new prescription for pioglitazone for 180 days, or end of the patient record, whichever comes first. The end of patient record occurred by death, migration from the database catchment area, or end of study.

Termination of pioglitazone was defined as the date of the last estimated drug intake, calculated by adding the estimated prescription length to the date of the last prescription for a pioglitazone-containing product. If death, emigration, or the end of the follow-up occurred before the end of the estimated prescription length plus 180 days (see last prescription definition), the

date of death, emigration, or end of follow-up was not considered as date of termination of pioglitazone, but follow-up was censored at this time.

Thus, according to these definitions, it was possible for a person to initiate or terminate pioglitazone use more than once during the study period. The definitions are presented in the figure below:



For patients whose use of pioglitazone continued beyond DHPC, a modified definition of termination was applied in order to accommodate unavailability of full 180 days of follow-up in the databases after DHPC. This definition was based on estimated date of switching from pioglitazone to another oral hypoglycaemic agent (OHA) among pioglitazone terminators who had ≥180 days of follow-up available after termination date (termination date=date of last prescription+prescription length). In this group of people, we defined termination according to the following algorithm:

- Find the date of the first OHA prescription after termination of pioglitazone
- Calculate 'time to switch', defined as number of days form the termination date until the date of the first post-termination OHA prescription
- Obtain 'median time to switch', defined as median number of days in the population of switchers to other OHAs with =>180 days of follow-up
- Use the 'median time to switch' instead of 180 days to define termination of pioglitazone for those whose pioglitazone use extends beyond DHPC date. The 'median time to switch' was estimated separately in each database.

The modified definition was used for analysis involving patient-level outcomes. For the drug utilisation analysis, the 180-day-based definition of termination and initiation was applied throughout the entire observation period.

4.4 ENDPOINTS

4.4.1 Utilization patterns

Changes in utilisation of pioglitazone over time were reported for new users, prevalent users, and prescriptions during the study period. Subsequently we described baseline characteristics of new users of pioglitazone containing products before and after the country-specific date of DHPC. The data included type of first pioglitazone-containing product prescribed; calendar year of pioglitazone initiation; sex; age at pioglitazone initiation; contraindications (heart failure, hepatic impairment, diabetic ketoacidosis, bladder cancer, any recorded haematuria); diabetes-related characteristics (glycated haemoglobin A [HbA1c]; fasting plasma glucose [FPG]; duration of type 2 diabetes); overall comorbidity (measured by Charlson comorbidity index[9]); history of medication use (lipid-lowering agents, antihypertensive agents, diuretics; nitrates; antiplatelet agents); and lifestyle factors whenever available (obesity [defined as body mass index ≥30 kg/m^2 or a relevant diagnostic code], smoking, and alcoholism). Measureable characteristics were database-specific.

The look-back period for assessment of the baseline covariates was based on the period covered by each database and by clinical relevance. History of cancer, and Charlson comorbidity index, medication use, obesity, smoking and alcoholism were assessed using the entire period available in each database. Diabetes-related characteristics were assessed within up to 24 months before the baseline. Duration of diabetes was defined as the time from diabetes onset until pioglitazone initiation date. Diabetes onset was defined as the date of the first-recorded prescription for an oral hypoglycaemic agent or the date of the first-recorded diabetes diagnosis.

Concomitant treatment of pioglitazone with other glucose lowering agents was assessed among new users of pioglitazone before and after DHPC. Presence of concomitant treatment with glucose-lowering agents was defined as at least one prescription for a given agent recorded during between the first and the last prescription for pioglitazone. Fixed combinations of pioglitazone with metformin, glimepiride or alogliptin were reported as concomitant treatment with the respective oral glucose lowering agent.

To assess switching to and from alternative therapies, among all new users of pioglitazone, we examined distribution of last glucose-lowering agent(s) prescribed before the initiation of pioglitazone. Among patients who terminated pioglitazone not as a result of death emigration or end of follow-up, we examined the distribution of the first glucose-lowering agent(s) prescribed after termination of pioglitazone.

To examine changes in pioglitazone utilisation around the time of DHPC, we identified a cohort of prevalent users of pioglitazone, i.e. those who started the drug before the DHPC date and a cohort of new pioglitazone users, i.e. those who started the drug on or after the DHPC date. The baseline among the prevalent users was the DHPC date. The baseline date for the new users was the initiation date. We examined:

- Prevalence of contraindications and risk factors for bladder cancer separately for the prevalent users and for the new users, by calendar month after the month of DHPC.
- How the investigation of haematuria affected utilisation of pioglitazone. We reported the number and the proportion of the prevalent pioglitazone users with a haematuria record

after DHPC, and among those, the number and proportion of patients subsequently terminating pioglitazone. Among patients initiating pioglitazone after DHPC, we examined the proportion of those with haematuria recorded after DHPC but before pioglitazone initiation.

- Whether periodic reviews of treatment took place. We counted, for each of the cohort members, the number of HbA1c measurements recorded from DHPC and until the end of the follow-up (for prevalent users) or from the first pioglitazone prescription until the end of the follow-up (for new users initiating after DHPC). We reported the distribution of the total number of the post-DHPC/post-initiation HbA1c measurements in this cohort (0, 1, >1).

- Outcomes of periodic treatment reviews. We identified patients failing to derive sufficient benefit from treatment. Failure to derive treatment benefit was defined as at least one measurement of HbA1c ≥7.5% recorded after DHPC (for prevalent users) or the initiation of pioglitazone (for new users). Among the patients identified as failing to derive sufficient treatment benefit, we reported the proportion receiving at least one prescription for pioglitazone after the date of the recorded HbA1c≥7.5%. We also assessed the proportion of prevalent (as of DHPC date) pioglitazone users who discontinue pioglitazone treatment after DHPC date in the absence of evidence of insufficient treatment benefit (patients without data on HbA1c or patients with HbA1c <7.5%).

To compare prescribing patterns in the elderly before and after DHPC, we compared new users of pioglitazone before DHPC with new users of pioglitazone after DHPC with respect to:

- Age distribution at the start of pioglitazone therapy;

- First prescribed dose, stratified by age group. In Denmark and in the Netherlands, an estimated first prescribed dose was calculated by dividing the total amount of pioglitazone dispensed at the initiation date by the time between the first and the second prescription for pioglitazone. The total amount dispensed was calculated by multiplying the number of pills by pill strength. In the CPRD, the actual first prescribed dose is recorded and was reported. To account for uncertainty about inter-prescription intervals, first-prescribed pill strength was reported.

- Prevalence of concomitant use of pioglitazone with insulin by age group. Concomitant use with insulin was defined as record of at least one prescription for insulin between the first-recorded and the last-recorded prescription for pioglitazone.

4.4.2 Patient-level endpoints

Patient-level outcomes were examined in the following two groups of patients: 1) all users of pioglitazone on/after DHPC (new and prevalent users combined); and 2) persons terminating pioglitazone after DHPC (group 2 is a subset of group 1).

For the analysis of the prevalent/new users, baseline was defined as the date of DHPC (for prevalent users) or date of the first prescription for pioglitazone after DHPC (for new users). For the analysis of terminating patients, baseline was defined as the date of termination of pioglitazone (date of the last prescription + prescription length).

Potential adverse events

We examined the occurrence of the following potential adverse events during the relevant follow-up, separately for prevalent/new and for pioglitazone users with last prescription for pioglitazone after DHPC:

- Death from all causes;
- Diabetes complications, defined as a compound outcome of acute renal failure, diabetic coma, or diabetic acidosis;
- Cardiovascular events, specifically:
    a. acute myocardial infarction,
    b. acute coronary syndrome,
    c. haemorrhagic stroke,
    d. ischaemic stroke.

The follow-up for this analysis started on the date of the relevant baseline and ended at the earliest of 45 days, emigration, or death. For pioglitazone users who terminated the drug after DHPC, only diabetes complications were examined. Other events (death and cardiovascular events) were not examined, because the current definition of termination would not capture deaths that occurred after DHPC but before the estimated termination date which is median time to switch after the end of the last pioglitazone prescription. This requirement may not be tenable for death, and cardiovascular outcomes, which have high mortality.

This analysis on measures of glycaemic control and other biochemical parameters was conducted using available data on laboratory tests in the three databases. In AU, laboratory data analysis was restricted to users of pioglitazone in northern Denmark, the area covered by the clinical laboratory information systems (the LABKA database[4]).

Glycated haemoglobin A (HbA1c) and fasting plasma glucose (FPG) served as measures of glycaemic control. Lipids were measured by fasting serum concentrations of total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides. Whenever available, renal function was measured using estimated glomerular filtration rate (eGFR), calculated based a standard formula using serum creatinine, age and sex (See Appendix 2 for study algorithms).

Baseline and post-baseline values in these parameters were compared for all users of pioglitazone who filled a prescription post-DHPC (prevalent and new users) and again for all for all pioglitazone users who stopped use after DHPC (post-DHPC terminators). For prevalent users, the baseline value of each laboratory parameter was the value recorded before or on, and most proximal in time, to the DHPC date. For new users, who started pioglitazone after the DHPC date, the baseline was the date of the first pioglitazone prescription. To identify the

baseline values the look-back period of 24 months before the baseline was used. For the comparison of lab values before and after the termination of pioglitazone, the baseline date was the estimated date of termination (date of the last prescription plus the estimated prescription length). Mean pre-/after baseline differences were estimated at 3, and 6 months post-baseline for all laboratory parameters, except eGFR. These periods were defined to provide non-overlapping, all-inclusive continuity of observation, with each period continuing until the time accumulated for the next period, as follows: >0-3 months=day 1 post-baseline through day–89 post-baseline; >3-6 months=day 90-post-baseline through day 180 post-baseline. Within each period, the earliest available post-baseline measurement was used as the follow-up value. Estimated glomerular filtration rate (eGFR) was calculated at the first available relevant measurement of serum creatinine during the follow-up. Relevant measurements of serum creatinine for calculating eGFR are measurements taken on day 1 though day 365 post-baseline.

4.5 ANALYSIS

To harmonize databases and information we applied a distributed network approach using JERBOA©. JERBOA is custom built JAVA-based software that has been created and used in other European funded projects (i.e. EU-ADR, VAESCO, SOS).[6] Each database created standardized input files (patients, events and prescriptions). JERBOA aggregated, anonymised the information and produced output files that were shared and stored centrally for the analysis. The harmonization was conducted for the important events addressed in this investigation, (haematuria, bladder cancer and cardiovascular outcomes). Incidence rates as well as the standardized incidence rates by age categories were compared among the three databases. In cases of a substantial discrepancy, algorithms were adjusted and harmonization run repeated.

We plotted, against calendar time the number of new users, prevalent users and the number of pioglitazone prescriptions for the three databases. The plots were constructed by calendar year and separately for months leading up to DHPC.

We calculated prevalences and distributions of variables in the descriptive utilisation tables (e.g., prevalence of users with history of bladder cancer, distribution of age groups). For adverse events, we reported 45-day risks with 95% confidence intervals. For changes in the laboratory parameters, we reported means and standard deviations. All analyses were descriptive.

Data analyses for the plots were conducted using the JERBOA tool at EMC. Data analyses for the tables were conducted using SAS software, version 9.2 (SAS, Inc., Cary, NC, USA).

5. DATA SOURCES

The following table provides brief description of the three automated databases in the European Union that will be used to in this project.

Type of data	DATABASE		
	AU	IPCI	CPRD
	Population-based medical registries	GP database	GP database
Coding system for drugs	ATC	ATC	Multilex
Coding system for events	ICD-8, ICD-10	ICPC 1	READ
Free text	No	Yes	Available on request
Availability of FU years	Drugs 2003-2011; hospital visits 1977-2011, including outpatient visits since 1995	2007 up to 2011 (for some subjects Feb 2012)	1990 to Mid-2012
Patient identifier used for linkage	The Danish Civil Registration System	Patient file	The CPRD administrative file
Deaths	The Danish Civil Registration System	Patient file	The CPRD event file plus death registry data where available.
Prescription medication	Aarhus University Prescription Database; reimbursed prescriptions filled in outpatient pharmacies	Prescriptions file: issued prescriptions	The CPRD drug file: issued prescriptions
Diagnoses	Inpatient and outpatient hospital-based diagnoses, recorded in the Danish National Registry of Patients	IPCI Journal file	The CPRD event file
Laboratory tests	The Laboratory Information Systems research database	Measurements file	The CPRD laboratory file
Smoking, alcohol use body mass index	Hospital codes for obesity and alcohol use will be used	Diagnosis file and Measurements file	The CPRD registration file

6. RESULTS

Figure 1-Figure 4 show utilisation patterns of pioglitazone-containing products over time in Denmark, Netherlands and the United Kingdom. The patterns are shown annually until 2011 and monthly for the months leading up to and after DHPC. Figure 1 shows the number of new users; Figure 2 the number of prevalent users; and Figure 3 the number of prescriptions in the three databases. Figure 4 summarises patterns of use by calendar month before and after DHCP in the three databases.

Before DHPC, there were 862 new users of pioglitazone in AU, 628 in IPCI and 32017 in the CPRD. After DHPC, there were 35 new users of pioglitazone in AU, 39 in IPCI and 1291 in the CPRD. Table 1 shows baseline characteristics of the new users of pioglitazone who initiated pioglitazone before DHPC and Table 2 shows baseline characteristics of the new users of pioglitazone on/after DHPC.

Table 3 shows database specific prevalences of concomitant treatment of pioglitazone with other antidiabetic drugs among persons initiating pioglitazone before DHPC, while Table 4 shows these data for patients initiating pioglitazone on/after DHPC.

Table 5 shows distribution of last glucose-lowering drugs prescribed before the initiation of pioglitazone for those initiating pioglitazone at any time during the study period. Table 6 shows the distribution of first antidiabetic drugs prescribed after termination of pioglitazone before and on/after DHPC. This table includes persons switching to other OHAs from pioglitazone and those for whom pioglitazone was removed from the treatment regimen.

The estimated median time to switch was 23 days in AU, 44 days in IPCI, and 21 days in CPRD. This period was used to define termination of pioglitazone after DHPC, as described in Methods. Table 7 shows termination of pioglitazone among pioglitazone users with contraindications and risk factors for bladder cancer as of the last pre-DHPC calendar month (June 2011 in CPRD and July 2011 in AU and IPCI). Table 8 shows prevalence of contraindications and risk factors for bladder cancer among persons who initiated pioglitazone on/after DHPC. There were few persons with contraindications or in older age groups.

Table 9 shows the distribution of first prescribed dose and first dispensed pill strength among new users of pioglitazone before DHPC, by age group and Table 10 shows these data for new users on/after DHPC. For AU and IPCI the prescribed dose was estimated based on dispensed amount and in CPRD the actual prescribed dose is shown. Table 11 and Table 12 show prevalence of concomitant use of pioglitazone with insulin, by age group, among new users of pioglitazone before and after DHPC, respectively. The bulk of data stems from the CPRD and base on those data, there is some evidence that prevalence of concomitant use with insulin decreased after DHPC.

Forty-five day risks of all adverse events among prevalent and new users of pioglitazone were low. There was one event of acute coronary syndrome among 209 persons at risk in Denmark, and one stroke among 382 subjects in IPCI. Few relevant events were observed in AU and IPCI. In CPRD there were 17 deaths among 15284 persons at risk (45-day risk 0.11%, 95% CI: 0.07% – 0.17%) (Table 13). Among those who terminated pioglitazone after DHPC (Table 14), in the CPRD there were six diabetes-related adverse events within 45 days of termination among 3270 persons who had the last pioglitazone prescription on/after DHPC, by database/country (45-day risk 0.18%, 95% CI: 0.07% – 0.38%). No diabetes-related observed event was observed in AU or IPCI during the available follow-up.

Table 15 shows mean differences in laboratory parameters before and on/after DHPC among prevalent and new users of pioglitazone at DHPC in the three databases. There were up to 6 months of follow-up available in AU and IPCI and up to 12 months in the CPRD. Table 16 shows mean differences in laboratory parameters before and after pioglitazone termination among patients terminating pioglitazone on/after DHPC. Termination in these analyses was defined as the last day of pioglitazone use followed by absence of a new prescription for pioglitazone for 23/44/21 days (the estimated median time to switch for AU/IPCI/CPRD). At 12 months post-baseline, CPRD data indicated a mean change estimate consistent with slight net increase for glycated haemoglobin and fasting plasma glucose (Table 15 and Table 16).

Table 17 and Table 18 show data on periodic treatment reviews among prevalent users of pioglitazone as of DHPC and among new users of pioglitazone on/after DHPC. Majority of patients had glycated haemoglobin measured while on pioglitazone. In Denmark, data were sparse. In IPCI, the proportion of subjects with evidence of lack of glycaemic control was 67.4% among prevalent users on/after DHPC and 91.7% among those who started pioglitazone after DHPC, however, that percentage is based on a total of 39 observations. Based on CPRD data, proportion of patients with evidence of insufficient benefit from pioglitazone receiving another pioglitazone prescription was 80.8% among prevalent users and 68.1% among new users after the DHPC.

7. COMMENT

This report contains descriptive data on utilisation of pioglitazone in Denmark, the Netherlands and the United Kingdom, as inferred from data available from routine automated databases in those countries. During the study period, there were 897 new users of pioglitazone identified in AU, 667 in the IPCI, and 33308 in the CPRD. After DHPC, there were 35 new users in AU, 39 in IPCI, and 1291 in the CPRD. In all three databases the number of new users of pioglitazone-containing products peaked in late 2010, whereupon it decreased or plateaued. The number of prevalent users has decreased, particularly in the second half of 2011. Based on CPRD data, 0.4% of new users of pioglitazone before DHPC had a history of bladder cancer; among new users after DHPC, 0.2% had a history of bladder cancer. Data were sparse for post-DHPC new users in AU or IPCI. In all three countries, majority of the pioglitazone users were using concomitantly metformin. There was evidence, from all three databases, of patients with history of bladder cancer, haematuria and patients older than 80 years being taken off pioglitazone in the months following DHPC. Risks of adverse events were low in pioglitazone users on/after DHPC. There was evidence, on patient level, of slight net mean increase in concentrations of glycated haemoglobin and fasting plasma glucose at 6 to 12 months following DHPC. Most pioglitazone users had a record of at least one glycated haemoglobin measurement taken after DHPC in all three databases. We did not exclude from the study population patients with type 1 diabetes, reasoning that the same safety concerns would apply to them as to patients with type 2 diabetes.

Because of routine data collection in the data sources involved, selection bias is expected to be negligible. Information bias may stem from inability to ascertain the actual drug intake from prescription issue or dispensation data; however, because diabetes is a chronic condition requiring treatment – including pioglitazone - high compliance with all glucose-lowering drugs will be assumed. It is acknowledged that exact timing of start and end of medication intake will inevitably be misclassified to a certain extent. This is general limitation of drug safety studies.
The most important limitation of the present analysis stems from balancing the attempt to define a washout period long enough to validly define initiation or termination of pioglitazone course of

treatment on the one hand, and the attempt to evaluate events following termination of pioglitazone after DHPC, on the other hand. In the drug utilisation analyses, we required a 180-day washout period without a pioglitazone prescription to define an episode of new use. Similarly, we required absence of a pioglitazone prescription for 180 days after the last estimated drug intake to define termination of the drug. Because the follow-up in AU and IPCI is available through the end of 2011 only, the requirement of 180 days pioglitazone-free time to define termination of the drug could not be fulfilled. To help refine our approach, we plan to conduct a sensitivity analysis, whereby we will examine whether and how results of both post-termination analyses and drug utilisation analyses change under different assumptions about the washout period. In that analysis we will consider washout periods of 90, 60 and 30 days.

Another limitation related to the requirement of a drug-free period of any length to define termination is the problem of “immortal person-time”, especially relevant for death and for acute outcomes with lethal potential, i.e., acute myocardial infarction, and stroke. If patients need to survive the length of the washout period to be defined as terminators of pioglitazone, any events during that period will be missed in the analysis. We therefore only included analysis of diabetes-related events after termination of pioglitazone-containing products.

Uninvestigated macroscopic haematuria is an important DHPC contraindication for continuing or starting pioglitazone. Based on available data, we are able to ascertain episodes of any haematuria (micro/macroscopic, investigated/uninvestigated). It can be indirectly inferred that for patients with a haematuria record, in whom pioglitazone was stopped, the haematuria was investigated and significant, i.e., considered a potential early sign of bladder cancer. However, in these patients, termination of pioglitazone for reasons of the than haematuria cannot be ruled out based on the measureable information.

Despite database limitations and differences in recording practices and coverage, the results from all three databases were overall consistent with one another other.

The present document is an interim analysis report addressing the impact of DHPC on utilisation of pioglitazone-containing products and patient outcomes among pioglitazone users in the European Union. These interim results indicate decrease of pioglitazone use in Denmark, the Netherlands and in the United Kingdom, which started before DHPC and continued thereafter. Furthermore, there is an indication of stopping the drug at least in some patients with a history of bladder cancer. The available data do not allow distinguishing whether haematuria was micro- or macroscopic or whether it was investigated. Before fully interpreting the data, the interim results will be subjected to a number of sensitivity analyses to test definitions of new use and termination of pioglitazone.

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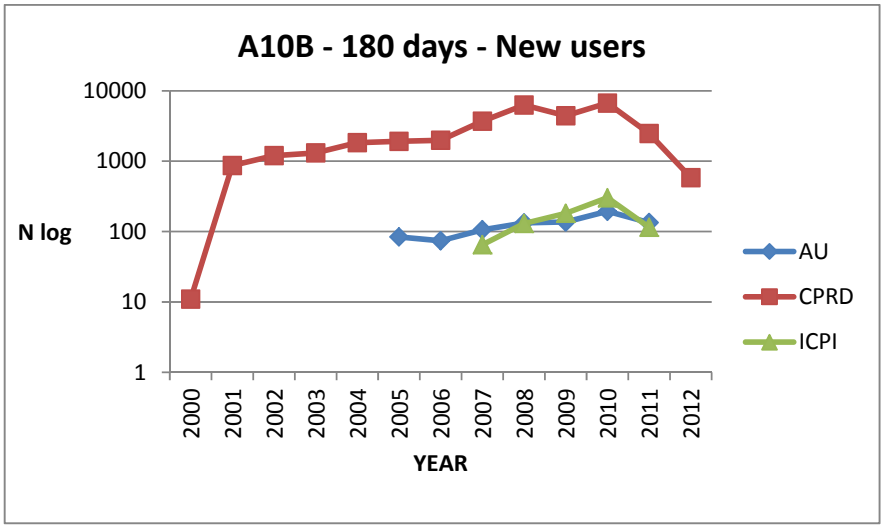
9. TABLES AND FIGURES

Figure 1. New users of pioglitazone-containing products over calendar time, by database.

New users by calendar year, by database



New users by calendar month around the time of DHCP

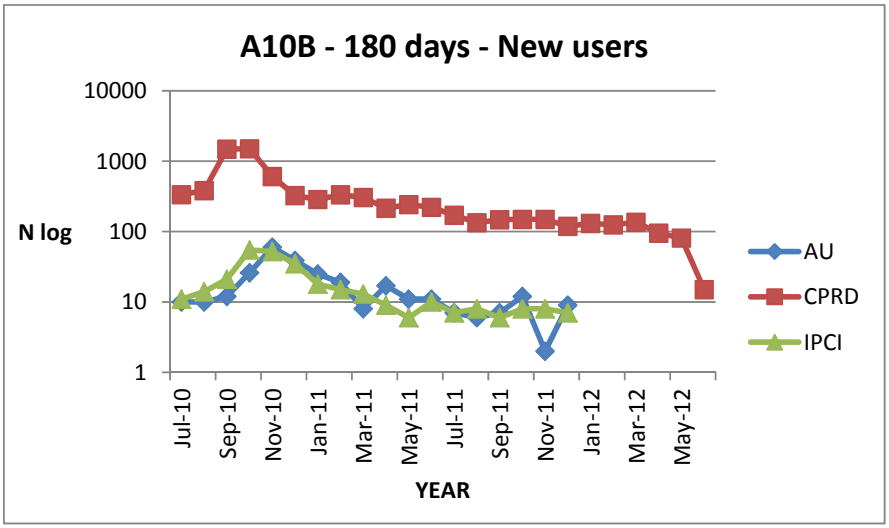
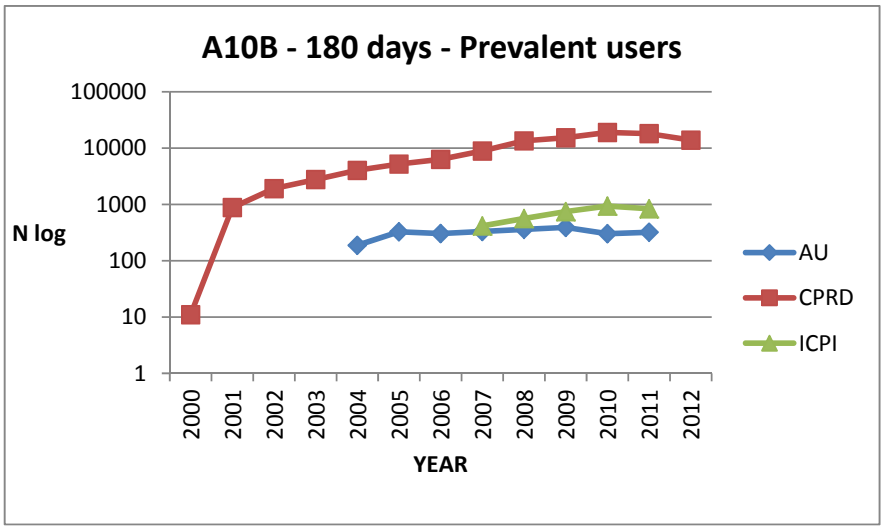


Figure 2. Prevalent users of pioglitazone-containing products over calendar time, by database.

Prevalent users by calendar year, by database



Prevalent users by calendar month around the time of DHCP

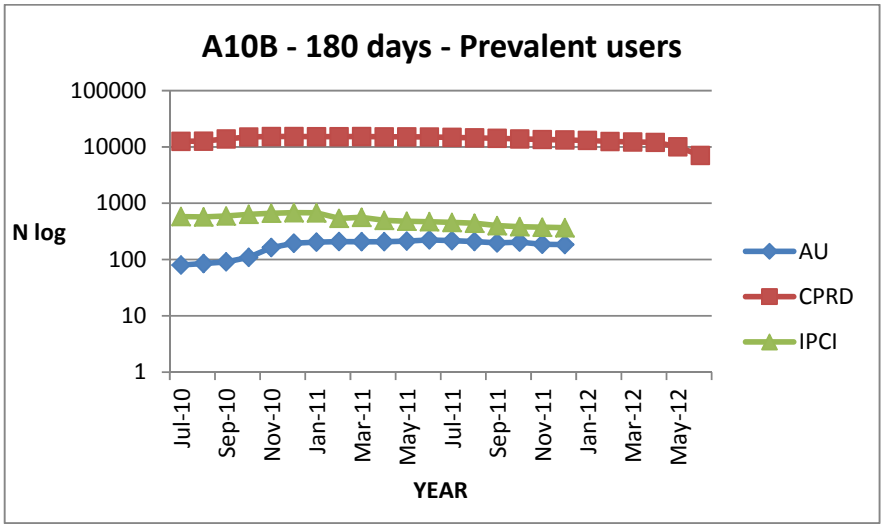
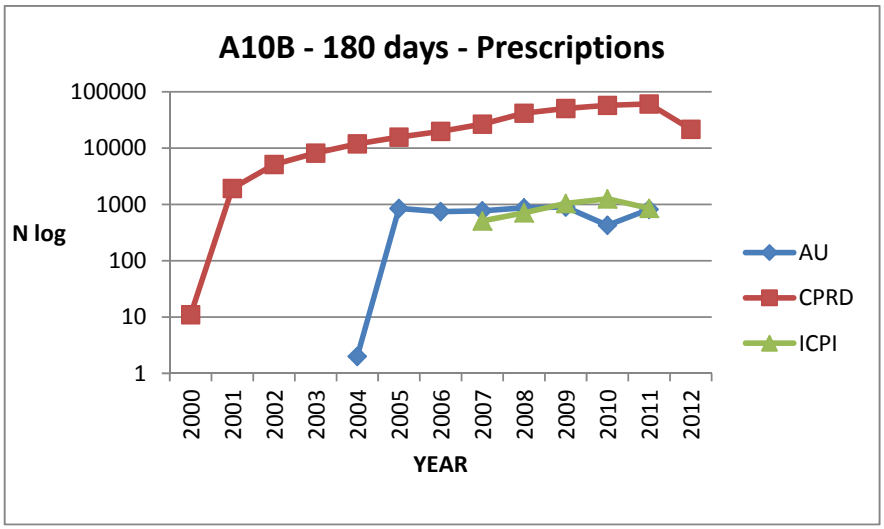


Figure 3. Prescriptions of pioglitazone-containing products over calendar time, by database.

Prescriptions by calendar year, by database



Prescriptions by calendar month around the time of DHCP

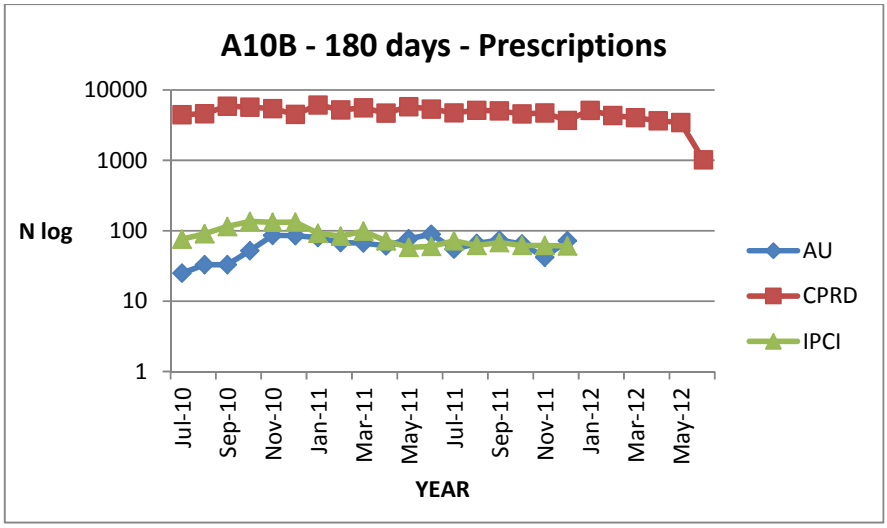
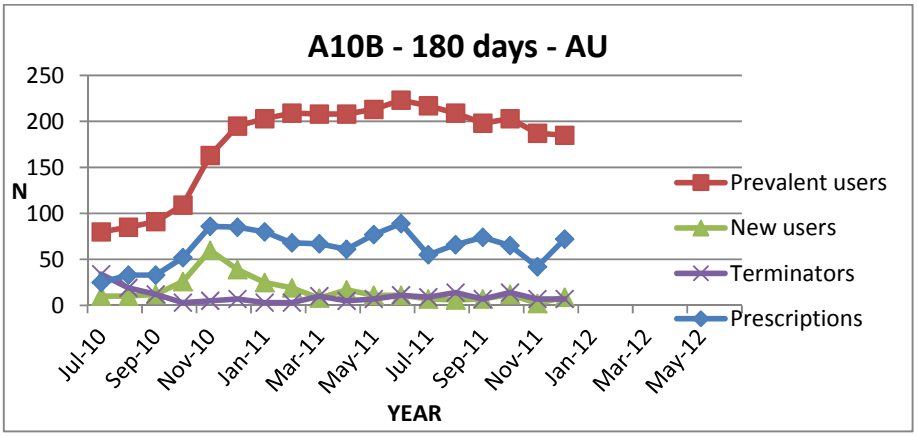
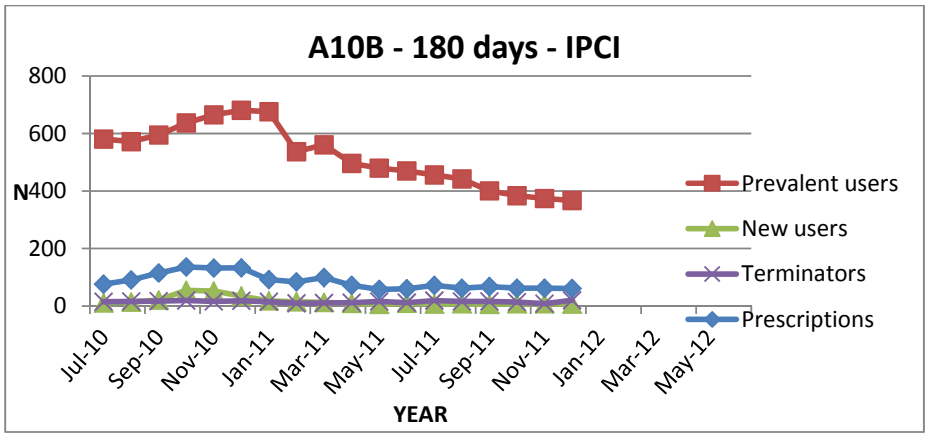


Figure 4. Summary of utilisation of pioglitazone by database/calendar month around DHPC





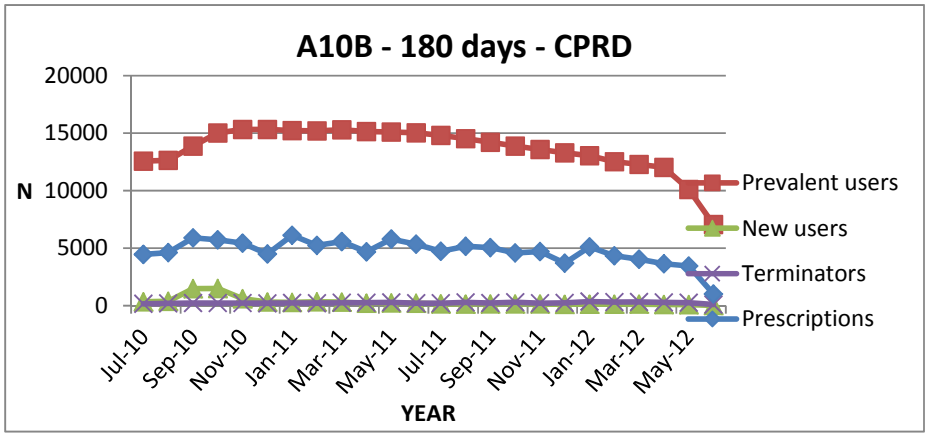


Table 1. Baseline characteristics of the new users of pioglitazone who initiate pioglitazone before DHPC (baseline=initiation date).

Characteristic	N (%) unless specified otherwise		
	AU	IPCI	CPRD
All new users in period	862	628	32017
Type of pioglitazone preparation			
All preparations			
Pioglitazone	629 (72.97)	408 (64.97)	20433 (63.8)
Pioglitazone and glimepiride	39 (4.52)	43 (6.85)	407 (1.3)
Pioglitazone and metformin	194 (22.51)	177 (28.18)	10771 (33.6)
Pioglitazone and metformin and glimepiride			406 (1.3)
Calendar year of pioglitazone initiation (all preparations)			
2000			11 (0.03)
2001			865 (2.7)
2002			1202 (3.8)
2003			1313 (4.1)
2004	35 (4.06)		1831 (5.7)
2005	84 (9.74)		1924 (6.0)
2006	73 (8.47)		1983 (6.2)
2007	105 (12.18)	20 (3.18)	3705 (11.6)
2008	134 (15.55)	89 (14.17)	6279 (19.6)
2009	137 (15.89)	157 (25.00)	4422 (13.8)
2010	194 (22.51)	285 (45.38)	6704 (20.9)
2011	100 (11.60)	77 (12.26)	1778 (5.6)
Sex			
Men	501 (58.12)	304 (48.41)	18393 (57.4)
Women	361 (41.88)	324 (51.59)	13624 (42.6)
Age group at initiation of pioglitazone-containing products, years			
<18			6 (0.02)
18-34	36 (4.18)	6 (0.96)	393 (1.2)
35-44	54 (6.26)	26 (4.14)	2054 (6.4)
45-54	182 (21.11)	100 (15.92)	5679 (17.7)
55-64	286 (33.18)	198 (31.53)	9442 (29.5)
65-74	193 (22.39)	160 (25.48)	9014 (28.2)
75-84	95 (11.02)	112 (17.83)	4738 (14.8)
≥85	16 (1.86)	26 (4.14)	691 (2.2)
History of potential contraindications any time before initiation			
Any contraindication	97 (11.25)	114 (18.15)	3612 (11.3)
Bladder cancer	3 (0.35)	3 (0.48)	139 (0.4)
Haematuria	38 (4.41)	34 (5.41)	2305 (7.2)
Mild hepatic impairment	25 (2.90)	14 (2.23)	498 (1.6)
Moderate to severe hepatic impairment	0 (0)	1 (0.16)	22 (0.07)
Diabetic ketoacidosis	4 (0.46)	2 (0.32)	91 (0.3)
Heart failure	34 (3.94)	71 (11.31)	824 (2.6)
Duration of type 2 diabetes, months, mean(SD)	75 (58)	117 (131)	147 (307)
Diabetes-related history in 24 months before initiation	N=190****		
Glycated haemoglobin A (HbA1c), %, mean (SD)*	8.3 (1.5)	7.7 (2.8)	8.4 (1.9)*
Inadequate glycaemic control (HbA1c ≥ 7.5%)	113 (59.47)	250 (39.81)	22110 (69.1)

Characteristic	N (%) unless specified otherwise		
	AU	IPCI	CPRD
Fasting plasma glucose, mmol/L, mean (SD)**	9.9 (3.8)	8.7 (2.6)	9.8 (3.7) **
Charlson comorbidity index any time before initiation			
Low (0)	534 (61.95)	186 (29.62)	17070 (53.3)
Medium (1-2)	263 (30.51)	221 (35.19)	11666 (36.4)
High (>2)	65 (7.54)	221 (35.19)	3281 (10.3)
History of medication use any time before initiation			
Lipid-lowering agents	610 (70.77)	499 (79.46)	26136 (81.6)
Antihypertensive agents	653 (75.75)	483 (76.91)	25795 (80.6)
Diuretics	393 (45.59)	216 (34.39)	15198 (47.5)
Nitrates	82 (9.51)	77 (12.26)	2726 (8.5)
Antiplatelet agents	380 (44.08)	232 (36.94)	2334 (7.3)
Lifestyle factors (whenever available)			
Obesity/ BMI***	199 (23.09)	363 (57.80)	18778 (58.7)
Smoking			
Current			4851 (15.2)
Former			11269 (35.2)
Never			15657 (48.9)
Missing			240 (0.7)
Alcoholism	20 (2.32)	22 (3.50)	1199 (3.7)

*Based on 31155 non-missing values
**Based on 8176 non-missing values
***Defined as either having a code for obesity or a BMI ≥ 30 kg/m^2
****Restricted to Northern Denmark, covered by the LABKA Database

Table 2. Baseline of the new users of pioglitazone who initiate pioglitazone on/after DHPC (baseline=initiation date).

Characteristic	N (%) unless specified otherwise		
	AU	IPCI	CPRD
All new users in period	35	39	1291
Type of pioglitazone preparation			
All preparations			
Pioglitazone	30 (85.71)	23 (58.97)	939 (72.7)
Pioglitazone and glimepiride	1 (2.86)	2 (5.13)	15 (1.2)
Pioglitazone and metformin	4 (11.43)	14 (35.90)	329 (25.5)
Pioglitazone and metformin and glimepiride			8 (0.6)
Calendar year of pioglitazone initiation (all preparations)			
2011	35	38 (97.44)	705 (54.6)
2012	No data	1 (2.56)	586 (45.4)
Sex			
Men	20 (57.14)	21 (53.85)	753 (58.3)
Women	15 (42.86)	18 (46.15)	538 (41.7)
Age at initiation of pioglitazone-containing products, years			
<18	-		1 (0.08)
18-34	1 (2.86)		23 (1.8)
35-44	1 (2.86)	4 (10.26)	88 (6.8)
45-54	10 (28.57)	5 (12.82)	284 (22.0)
55-64	10 (28.57)	12 (30.77)	366 (28.4)
65-74	9 (25.51)	11 (28.21)	325 (25.2)
75-84	4 (11.43)	7 (17.95)	174 (13.5)
≥85	-		30 (2.3)
History of potential contraindications any time before initiation			
Any contraindication	4 (11.43)	9 (23.08)	147 (11.4)
Bladder cancer	0	1 (2.56)	3 (0.2)
Haematuria	1 (2.86)	2 (5.13)	85 (6.6)
Mild hepatic impairment	1 (2.86)	2 (5.13)	45 (3.5)
Moderate to severe hepatic impairment	0	0	3 (0.2)
Diabetic ketoacidosis	0	0	4 (0.3)
Heart failure	2 (5.71)	5 (12.82)	17 (1.3)
Duration of type 2 diabetes, months, mean (SD)	92 (58)	122 (103)	135.9 (263)
Diabetes-related history in 24 months before initiation	N=9****		
Glycated haemoglobin A (HbA1c), %, mean (SD)*	Sparse data	7.6 (1.1)	9.0 (2.1)*
Inadequate glycaemic control (HbA1c ≥ 7.5%)		15 (38.46)	1061 (82.2)
Fasting plasma glucose, mmol/L, mean (SD)**		8.8 (2.8)	10.6 (3.8)**
Charlson comorbidity index any time before initiation			
Low (0)	24 (85.71)	13 (33.33)	696 (53.9)
Medium (1-2)	9 (25.71)	16 (41.03)	457 (35.4)
High (>2)	2 (5.71)	10 (25.64)	138 (10.7)
History of medication use any time before initiation			
Lipid-lowering agents	30 (22.86)	35 (89.74)	1113 (86.2)
Antihypertensive agents	27 (77.14)	26 (66.67)	1019 (78.9)
Diuretics	23 (65.71)	12 (30.77)	549 (42.5)

Characteristic	N (%) unless specified otherwise		
	AU	IPCI	CPRD
Nitrates	5 (14.29)	3 (7.69)	80 (6.2)
Antiplatelet agents	22 (62.86)	18 (46.15)	91 (7.0)
Lifestyle factors (whenever available)			
Obesity/ BMI***	12 (34.29)	22 (56.41)	782 (60.6)
Smoking			
Current			217 (16.8)
Former			449 (34.8)
Never			621 (48.1)
Missing			4 (0.3)
Alcoholism	4 (11.43)	2 (5.13)	53 (4.1)

*Based on 1251 non-missing values
**Based on 297 non-missing values
***Defined as either having a code for obesity or a BMI ≥ 30 kg/m^2
****Restricted to Northern Denmark, covered by the LABKA Database

Table 3. Concomitant treatment of pioglitazone with other glucose-lowering agents before DHPC (new users starting before DHPC).

Drug/ATC code	AU N= 862	IPCI N=628	CPRD N = 32017
Insulins and analogues A10A	176 (20.4)	72 (11.5)	4313 (13.5)
Biguanides			
Metformin A10BA02	548 (63.6)	371 (59.1)	25722 (80.3)
Sulfonamides, urea derivatives A10BB		296 (47.1)	
Glibenclamide (aka Glyburide) A10BB01	26 (3.0)	19 (3.0)	666 (2.1)
Chlorpropamide A10BB02			
Tolbutamide A10BB03	6 (0.7)	59 (9.4)	218 (0.7)
Glibornuride A10BB04			
Tolazamide A10BB05			
Glipizide A10BB07	26 (3.0)		781 (2.4)
Gliquidone A10BB08			5 (0.02)
Gliclazide A10BB09	61 (7.1)	63 (10.0)	15499 (48.4)
Glimepiride A10BB12	326 (37.8)	160 (25.5)	2565 (8.0)
Acetohexamide A10BB31			
Sulfonamides (heterocyclic)			
Glymidine A10BC01			
Combinations of oral blood glucose lowering drugs			
Rosiglitazone + metformin A10BD03	6 (0.7)		328 (1.0)
Rosiglitazone + glimepiride A10BD04			
Vildagliptin + metformin A10BD08	19 (2.2)	2 (0.3)	131 (0.4)
Metformin + sitagliptin A10BD07	16 (1.9)	5 (0.8)	87 (0.3)
Alpha glucosidase inhibitors			
Acarbose A10BF01	10 (1.2)		469 (1.5)
Thiazolidinediones			
Troglitazone A10BG01			
Rosiglitazone A10BG02	34 (3.9)	14 (2.2)	489 (1.5)
Dipeptidyl peptidase 4 (DPP-4) inhibitors			
Sitagliptin A10BH01	84 (9.7)	32 (5.1)	2797 (8.7)
Vildagliptin A10BH02	7 (0.8)	9 (1.4)	
Saxagliptin A10BH03	4 (0.5)	1 (0.2)	269 (0.8)
Linagliptin A10BH05			28 (0.09)
Other blood glucose lowering drugs, excl. insulins			
Guar gum A10BX01			1 (0.0)
Repaglinide A10BX02	14 (1.6)		299 (0.9)
Nateglinide A10BX03			135 (0.4)
Exenatide A10BX04	31 (3.6)	3 (0.5)	856 (2.7)
Liraglutide A10BX07	74 (8.6)	5 (0.8)	625 (2.0)

Table 4. Concomitant treatment of pioglitazone with other glucose-lowering agents on/after DHPC (new users starting after DHPC).

Drug/ATC code	AU N=35	IPCI N=39	CPRD N=1291
Insulins and analogues A10A	7 (20.0)	3 (7.7)	103 (8.0)
Biguanides			
Metformin A10BA02	17 (48.6)	21 (53.8)	979 (75.8)
Sulfonamides, urea derivatives			
Glibenclamide (aka Glyburide) A10BB01			5 (0.4)
Chlorpropamide A10BB02			
Tolbutamide A10BB03		2 (5.1)	5 (0.4)
Glibornuride A10BB04			
Tolazamide A10BB05			
Glipizide A10BB07			19 (1.5)
Gliquidone A10BB08			0
Gliclazide A10BB09		1 (2.6)	593 (45.9)
Glimepiride A10BB12	7 (20.0)	9 (23.1)	64 (5.0)
Acetohexamide A10BB31		0	
Sulfonamides (heterocyclic)			
Glymidine A10BC01			
Combinations of oral blood glucose lowering drugs			
Rosiglitazone + metformin A10BD03		1 (2.6)	
Rosiglitazone + glimepiride A10BD04			
Vildagliptin + metformin A10BD08	1 (2.9)		6 (0.5)
Metformin + sitagliptin A10BD07	1 (2.9)	1 (2.6)	9 (0.7)
Alpha glucosidase inhibitors			
Acarbose A10BF01			6 (0.5)
Thiazolidinediones			
Troglitazone A10BG01			
Rosiglitazone A10BG02			
Dipeptidyl peptidase 4 (DPP-4) inhibitors			
Sitagliptin A10BH01	2 (5.7)	1 (2.6)	152 (11.8)
Saxagliptin A10BH03		2 (5.1)	28 (2.2)
Linagliptin A10BH05			9 (0.7)
Other blood glucose lowering drugs, excl. insulins			
Guar gum A10BX01			
Repaglinide A10BX02			
Nateglinide A10BX03			1 (0.08)
Exenatide A10BX04	3 (8.6)		28 (2.2)
Liraglutide A10BX07	3 (8.6)	3 (7.7)	48 (3.7)

Table 5. Distribution of last glucose-lowering drugs prescribed before the initiation pioglitazone (all new users).

Drug/ATC code	AU N=897	IPCI N=667	CPRD N=33308
Insulins and analogues A10A	99 (11.0)	45 (6.7)	1768 (5.3)
Biguanides			
Metformin A10BA02	432 (48.2)	353 (52.9)	21602 (64.9)
Sulfonamides, urea derivatives			
Glibenclamide (aka Glyburide) A10BB01	24 (2.7)	25 (3.7)	687 (2.1)
Chlorpropamide A10BB02			
Tolbutamide A10BB03	7 (0.8)	65 (9.7)	206 (0.6)
Glibornuride A10BB04			
Tolazamide A10BB05			
Glipizide A10BB07	22 (2.5)		707 (2.1)
Gliquidone A10BB08			3 (<0.01)
Gliclazide A10BB09	48 (5.4)	61 (9.1)	13022 (39.1)
Glimepiride A10BB12	233 (26.0)	164 (24.6)	2194 (6.6)
Acetohexamide A10BB31			
Sulfonamides (heterocyclic)			
Glymidine A10BC01			
Combinations of oral blood glucose lowering drugs			
Rosiglitazone + metformin A10BD03	42 (4.7)	36 (5.4)	3081 (9.3)
Rosiglitazone + glimepiride A10BD04			
Vildagliptin + metformin A10BD08	10 (1.1)	2 (0.3)	52 (0.2)
Metformin + sitagliptin A10BD07	11 (1.2)		15 (0.05)
Alpha glucosidase inhibitors			
Acarbose A10BF01	5 (0.6)		349 (1.0)
Thiazolidinediones			
Troglitazone A10BG01			
Rosiglitazone A10BG02	57 (6.4)	86 (12.9)	5045 (15.1)
Dipeptidyl peptidase 4 (DPP-4) inhibitors			
Sitagliptin A10BH01	36 (4.0)	10 (1.5)	762 (2.3)
Vildagliptin A10BH02	2 (0.2)	4 (0.6)	
Saxagliptin A10BH03		1 (0.1)	53 (0.2)
Linagliptin A10BH05			2 (<0.01)
Other blood glucose lowering drugs, excl. insulins			
Guar gum A10BX01			1 (<0.01)
Repaglinide A10BX02	10 (1.1)	1 (0.1)	255 (0.8)
Nateglinide A10BX03			113 (0.3)
Exenatide A10BX04	7 (0.8)	1 (0.1)	142 (0.4)
Liraglutide A10BX07	31 (3.5)	6 (0.9)	97 (0.3)

Table 6. Distribution of first glucose-lowering drugs prescribed after termination of pioglitazone before and on/after DHPC

Drug/ATC code	AU N=854	IPCI N=501	CPRD N=13589
***Termination** before DHPC*			
Insulins and analogues A10A	170 (19.9)	68 (13.6)	2986 (22.0)
Biguanides			
Metformin A10BA02	393 (46.0)	247 (49.3)	7659 (56.4)
Sulfonamides, urea derivatives			
Glibenclamide (aka Glyburide) A10BB01	26 (3.0)	10 (2.0)	169 (1.2)
Chlorpropamide A10BB02			
Tolbutamide A10BB03	2 (0.2)	34 (6.8)	61 (0.4)
Glibornuride A10BB04			
Tolazamide A10BB05			
Glipizide A10BB07	15 (1.8)		190 (1.4)
Gliquidone A10BB08			2 (0.01)
Gliclazide A10BB09	45 (5.3)	43 (8.6)	4739 (34.9)
Glimepiride A10BB12	160 (18.7)	100 (20.0)	826 (6.1)
Acetohexamide A10BB31			
Sulfonamides (heterocyclic)			
Glymidine A10BC01			
Combinations of oral blood glucose lowering drugs			
Rosiglitazone + metformin A10BD03	17 (2.0)	1 (0.2)	183 (1.3)
Rosiglitazone + glimepiride A10BD04			
Vildagliptin + metformin A10BD08	15 (1.8)	2 (0.4)	60 (0.4)
Metformin + sitagliptin A10BD07	11 (1.3)	6 (1.2)	32 (0.2)
Alpha glucosidase inhibitors			
Acarbose A10BF01	9 (1.1)		119 (0.9)
Thiazolidinediones			
Troglitazone A10BG01			
Rosiglitazone A10BG02	49 (5.7)		242 (1.8)
Dipeptidyl peptidase 4 (DPP-4) inhibitors			
Sitagliptin A10BH01	53 (6.2)	37 (7.4)	999 (7.4)
Vildagliptin A10BH02	6 (0.7)	6 (1.2)	
Saxagliptin A10BH03	3 (0.4)	2 (0.4)	68 (0.5)
Linagliptin A10BH05			
Other blood glucose lowering drugs, excl. insulins			
Guar gum A10BX01			
Repaglinide A10BX02	6 (0.7)	1 (0.2)	89 (0.7)
Nateglinide A10BX03			51 (0.4)
Exenatide A10BX04	10 (1.2)	2 (0.4)	325 (2.4)
Liraglutide A10BX07	30 (3.5)	2 (0.4)	161 (1.2)
Termination on/after DHPC***			
	N=74	N=67	N = 3270
Insulins and analogues A10A	12 (16.2)	5 (7.5)	343 (10.5)
Biguanides			
Metformin A10BA02	15 (20.3)	22 (32.8)	1699 (52.0)
Sulfonamides, urea derivatives			
Glibenclamide (aka Glyburide) A10BB01	2 (2.7)	2 (3.0)	19 (0.6)

Drug/ATC code	AU N=854	IPCI N=501	CPRD N=13589
Chlorpropamide A10BB02			
Tolbutamide A10BB03		10 (14.9)	13 (0.4)
Glibornuride A10BB04			
Tolazamide A10BB05			
Glipizide A10BB07	1 (1.4)		38 (1.2)
Gliquidone A10BB08			
Gliclazide A10BB09	2 (2.7)	3 (4.5)	1057 (32.3)
Glimepiride A10BB12	6 (8.1)	9 (13.4)	147 (4.5)
Acetohexamide A10BB31			
Sulfonamides (heterocyclic)			
Glymidine A10BC01			
Combinations of oral blood glucose lowering drugs			
Rosiglitazone + metformin A10BD03			
Rosiglitazone + glimepiride A10BD04			
Vildagliptin + metformin A10BD08	2 (2.7)		23 (0.7)
Metformin + sitagliptin A10BD07	2 (2.7)		22 (0.7)
Alpha glucosidase inhibitors			
Acarbose A10BF01	2 (2.7)		16 (0.5)
Thiazolidinediones			
Troglitazone A10BG01			
Rosiglitazone A10BG02			
Dipeptidyl peptidase 4 (DPP-4) inhibitors			
Sitagliptin A10BH01	1 (1.4)	7 (10.4)	465 (14.2)
Saxagliptin A10BH03	1 (1.4)		78 (2.4)
Linagliptin A10BH05			15 (0.5)
Other blood glucose lowering drugs, excl. insulins			
Guar gum A10BX01			
Repaglinide A10BX02			21 (0.6)
Nateglinide A10BX03			3 (0.09)
Exenatide A10BX04			50 (1.5)
Liraglutide A10BX07	15 (20.3)	1 (1.5)	93 (2.8)

*This table includes persons switching to other OHAs from pioglitazone and those in whom pioglitazone was removed from the treatment regimen

**Defined as a person who has a pioglitazone prescription followed by 180 days in the database with no subsequent pioglitazone prescription.

***Defined as a person who has a last pioglitazone prescription followed by 23//44/21 days (median time to switch) in the AU/IPCI/CPRD

Table 7. Termination of pioglitazone among prevalent with contraindications and risk factors* for bladder cancer*

AU (Denmark)

Contraindication/ risk factor	Pioglitazone users with contraindication as of 31 July 2011	MONTH, 2011 Number of terminators** among those with contraindications/risk factors					Total number of terminators with each contraindication/risk factor
		August	September	October	November	December	
Heart Failure	10	0 (0.0%)	3 (30.0%)	2 (20.0%)	1 (10.0%)	0 (0.0%)	6 (60.0%)
Mild hepatic impairment	3	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (33.3%)	0 (0.0%)	1 (33.3%)
Moderate to severe hepatic impairment	0						
Diabetic ketoacidosis	1	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)	1 (100.0%)
History of bladder cancer	0						
Haematuria	14	0 (0.0%)	3 (21.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (21.4%)
Age group, years							
<18	0						
18-34	3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
35-44	6	1 (16.7%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (33.3%)
45-54	46	4 (8.7%)	5 (10.9%)	1 (2.2%)	2 (4.3%)	2 (4.3%)	14 (30.4%)
55-64	66	3 (4.5%)	4 (6.1%)	2 (3.0%)	6 (9.1%)	1 (1.5%)	16 (24.2%)
65-74	69	3 (4.3%)	5 (7.2%)	5 (7.2%)	10 (14.5%)	1 (1.4%)	24 (34.8%)
75-84	33	1 (3.0%)	2 (6.1%)	1 (3.0%)	1 (3.0%)	1 (3.0%)	6 (18.2%)
85+	3	0 (0.0%)	1 (33.3%)	0 (0.0%)	1 (33.3%)	0 (0.0%)	2 (66.7%)
History of smoking							

*Users in the calendar month before the DHPC
**Defined as a person who has a last pioglitazone prescription followed by 23 days (median time to switch) in the AU.

IPCI (The Netherlands)

Contraindication/ risk factor	Pioglitazone users with contraindication as of 31 July 2011	MONTH, 2011 Number of terminators** among those with contraindications/risk factors					Total number of terminators with each contraindication/risk factor
		August	September	October	November	December	
Heart Failure	73	3 (4.1%)	2 (2.7%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	6 (8.2%)
Mild hepatic impairment	9	0 (0.0%)	1 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (11.1%)
Moderate to severe hepatic impairment	3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Diabetic ketoacidosis	2	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)
History of bladder cancer	3	0 (0.0%)	0 (0.0%)	1 (33.3%)	0 (0.0%)	0 (0.0%)	1 (33.3%)
Haematuria	25	1 (4.0%)	3 (12.0%)	0 (0.0%)	1 (4.0%)	1 (4.0%)	6 (24.0%)
Age group, years							
<18	0						
18-34	4	0 (0.0%)	2 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (50.0%)
35-44	9	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
45-54	77	1 (1.3%)	2 (2.6%)	3 (3.9%)	4 (5.2%)	0 (0.0%)	10 (13.0%)
55-64	121	3 (2.5%)	8 (6.6%)	3 (2.5%)	2 (1.7%)	0 (0.0%)	16 (13.2%)
65-74	133	2 (1.5%)	5 (3.8%)	6 (4.5%)	2 (1.5%)	0 (0.0%)	15 (11.3%)
75-84	75	2 (2.7%)	5 (6.7%)	4 (5.3%)	2 (2.7%)	1 (1.3%)	14 (18.7%)
85+	19	1 (5.3%)	0 (0.0%)	2 (10.5%)	1 (5.3%)	0 (0.0%)	4 (21.1%)
History of smoking							

**Defined as a person who has a last pioglitazone prescription followed by 44 days (median time to switch) in the IPCI.

CPRD (UK)

Contraindication/ risk factor	Pioglitazone users with contraindication as of 30 June 2011	MONTH, 2011 Number of terminators** among those with contraindications/risk factors						Sub-Total number of terminators** with each contraindication/risk factor in 2011
		July	Aug	Sep	Oct	Nov	Dec	
Contraindication								
Heart failure	206	0	11 (5.3)	9 (4.4)	9 (4.4)	3 (1.5)	4 (1.9)	36 (17.5)
Mild hepatic impairment	278	0	14 (5.0)	7 (2.5)	6 (2.2)	7 (2.5)	7 (2.5)	41 (14.7)
Moderate or severe hepatic impairment	12	0	1 (8.3)	0	0	0	0	1 (8.3)
Diabetic ketoacidosis	31	0	2 (6.5)	1 (3.2)	1 (3.2)	0	1 (3.2)	5 (16.1)
History of bladder cancer	73	1 (1.4)	9 (12.3)	4 (5.5)	2 (2.7)	4 (5.5)	0	20 (27.4)
Haematuria	1235	4 (0.3)	38 (3.1)	28 (2.3)	21 (1.7)	31 (2.5)	29 (2.3)	151 (12.2)
Risk factors for bladder cancer								
Age group, years								
<50	1407	2 (0.1)	43 (3.1)	37 (2.6)	28 (2.0)	36 (2.6)	31 (2.2)	177 (12.6)
50-<55	1348	1 (0.07)	32 (2.4)	34 (2.5)	31 (2.3)	32 (2.4)	17 (1.3)	147 (10.9)
55-<60	1729	4 (0.2)	56 (3.2)	43 (2.5)	39 (2.3)	37 (2.1)	31 (1.8)	210 (12.1)
60-<65	2217	7 (0.3)	59 (2.7)	48 (2.2)	50 (2.3)	59 (2.7)	32 (1.4)	255 (11.5)
65-<70	2293	2 (0.09)	59 (2.6)	45 (2.0)	56 (2.4)	35 (1.5)	46 (2.0)	243 (10.6)
70-<75	2006	4 (0.2)	39 (1.9)	51 (2.5)	56 (2.8)	38 (1.9)	37 (1.8)	225 (11.2)
75-<80	1628	2 (0.1)	38 (2.3)	39 (2.4)	37 (2.3)	40 (2.5)	21 (1.3)	177 (10.9)
80-<85	938	4 (0.4)	22 (2.3)	18 (1.9)	31 (3.3)	15 (1.6)	21 (2.2)	111 (11.8)
≥85	427	0	16 (3.7)	12 (2.8)	12 (2.8)	9 (2.1)	6 (1.4)	55 (12.9)
History of smoking								
Current	1916	2 (0.1)	55 (2.9)	50 (2.6)	47 (2.5)	48 (2.5)	42 (2.2)	244 (12.7)
Former	5229	10 (0.2)	134 (2.6)	107 (2.0)	124 (2.4)	102 (2.0)	94 (1.8)	571 (10.9)
Never	6847	14 (0.2)	175 (2.6)	170 (2.5)	169 (2.5)	151 (2.2)	106 (1.5)	785 (11.5)
Missing	1	0	0	0	0	0	0	0

* Contraindications and risk factors assessed in the calendar month preceding DHPC

Table 7. continued (CPRD)

Contraindication/ risk factor	Pioglitazone users with contraindication as of 30 June 2011	MONTH, 2012 Number of terminators** among those with contraindications/risk factors						Sub-Total number of terminators** with each contraindication/risk factor in 2012
		January	February	March	April	May	June	
Contraindication								
Heart failure	206	4 (1.9)	5 (2.4)	5 (2.4)	7 (3.4)	5 (2.4)	0	26 (12.6)
Mild hepatic impairment	278	3 (1.1)	3 (1.1)	12 (4.3)	8 (2.9)	5 (1.8)	0	31 (11.2)
Moderate or severe hepatic impairment	12	0	0	1 (8.3)	0	1 (8.3)	0	2 (16.7)
Diabetic ketoacidosis	31	0	0	0	0	2 (6.5)	0	2 (6.5)
History of bladder cancer	73	1 (1.4)	0	4 (5.5)	3 (4.1)	1 (1.4)	0	9 (12.3)
Haematuria	1235	15 (1.2)	22 (1.8)	29 (2.3)	25 (2.0)	21 (1.7)	0	112 (9.1)
Risk factors for bladder cancer								
Age group, years								
<50	1407	21 (1.5)	34 (2.4)	33 (2.3)	41 (2.9)	41 (2.9)	0	170 (12.1)
50-<55	1348	26 (1.9)	24 (1.8)	20 (1.5)	31 (2.3)	37 (2.7)	0	138 (10.2)
55-<60	1729	19 (1.1)	31 (1.8)	36 (2.1)	38 (2.2)	41 (2.4)	0	165 (9.5)
60-<65	2217	23 (1.0)	28 (1.3)	52 (2.3)	40 (1.8)	52 (2.3)	0	195 (8.8)
65-<70	2293	27 (1.2)	28 (1.2)	41 (1.8)	45 (2.0)	42 (1.8)	0	183 (8.0)
70-<75	2006	37 (1.8)	29 (1.4)	38 (1.9)	32 (1.6)	36 (1.8)	1 (0.05)	173 (8.6)
75-<80	1628	22 (1.4)	33 (2.0)	37 (2.3)	32 (2.0)	29 (1.8)	0	153 (9.4)
80-<85	938	15 (1.6)	15 (1.6)	36 (3.8)	17 (1.8)	17 (1.8)	0	100 (10.7)
≥85	427	13 (3.0)	11 (2.6)	13 (3.0)	9 (2.1)	5 (1.2)	0	51 (11.9)
History of smoking								
Current	1916	33 (1.7)	36 (1.9)	47 (2.5)	38 (2.0)	50 (2.6)	1 (0.05)	205 (10.7)
Former	5229	72 (1.4)	85 (1.6)	111 (2.1)	102 (2.0)	103 (2.0)	0	473 (9.0)
Never	6847	98 (1.4)	112 (1.6)	148 (2.2)	145 (2.1)	147 (2.1)	0	650 (9.5)
Missing	1	0	0	0	0	0	0	0

* Contraindications and risk factors assessed before 30 June 2011.
** Defined as a person who has a last pioglitazone prescription followed by 21 days (median time to switch) in the CPRD.

Table 8. Prevalence of contraindications and risk factors for bladder cancer among users of pioglitazone who start pioglitazone on/after DHPC

AU (Denmark)

Contraindication/ risk factor	MONTH, 2011 Number of terminators** among those with contraindications/risk factors				
	August	September	October	November	December
Number of new users	5	7	12	2	9
Heart Failure	0 (0.0%)	0 (0.0%)	2 (16.7%)	0 (0.0%)	0 (0.0%)
Mild hepatic impairment	0 (0.0%)	0 (0.0%)	1 (8.3%)	0 (0.0%)	0 (0.0%)
Moderate to severe hepatic impairment	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Diabetic ketoacidosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
History of bladder cancer	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Haematuria	0 (0.0%)	0 (0.0%)	1 (8.3%)	0 (0.0%)	0 (0.0%)
Age group, years					
<18	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
18-34	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (11.1%)
35-44	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)
45-54	1 (20.0%)	2 (28.6%)	5 (41.7%)	0 (0.0%)	2 (22.2%)
55-64	1 (20.0%)	4 (57.1%)	4 (33.3%)	1 (50.0%)	0 (0.0%)
65-74	3 (60.0%)	0 (0.0%)	2 (16.7%)	0 (0.0%)	4 (44.4%)
75-84	0 (0.0%)	1 (14.3%)	1 (8.3%)	0 (0.0%)	2 (22.2%)
85+	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
History of smoking					

Table 8 cont'd IPCI (The Netherlands)

Contraindication/ risk factor	MONTH, 2011 Number of terminators** among those with contraindications/risk factors				
	August	September	October	November	December
Number of new users	7	8	7	9	7
Heart Failure	1 (14.3%)	1 (12.5%)	1 (14.3%)	1 (11.1%)	1 (14.3%)
Mild hepatic impairment	0 (0.0%)	0 (0.0%)	1 (14.3%)	1 (11.1%)	0 (0.0%)
Moderate to severe hepatic impairment	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Diabetic ketoacidosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
History of bladder cancer	0 (0.0%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Haematuria	0 (0.0%)	2 (25.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Age group, years					
<18	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
18-34	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
35-44	1 (14.3%)	0 (0.0%)	1 (14.3%)	1 (11.1%)	1 (14.3%)
45-54	1 (14.3%)	0 (0.0%)	0 (0.0%)	3 (33.3%)	0 (0.0%)
55-64	2 (28.6%)	4 (50.0%)	0 (0.0%)	1 (11.1%)	5 (71.4%)
65-74	2 (28.6%)	1 (12.5%)	4 (57.1%)	3 (33.3%)	1 (14.3%)
75-84	1 (14.3%)	3 (37.5%)	2 (28.6%)	1 (11.1%)	0 (0.0%)
85+	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
History of smoking					

Table 8 cont'd CPRD (UK)

Contraindication/ risk factor	MONTH, 2011					
	July	August	September	October	November	December
Number of new users	4	135	149	149	149	149
Contraindication						
Heart failure	0	3 (2.2)	2 (1.3)	6 (4.0)	0	0
Mild hepatic impairment	0	3 (2.2)	2 (1.3)	4 (2.7)	8 (5.4)	7 (5.9)
Moderate or severe hepatic impairment	0	0	0	0	0	0
Diabetic ketoacidosis	0	1 (0.7)	0	1 (0.7)	0	2 (1.7)
History of bladder cancer	0	0	2 (1.3)	0	1 (0.7)	0
Haematuria	0	7 (5.2)	12 (8.1)	8 (5.4)	14 (9.4)	4 (3.4)
Risk factors for bladder cancer						
Age group, years						
<50	1 (25.0)	23 (17.0)	28 (18.8)	36 (24.2)	31 (20.8)	27 (22.7)
50-<55	1 (25.0)	14 (10.4)	21 (14.1)	24 (16.1)	20 (13.4)	12 (10.1)
55-<60	0	17 (12.6)	11 (7.4)	22 (14.8)	27 (18.1)	18 (15.1)
60-<65	1 (25.0)	18 (13.3)	24 (16.1)	19 (12.8)	17 (11.4)	18 (15.1)
65-<70	0	17 (12.6)	16 (10.7)	16 (10.7)	23 (15.4)	17 (14.3)
70-<75	1 (25.0)	21 (15.6)	24 (16.1)	11 (7.4)	14 (9.4)	12 (10.1)
75-<80	0	11 (8.1)	17 (11.4)	11 (7.4)	13 (8.7)	8 (6.7)
80-<85	0	8 (5.9)	4 (2.7)	8 (5.4)	3 (2.0)	7 (5.9)
≥85	0	6 (4.4)	4 (2.7)	2 (1.3)	1 (0.7)	0
History of smoking						
Current	1 (25.0)	24 (17.8)	33 (22.1)	30 (20.1)	20 (13.4)	18 (15.1)
Former	2 (50.0)	55 (40.7)	46 (30.9)	45 (30.2)	50 (33.6)	46 (38.7)
Never	1 (25.0)	56 (41.5)	69 (46.3)	74 (49.7)	79 (53.0)	53 (44.5)
Missing	0	0	1 (0.7)	0	0	2 (1.7)

Table 8. continued (CPRD)

	MONTH, 2012					
	January	February	March	April	May	June
Number of new users	130	126	137	95	83	15
Contraindication						
Heart failure	0	3 (2.4)	0	3 (3.2)	0	0
Mild hepatic impairment	1 (0.8)	8 (6.3)	5 (3.6)	2 (2.1)	4 (4.8)	1 (6.7)
Moderate or severe hepatic impairment	1 (0.8)	1 (0.8)	0	1 (1.1)	0	0
Diabetic ketoacidosis	0	0	0	0	0	0
History of bladder cancer	0	0	0	0	0	0
Haematuria	7 (5.4)	8 (6.3)	12 (8.8)	6 (6.3)	7 (8.4)	0
Risk factors for bladder cancer						
Age group, years						
<50	18 (13.8)	17 (13.5)	20 (14.6)	12 (12.6)	10 (12.0)	5 (33.3)
50-<55	17 (13.1)	15 (11.9)	20 (14.6)	12 (12.6)	7 (8.4)	5 (33.3)
55-<60	14 (10.8)	15 (11.9)	25 (18.2)	12 (12.6)	10 (12.0)	1 (6.7)
60-<65	20 (15.4)	28 (22.2)	19 (13.9)	14 (14.7)	16 (19.3)	0
65-<70	21 (16.2)	17 (13.5)	25 (18.2)	12 (12.6)	14 (16.9)	1 (6.7)
70-<75	15 (11.5)	15 (11.9)	8 (5.8)	16 (16.8)	7 (8.4)	2 (13.3)
75-<80	16 (12.3)	13 (10.3)	10 (7.3)	9 (9.5)	12 (14.5)	1 (6.7)
80-<85	5 (3.8)	2 (1.6)	7 (5.1)	5 (5.3)	4 (4.8)	0
≥85	4 (3.1)	4 (3.2)	3 (2.2)	3 (3.2)	3 (3.6)	0
History of smoking						
Current	18 (13.8)	24 (19.0)	22 (16.1)	11 (11.6)	13 (15.7)	3 (20.0)
Former	50 (38.5)	45 (35.7)	40 (29.2)	39 (41.1)	26 (31.3)	5 (33.3)
Never	62 (47.7)	57 (45.2)	74 (54.0)	45 (47.4)	44 (53.0)	7 (46.7)

Missing	0	0	1 (0.7)	0	0	0

*Contraindications and risk factors for bladder cancer measured before the first pioglitazone prescription.

Table 9. Estimated first prescribed dose/dispensed strength (mg) among new users of pioglitazone, before DHPC, by age group

Age group, years	AU	IPCI	CPRD*
	N=862	N=628	N = 32017
	Estimated* first prescribed dose, median (quartiles)		
<50	25 (17 - 35)	31 (20-43)	15 (15 – 30)
50-<55	29 (17 - 35)	32 (23-45)	15 (15 – 30)
55-<60	28 (16 - 38)	32 (25-54)	15 (15 – 30)
60-<65	28 (17 - 40)	38 (25-60)	15 (15 – 30)
65-<70	26 (16 - 39)	31 (17-56)	15 (15 – 30)
70-<75	31 (17 - 24)	30 (18-45)	15 (15 – 30)
75-<80	21 (15 - 32)	32 (21-48)	15 (15 – 30)
>80	31 (15 - 39)	30 (13-60)	15 (15 – 30)
	First prescribed pill strength median (quartiles)		
<50	15 (15 – 30)	30 (30-30)	15 (15 – 30)
50-<55	15 (15 – 30)	30 (30-30)	15 (15 – 30)
55-<60	15 (15 – 30)	30 (30-30)	15 (15 – 30)
60-<65	15 (15 – 30)	30 (30-30)	15 (15 – 30)
65-<70	15 (15 – 30)	30 (30-30)	15 (15 – 30)
70-<75	15 (15 – 30)	30 (30-30)	15 (15 – 30)
75-<80	15 (15 – 30)	30 (30-30)	15 (15 – 30)
>80	15 (15 – 30)	30 (30-30)	15 (15 – 30)

*Actual prescribed daily dose was reported for CPRD

Table 10. Estimated first prescribed dose/dispensed strength (mg) among new users of pioglitazone, on/after DHPC, by age group

Age group, years	AU	IPCI	CPRD*
	N = 35	N= 39	N = 1291
	Estimated* first dose, median (quartiles)		
<50	30 (23 – 37)	109 (26-193)	15 (15 – 30)
50-<55	40 (28 – 47)	45 (40-50)	15 (15 – 30)
55-<60	18 (14 – 27)	0	15 (15 – 30)
60-<65	20 (15 – 23)	38 (24-64)	15 (15 – 30)
65-<70	22 (16 – 28)	10 (10-10)	15 (15 – 30)
70-<75	16 (16 – 17)	39 (14-64)	15 (15 – 30)
75-<80	27 (27 – 27)	28 (13-54)	15 (15 – 30)
>80			15 (15 – 30)
	First prescribed pill strength median (quartiles)		
<50	15 (15 – 30)	30 (30-30)	15 (15 – 30)
50-<55	15 (15 – 30)	30 (30-30)	15 (15 – 30)
55-<60	15 (15 – 15)	30 (30-30)	15 (15 – 30)
60-<65	15 (15 – 15)	30 (30-30)	15 (15 – 30)
65-<70	15 (15 – 15)	30 (30-30)	15 (15 – 30)
70-<75	15 (15 – 15)	30 (30-30)	15 (15 – 30)
75-<80	15 (15 – 30)	30 (30-30)	15 (15 – 15)
>80	15 (15 – 15)	38 (30-45)	15 (15 – 30)

*Actual prescribed daily dose was reported for CPRD

Table 11. Prevalence of concomitant use with insulin, new users before DHPC, by age group

Age group, years	AU N=862	IPCI N=628	CPRD N = 32017
	Number (%)		
<50	38 (23.90)	10 (13.89)	866 (2.7)
50-<55	24 (21.24)	9 (15.00)	470 (1.5)
55-<60	32 (26.23)	15 (16.85)	632 (2.0)
60-<65	39 (23.78)	9 (8.26)	646 (2.0)
65-<70	20 (18.52)	10 (14.08)	612 (1.9)
70-<75	12 (14.12)	5 (5.62)	475 (1.5)
75-<80	9 (15.00)	7 (11.11)	357 (1.1)
>80	2 (3.92)	7 (9.33)	255 (0.8)

Table 12.Prevalence of concomitant use with insulin, new users on/after DHPC, by age group

Age group, years	AU N=35	IPCI N=39	CPRD N=1291
	Number (%)		
<50	1 (20.00)		30 (2.3)
50-<55	4 (57.14)		12 (0.9)
55-<60	2 (33.33)		11 (0.9)
60-<65		1 (10.00)	14 (1.1)
65-<70			10 (0.8)
70-<75			9 (0.7)
75-<80		2 (40.00)	7 (0.5)
>80			10 (0.8)

Table 13. Potential adverse events among prevalent and new users of pioglitazone on/after DHPC within 45 days of baseline. Baseline=DHPC/initiation date.

AU (Denmark)

Adverse event	AU		
	N at risk	Events	45-day risk* (95% CI)
Death of all causes	209	0	0.0 (0.0;1.2)
Diabetes complications	209	0	0.0 (0.0;1.2)
Acute myocardial infarction	209	0	0.0 (0.0;1.2)
Acute coronary syndrome	209	1	0.0 (0.0;1.2)
Haemorrhagic stroke	209	0	0.0 (0.0;1.2)
Ischemic stroke	209	0	0.0 (0.0;1.2)

IPCI (The Netherlands)

Adverse event	IPCI		
	N at risk	Events	45-day risk* (95% CI)
Death of all causes	382	0	0.0 (0.0; 0.7)
Diabetes complications	382	0	0.0 (0.0; 0.7)
Acute myocardial infarction	382	0	0.0 (0.0; 0.7)
Acute coronary syndrome	382	0	0.0 (0.0; 0.7)
Haemorrhagic stroke	382	0	0.0 (0.0; 0.7)
Ischemic stroke*	382	1	0.0 (0.0; 1.5)

*Unspecified type of stroke.

CPRD (UK)

Adverse event	CPRD		
	N at risk	Events	45-day risk* (95% CI)
Death of all causes	15284	17	0.11 (0.07; 0.17)
Diabetes complications	15284	2	0.01 (0.002; 0.04)
Acute myocardial infarction	15284	6***	0.04 (0.02; 0.08)
Acute coronary syndrome	15284	8****	0.05 (0.02; 0.10)
Haemorrhagic stroke	15284	1	0.007 (0.0004; 0.03)
Ischemic stroke	15284	6*****	0.04 (0.02; 0.08)

*Risk measured in percent
**Unspecified stroke
***Including one patient with a long history of cardiovascular disease
****Including two patients with a long history of cardiovascular disease
***** Including one patient with a history of stroke

Table 14. Diabetes related adverse events among persons who have the last pioglitazone prescription on/after DHPC, within 45 days of termination, by database/country. Baseline = termination date.

AU (Denmark)

Adverse event	N at risk	Events	45-day risk* (95% CI)
Diabetes complications	60	0	0.0 (0.0; 4.1)

IPCI (The Netherlands)

Adverse event	N at risk	Events	45-day risk* (95% CI)
Diabetes complications	67	0	0.0 (0.0; 3.7)

CPRD (UK)

Adverse event	N at risk	Events	45-day risk* (95% CI)
Diabetes complications	3270	6	0.18 (0.07 – 0.38)

*Risk measured in percent

Table 15. Mean differences in laboratory parameters before and on/after DHPC among prevalent and new users of pioglitazone at DHPC (Baseline=DHPC/initiation date).

AU (Northern Denmark)

Variable	N=58	
	3 months	6 months
HbA1c, %		
N with both measurements	39	16
Baseline mean (SD)	7.71 (1.30)	8.20 (1.25)
Follow-up mean (SD)	7.65 (1.09)	7.84 (1.09)
Change from baseline, mean (95%CI)	-0.06 (-1.55;1.44]	-0.36 (-2.23;1.51]
FPG, mmol/L		
N with both measurements	3	1
Baseline mean (SD)	8.57 (3.96)	15.80 (.)
Follow-up mean (SD)	12.77 (1.86)	15.30 (.)
Change from baseline, mean (95%CI)	4.20 (-2.42;10.82]	-0.50 (.;.]
Total cholesterol, mmol/L		
N with both measurements	23	10
Baseline mean (SD)	4.50 (1.00)	4.07 (1.27)
Follow-up mean (SD)	4.25 (0.99)	4.38 (1.20)
Change from baseline, mean (95%CI)	-0.24 (-1.94;1.45]	0.31 (-1.39;2.01]
HDL cholesterol, mmol/L		
N with both measurements	21	10
Baseline mean (SD)	1.11 (0.27)	1.10 (0.11)
Follow-up mean (SD)	1.17 (0.28)	1.21 (0.18)
Change from baseline, mean (95%CI)	0.06 (-0.33;0.44]	0.12 (-0.16;0.39]
LDL cholesterol, mmol/L		
N with both measurements	22	9
Baseline mean (SD)	2.30 (0.91)	2.32 (1.00)
Follow-up mean (SD)	2.08 (0.71)	2.52 (1.06)
Change from baseline, mean (95%CI)	-0.22 (-1.73;1.28]	0.20 (-1.26;1.66]
Triglycerides, mmol/L		
N with both measurements	6	4
Baseline mean (SD)	2.08 (0.80)	1.99 (1.11)
Follow-up mean (SD)	2.32 (0.93)	2.00 (0.98)
Change from baseline, mean (95%CI)	0.24 (-1.43;1.90]	0.01 (-0.75;0.76]
eGFR, ml/min/1.73m^2	First measurement after baseline up to 12-months post-baseline	
N with both measurements	35	
Baseline mean (SD)	85.42 (26.26)	
Follow-up mean (SD)	82.74 (26.54)	
Change from baseline, mean (95%CI)	-2.69 (-18.7;13.36]	

Table 15 cont'd IPCI (The Netherlands)

Variable	N=385	
	3 months	6 months
HbA1c, %		
N with both measurements	189	161
Baseline mean (SD)	6.88 (0.80)	6.87 (0.78)
Follow-up mean (SD)	7.26 (4.52)	6.90 (1.05)
Change from baseline, mean (95%CI)	0.39 (-8.39;9.16]	0.03 (-1.59;1.65]
FPG, mmol/L		
N with both measurements	250	202
Baseline mean (SD)	7.25 (1.64)	7.16 (1.60)
Follow-up mean (SD)	7.21 (1.70)	7.42 (1.89)
Change from baseline, mean (95%CI)	-0.04 (-3.16;3.07]	0.25 (-2.87;3.37]
Total cholesterol, mmol/L		
N with both measurements	92	65
Baseline mean (SD)	4.74 (1.09)	4.72 (1.09)
Follow-up mean (SD)	4.59 (1.09)	4.59 (0.96)
Change from baseline, mean (95%CI)	-0.14 (-1.82;1.54]	-0.14 (-1.54;1.27]
HDL cholesterol, mmol/L		
N with both measurements	92	65
Baseline mean (SD)	1.37 (0.67)	1.32 (0.33)
Follow-up mean (SD)	1.30 (0.34)	1.36 (0.39)
Change from baseline, mean (95%CI)	-0.07 (-1.21;1.06]	0.04 (-0.39;0.46]
LDL cholesterol, mmol/L		
N with both measurements	92	65
Baseline mean (SD)	2.69 (0.93)	2.69 (0.93)
Follow-up mean (SD)	2.51 (0.88)	2.56 (0.86)
Change from baseline, mean (95%CI)	-0.17 (-1.57;1.22]	-0.14 (-1.27;1.00]
Triglycerides, mmol/L		
N with both measurements	92	66
Baseline mean (SD)	1.70 (0.90)	1.75 (1.38)
Follow-up mean (SD)	1.71 (1.07)	1.62 (1.06)
Change from baseline, mean (95%CI)	0.01 (-1.57;1.60]	-0.13 (-1.34;1.08]
eGFR, ml/min/1.73m^2	First measurement after baseline up to 12-months post-baseline	
N with both measurements	167	
Baseline mean (SD)	81.10 (21.31)	
Follow-up mean (SD)	80.70 (20.41)	
Change from baseline, mean (95%CI)	-0.40 (-20.6;19.83]	

Table 15 cont'd CPRD (UK)

Variable	(N = 15284)		
	3 months	6 months	12 months
HbA1c, %			
N with both measurements	6241	5802	6999
Baseline mean (SD)	7.63 (1.85)	7.60 (1.82)	7.52 (1.78)
Follow-up mean (SD)	7.55 (1.73)	7.57 (1.70)	7.73 (1.76)
Change from baseline, mean (95% CI)	-0.08 (-0.12; -0.04)	-0.02 (-0.07; 0.02)	0.21 (0.17; 0.25)
FPG, mmol/L			
N with both measurements	565	508	632
Baseline mean (SD)	8.06 (2.71)	8.04 (2.71)	8.24 (2.76)
Follow-up mean (SD)	7.81 (2.67)	8.07 (2.84)	8.49 (3.11)
Change from baseline, mean (95% CI)	-0.25 (-0.46; -0.03)	0.03 (-0.21; 0.27)	0.25 (0.02; 0.48)
Total cholesterol, mmol/L			
N with both measurements	4578	4298	5532
Baseline mean (SD)	4.14 (0.97)	4.13 (0.98)	4.12 (0.97)
Follow-up mean (SD)	4.13 (1.08)	4.16 (1.18)	4.12 (0.98)
Change from baseline, mean (95% CI)	-0.01 (-0.04; 0.01)	0.03 (0; 0.06)	0 (-0.03; 0.02)
HDL cholesterol, mmol/L			
N with both measurements	3818	3573	4596
Baseline mean (SD)	1.24 (0.34)	1.23 (0.34)	1.25 (0.34)
Follow-up mean (SD)	1.25 (0.33)	1.25 (0.34)	1.26 (0.35)
Change from baseline, mean (95% CI)	0.01 (0.01; 0.02)	0.02 (0.01; 0.03)	0.01 (0; 0.02)
LDL cholesterol, mmol/L			
N with both measurements	2838	2610	3327
Baseline mean (SD)	2.13 (0.78)	2.10 (0.79)	2.14 (0.81)
Follow-up mean (SD)	2.12 (0.81)	2.13 (0.79)	2.12 (0.82)
Change from baseline, mean (95% CI)	-0.01 (-0.04; 0.01)	0.02 (0; 0.05)	-0.02 (-0.04; 0)
Triglycerides mmol/L			
N with both measurements	3289	3047	3843
Baseline mean (SD)	1.78 (1.22)	1.84 (1.84)	1.75 (1.51)
Follow-up mean (SD)	1.73 (1.36)	1.76 (1.17)	1.67 (1.02)
Change from baseline, mean (95% CI)	-0.06 (-0.09; -0.02)	-0.08 (-0.14; -0.03)	-0.07 (-0.11; -0.04)
eGFR, ml/min/1.73m^2	First measurement after baseline up to 12-months post-baseline		
N with both measurements	12156		
Baseline mean (SD)	87.94 (32.31)		
Follow-up mean (SD)	89.14 (35.10)		
Change from baseline, mean (95% CI)	1.21 (0.90; 1.51)		

Table 16. Mean differences in laboratory parameters before and after pioglitazone termination among patients terminating pioglitazone on/after DHPC. Baseline=date of termination.*

AU (Northern Denmark)

Variable	N=23	
	3 months	6 months
HbA1c, %		
N with both measurements	12	2
Baseline mean (SD)	7.35 (0.90)	7.70 (0.14)
Follow-up mean (SD)	7.30 (0.76)	7.60 (0.14)
Change from baseline, mean (95%CI)	-0.05 (-1.11; 1.01]	-0.10 (-0.65;0.45]
FPG, mmol/L		
N with both measurements	1	0
Baseline mean (SD)	10.20 (.)	
Follow-up mean (SD)	10.30 (.)	
Change from baseline, mean (95%CI)	0.10 (.; .]	
Total cholesterol, mmol/L		
N with both measurements	8	1
Baseline mean (SD)	3.98 (1.02)	4.90 (.)
Follow-up mean (SD)	4.08 (0.93)	4.10 (.)
Change from baseline, mean (95%CI)	0.10 (-0.84; 1.04]	-0.80 (.;.]
HDL cholesterol, mmol/L		
N with both measurements	8	1
Baseline mean (SD)	1.06 (0.16)	0.87 (.)
Follow-up mean (SD)	1.17 (0.36)	0.77 (.)
Change from baseline, mean (95%CI)	0.11 (-0.40; 0.62]	-0.10 (.;.]
LDL cholesterol, mmol/L		
N with both measurements	8	1
Baseline mean (SD)	2.08 (0.79)	2.40 (.)
Follow-up mean (SD)	2.14 (0.92)	2.00 (.)
Change from baseline, mean (95%CI)	0.06 (-0.60; 0.72]	-0.40 (.;.]
Triglycerids, mmol/L		
N with both measurements	3	1
Baseline mean (SD)	1.64 (1.09)	3.80 (.)
Follow-up mean (SD)	2.10 (0.79)	4.50 (.)
Change from baseline, mean (95%CI)	0.46 (-0.50; 1.42]	0.70 (.;.]
eGFR, ml/min/1.73m^2	First measurement after baseline up to 12-months post-baseline	
N with both measurements	9	
Baseline mean (SD)	78.51 (25.49)	
Follow-up mean (SD)	75.42 (25.66)	
Change from baseline, mean (95%CI)	-3.09 (-27.9; 21.71]	

* Defined as a person who has a last pioglitazone prescription followed by 23 days (median time to switch) in the AU.

Table 16 cont'd IPCI (The Netherlands)

Variable	N=67	
	3 months	6 months
HbA1c, %		
N with both measurements	30	13
Baseline mean (SD)	7.05 (0.99)	6.99 (0.89)
Follow-up mean (SD)	7.14 (1.29)	7.22 (1.18)
Change from baseline, mean (95%CI)	0.09 (-1.58; 1.76]	0.23 (-1.50; 1.96]
FPG, mmol/L		
N with both measurements	36	15
Baseline mean (SD)	7.71 (2.55)	7.55 (2.18)
Follow-up mean (SD)	8.02 (2.48)	7.77 (2.29)
Change from baseline, mean (95%CI)	0.31 (-4.68; 5.30]	0.21 (-3.46; 3.89]
Total cholesterol, mmol/L		
N with both measurements	11	5
Baseline mean (SD)	3.86 (0.90)	4.95 (0.79)
Follow-up mean (SD)	3.87 (0.74)	4.75 (1.34)
Change from baseline, mean (95%CI)	0.01 (-0.77; 0.79]	-0.20 (-2.27; 1.87]
HDL cholesterol, mmol/L		
N with both measurements	11	5
Baseline mean (SD)	1.13 (0.22)	1.37 (0.24)
Follow-up mean (SD)	1.11 (0.26)	1.35 (0.31)
Change from baseline, mean (95%CI)	-0.01 (-0.28; 0.25]	-0.02 (-0.56; 0.53]
LDL cholesterol, mmol/L		
N with both measurements	10	5
Baseline mean (SD)	1.89 (0.52)	2.94 (0.73)
Follow-up mean (SD)	1.98 (0.40)	2.68 (1.10)
Change from baseline, mean (95%CI)	0.09 (-0.48; 0.65]	-0.26 (-2.18; 1.66]
Triglycerids, mmol/L		
N with both measurements	11	5
Baseline mean (SD)	1.88 (1.17)	1.42 (0.69)
Follow-up mean (SD)	1.85 (1.38)	1.60 (1.04)
Change from baseline, mean (95%CI)	-0.03 (-2.08; 2.01]	0.18 (-0.60; 0.95]
eGFR, ml/min/1.73m^2	First measurement after baseline up to 12-months post-baseline	
N with both measurements	22	
Baseline mean (SD)	81.45 (29.19)	
Follow-up mean (SD)	79.15 (27.92)	
Change from baseline, mean (95%CI)	-2.30 (-20.6; 16.00]	

*Defined as a person who has a last pioglitazone prescription followed by 44 days (median time to switch) in the IPCI.

Table 16 cont'd CPRD (UK)

Variable	CPRD N = 3270		
	3 months	6 months	12 months
HbA1c, %			
N with both measurements	1108	715	388
Baseline mean (SD)	7.93 (2.00)	7.73 (2.01)	7.82 (2.07)
Follow-up mean (SD)	7.96 (1.98)	8.41 (1.92)	8.45 (2.20)
Change from baseline, mean (95% CI)	0.03 (-0.09; 0.14)	0.69 (0.54; 0.83)	0.64 (0.40; 0.87)
FPG, mmol/L			
N with both measurements	76	67	32
Baseline mean (SD)	8.31 (2.79)	8.74 (3.41)	8.95 (3.07)
Follow-up mean (SD)	8.86 (3.15)	9.38 (3.40)	10.84 (4.09)
Change from baseline, mean (95% CI)	0.55 (-0.20; 1.29)	0.64 (-0.33; 1.60)	1.89 (0.39; 3.40)
Total cholesterol, mmol/L			
N with both measurements	669	485	293
Baseline mean (SD)	4.25 (1.08)	4.26 (1.04)	4.33 (1.10)
Follow-up mean (SD)	4.15 (1.06)	4.19 (1.04)	4.15 (1.08)
Change from baseline, mean (95% CI)	-0.10 (-0.17; -0.03)	-0.07 (-0.14; 0)	-0.18 (-0.28; -0.07)
HDL cholesterol, mmol/L			
N with both measurements	556	397	243
Baseline mean (SD)	1.21 (0.32)	1.24 (0.32)	1.23 (0.36)
Follow-up mean (SD)	1.18 (0.32)	1.17 (0.30)	1.16 (0.33)
Change from baseline, mean (95% CI)	-0.04 (-0.05; -0.02)	-0.08 (-0.10; -0.06)	-0.07 (-0.10; -0.04)
LDL cholesterol, mmol/L			
N with both measurements	387	292	176
Baseline mean (SD)	2.27 (0.87)	2.26 (0.91)	2.44 (0.95)
Follow-up mean (SD)	2.23 (0.85)	2.17 (0.84)	2.27 (0.90)
Change from baseline, mean (95% CI)	-0.04 (-0.11; 0.03)	-0.10 (-0.17; -0.02)	-0.17 (-0.28; -0.06)
Triglycerides mmol/L			
N with both measurements	461	343	192
Baseline mean (SD)	1.87 (1.32)	1.79 (0.99)	1.82 (1.13)
Follow-up mean (SD)	1.83 (1.11)	1.85 (0.98)	1.78 (0.94)
Change from baseline, mean (95% CI)	-0.03 (-0.13; 0.07)	0.06 (-0.02; 0.14)	-0.04 (-0.16; 0.09)
eGFR, ml/min/1.73m^2	First measurement after baseline up to 12-months post-baseline		
N with both measurements	1559		
Baseline mean (SD)	92.50 (46.34)		
Follow-up mean (SD)	91.66 (44.54)		
Change from baseline, mean (95% CI)	-0.84 (-2.49; 0.80)		

* Defined as a person who has a last pioglitazone prescription followed by 21 days (median time to switch) in the CPRD.

Table 17. Periodic treatment reviews among prevalent users of pioglitazone as of DHPC

	AU (Northern Denmark)	IPCI	CPRD
Prevalent users of pioglitazone as of DHPC	49	346	13993
Total of HbA1c measurements taken after DHPC	.		
0	8	108	2097
1	28	115	3135
>1	13	123	8761
Patients with evidence of insufficient benefit*	20	46	5780
Patients with prescription for pioglitazone after evidence of insufficient benefit**	17(85.0%)	31 (67.4%)	4671 (80.8%)

*Defined as patient with at least one measurement of HbA1c≥7.5% after DHPC

**Defined as patients with evidence of insufficient benefit who receive at least one pioglitazone prescription after the earliest HbA1c ≥7.5% measurement recorded after DHPC

Table 18. Periodic treatment reviews among new users of pioglitazone on/after DHPC

	AU (Northern Denmark)	IPCI	CPRD
Total number of new users after DHPC	9	39	1291
Total of HbA1c measurements taken after first pioglitazone prescription			
0	1	15	539
1	2	9	308
>1	6	15	444
Patients with evidence of insufficient benefit*	7	12	555
Patients with prescription for pioglitazone after evidence of insufficient benefit**	7 (100.0%)	11 (91.7%)	378 (68.1%)

*Defined as patient with at least one measurement of HbA1c≥7.5% after first prescription for pioglitazone
**Defined as patients with evidence of insufficient benefit who receive at least one pioglitazone prescription after the earliest HbA1c ≥7.5% measurement recorded after the first prescription for pioglitazone

10. APPENDICES

10.1 APPENDIX 1. LIST OF PROTOCOL AMENDMENTS

The following amendments were made to the protocol dated 20 May 2012.

Algorithms to define acute events, following advice of expert diabetologist:

- acute MI and acute coronary syndrome to be reported as separate outcomes
- haemorrhagic and ischemic stroke each to be reported as separate outcome
- These decisions follow a discussion with the expert diabetologist at Aarhus,
- Acute diabetic outcomes include acute renal failure, in addition to diabetic coma/acidosis

The following amendments have been made to the protocol:

1. To unify definition of initiation and termination for of pioglitazone products in all databases, a period of 180 days was used to define initiation of a new treatment course of pioglitazone and to define termination of pioglitazone after last use.
2. Figure 4 was added to summarise database-specific utilisation pioglitazone around the time of DHCP.
3. To capture patient outcomes before 180 days post-termination for patients who may terminate pioglitazone as a result of DHPC, a shorter period was defined based on database-specific median time to switch to the next oral hypoglycaemic drug (as described in the Methods section of the current report).
4. Added reporting estimated prescribed dose and dispensed dose
5. Data reported in Tables 7 and 8 are slightly different from the earlier setup: we are now reporting the number of terminators among the prevalent with contraindications, by calendar month following DHPC
6. Redefined time windows for 3- and 6-month and 12-month follow-up periods for comparing pre- and post-baseline laboratory values

All changes are marked in colour in the amended Protocol, sent together with this Deliverable. The Methods section reflects the applied amendments.

10.2 APPENDIX 2. ALGORITHMS USED TO IDENTIFY STUDY VARIABLES

Attached as a separate document due to length.