Pan European Multi-Database Bladder Cancer Risk Characterisation Study

Table shells

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Appendix 6, 22 January 2014

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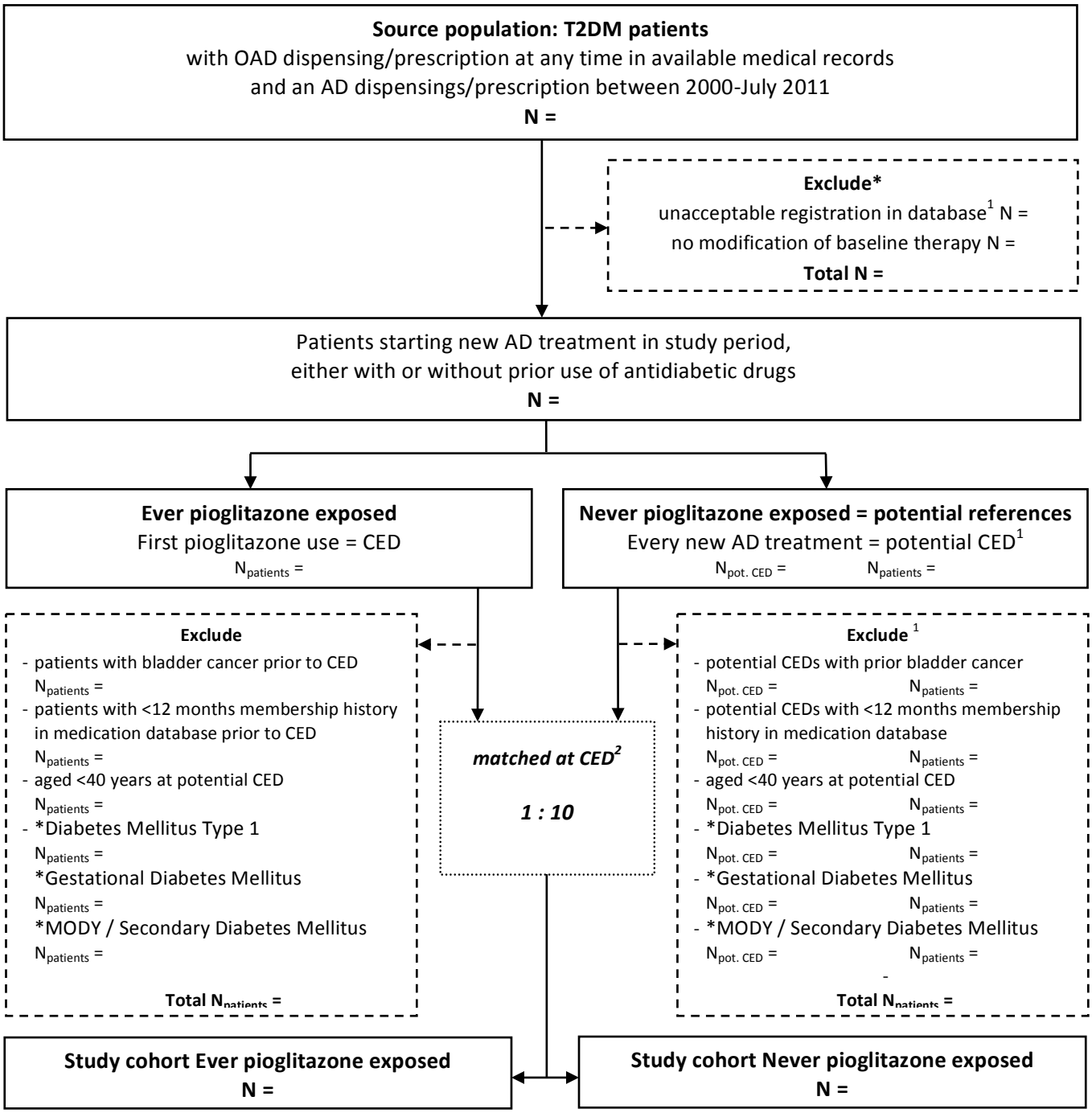
1. Population summary

1.1 Patient selection



[1] e.g. indeterminate gender, incorrect birth date, temporary registration, etc. [2] potential references can be matched at several times of potential CED, but potential CEDs with prior bladder cancer will be excluded from the matching procedure., as will potential CEDs with insufficient history of database enrolment; [2] matching takes into account that patients have similar disease history at the time of CED (see methods section); T2DM: type 2 diabetes mellitus; OAD = oral antidiabetic drug; AD = antidiabetic drug; CED =cohort entry date

* Dutch databases will apply criteria at first exclusion box because diagnoses are missing for large numbers, and occasional mention of diagnoses should be applied retrospectively , other databases apply criteria only prior to CED.

Figure 1.1.1 Flowchart of selection study population

1.2 Baseline patient and clinical characteristics

Table 1.2.1 General characteristics at cohort entry

	Ever pioglitazone exposed N = n (%)	**Never pioglitazone exposed N =** n (%)	**Ever vs. never pioglitazone exposed** OR (95% CI)
Age (years)			
40-<50			reference
50-<60			
60-<70			
≥70			
Gender			
male			reference
female			
Year of cohort entry			
2000-2003			reference
2004-2007			
2008-2010			
Duration of medication database membership[1] before cohort entry (years)			
1-<3			reference
3-<5			
5-<7			
≥7			
mean (±SD)			-
median (IQR)			-
Duration of medication database membership[1] after cohort entry (years)			
0-<2			reference
2-<4			
4-<6			
6-<8			
8-<10			
≥10			
mean (±SD)			-
median (IQR)			-

[1] in prescription/dispensing database; SD: standard deviation; IQR: inter quartile range;

Table 1.2.2 Clinical parameters at cohort entry

	Ever pioglitazone exposed **N =** n (%)	**Never pioglitazone exposed** **N =** n (%)	**Ever vs. never pioglitazone exposed** OR (95% CI)
HbA1c (%)			
missing			-
mean (±SD)			-
<7.5 %			reference
7.5-<9			
≥ 9%			
BMI (kg/m^2)			
missing			-
<30.0			reference
30.0-<35.0			
≥35.0			
Smoking			
missing			-
never			reference
ever			

BMI: Body Mass Index; SD: standard deviation;

Table 1.2.3 Antidiabetic and other treatment characteristics before and at cohort entry

	Ever pioglitazone exposed N = n (%)	Never pioglitazone exposed N = n (%)	Ever vs. never pioglitazone exposed OR (95% CI)
Treatment before CED			
Number of different antidiabetic drug classes ever prior to CED [1]			
0			reference
1			
2			
3			
>3			
Prior use of other TZD at any time			
Yes (vs. no)			
Prior antidiabetic treatment classes[2]			
metformin only			reference
SU only			
metformin and SU			
insulin (only or in combination)			
other			
no treatment			
Other medication use			
statin			
ARB			
ACE			
BPH drugs			
Treatment at CED			
Number of different antidiabetic treatments[1] **at CED**			
1			reference
2			
3			
>3			
Type of treatment change at CED			
add-on to no previous treatment[3]			reference
add-on to prior treatment			
switch			
Antidiabetic treatment at CED			
pioglitazone only		-	reference
metformin only [4]			
SU only [4]			
metformin and SU [4]			
insulin only [4]			
insulin and metformin [4]			
insulin and SU [4]			
other [4]			

CED: cohort entry date; [1] number of distinct classes of AD treatment used in entire available history before CED (see protocol appendix 1 for drug classes); [2] treatment immediately before CED: includes interruptions of treatment after permissible gap/grace period as 'no treatment', if period before CED falls within permissible gap/grace period then report last treatment before CED (see protocol appendix 2 for definition of permissible gap / grace period); [3] immediately before CED; ARB: angiotensin receptor blockers; ACE: angiotensin converting enzyme; BPH: benign prostatic hypertrophy; [4] Ever pioglitazone exposed group = +pioglitazone;

Table 1.2.4 Treatment changes at cohort entry

		Antidiabetic treatment prior to CED								
Antidiabetic treatment at CED[4]		no treatment	metformin only	SU only	metformin + SU	insulin only	insulin + metformin	insulin + SU	insulin + other	Other
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Ever pioglitazone exposed	pioglitazone only							-		
	pioglitazone +metformin									
	pioglitazone + SU									
	pioglitazone +metformin + SU									
	pioglitazone + insulin									
	pioglitazone +insulin + metformin									
	pioglitazone +insulin + SU									
	pioglitazone +insulin + other									
	pioglitazone +other									
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Never pioglitazone exposed	metformin only									
	SU only									
	metformin + SU									
	insulin only									
	insulin + metformin									
	insulin + SU									
	insulin + other									
	other									

NOTE: per exposure group all rows and columns combined will add up to 100%

Table 1.2.5 History of diabetic complications, other comorbidities and bladder comorbidities before cohort entry

	Ever pioglitazone exposed N = n (%)	Never pioglitazone exposed N = n (%)	Ever vs. never pioglitazone exposed OR (95% CI)
Duration of treated diabetes mellitus[1] (years)			
mean (±SD)			-
<1			reference
1-<2			
2-<4			
4-<6			
>=6			
Diabetic complications[2]			
diabetic retinopathy or maculopathy			
lower limb severe complications			
diabetic renal complications			
proteinuria assessment			
missing			reference
negative			
positive			
ketoacidosis			
hyperosmolar/ketoacidotic coma			
Other comorbidities			
other urinary tract cancer[4]			
other cancer[5]			
MI or stroke			
congestive heart failure			
COPD			
Bladder comorbidities			
urinary incontinence			
urinary tract infection			
pyelonephritis			
urolithiasis			
haematuria			
urinary retention			
neurogenic bladder			
catheterization			

CED: cohort entry date; SD: standard deviation; COPD: chronic obstructive pulmonary disease; MI: myocardial infarction; [1]time between first diabetes mellitus related data entry (diagnosis or OAD use) and CED; [2]during total database enrolment before CED; [3] including renal dialysis and transplant [4]excluding bladder cancer; [5]excluding all urinary tract cancer;

1.3 Patient and clinical characteristic before censoring

note: although these are time dependant variables and therefore subjected to change, we suggest to show any occurrence of these variables before censoring

Table 1.3.1 General characteristics before censoring

	Ever pioglitazone exposed **N =** n (%)	**Never pioglitazone exposed** **N =** n (%)
Time between CED and censoring (years)		
mean (±SD)		
median (IQR)		
Highest HbA1c (%)		
missing (no measurements at all)		
number of measurements		
mean (±SD)		
mean HbA1c (±SD)		
<7 %		
≥ 7%		
Highest BMI (kg/m^2)		
missing (no measurements at all)		
number of measurements		
mean (±SD)		
<25.0		
25.0-<30.0		
30.0-<35.0		
≥35.0		
Smoking		
missing (no measurements at all)		
never		
ever		

BMI: Body Mass Index; SD: standard deviation; IQR: inter quartile range

Table 1.3.2 Antidiabetic and other treatment characteristics at any time before censoring

	Ever pioglitazone exposed **N =** n (%)	**Never pioglitazone exposed** **N =** n (%)
Diabetic medication use[1]		
Pioglitazone		
Metformin		
Sulphonylureas		
Other non-insulin antidiabetic drug		
Insulin		
Other medication use		
statin		
ARB		
ACE		
BPH drugs		

[1] from CED onwards; ARB: angiotensin receptor blockers; ACE: angiotensin converting enzyme; BPH: benign prostatic hypertrophy;

Table 1.3.3 Pioglitazone exposure

	Ever pioglitazone exposed **N =** n (%)
Duration of pioglitazone exposure (months)[1]	
<12	
12-<24	
24-<48	
≥48	
Cumulative pioglitazone dose (mg)	
1-10,500mg	
10,501-28,000mg	
>28,000 mg	
Time since last exposure (years)[2]	
current	
<1	
1-2	
2-3	
3-4	
>4	

[1]cumulative durations: sum of all periods of exposure even if there are gaps in treatment;[2] time between last prescription/dispensing + it's duration and censoring

Table 1.3.4 Diabetic complications, other comorbidities and bladder comorbidities before censoring

	Ever pioglitazone exposed N = n (%)	Never pioglitazone exposed N = n (%)
Diabetic complications		
diabetic retinopathy		
lower limb severe complications		
diabetic renal complications		
proteinuria assessment [1]		
missing		
positive		
negative		
ketoacidosis		
hyperosmolar/ketoacidotic coma		
Other comorbidities		
other urinary tract cancer[2]		
other cancer[3]		
MI or stroke		
congestive heart failure		
COPD		
Bladder comorbidities		
urinary incontinence		
urinary tract infection		
pyelonephritis		
urolithiasis		
haematuria		
urinary retention		
neurogenic bladder		
cathetarization		

CED: cohort entry date; SD: standard deviation; COPD: chronic obstructive pulmonary disease; MI: myocardial infarction; [1] laboratory data not available for FIN,SWL &NL PHARMACY-Hospital datasets; [2]excluding bladder cancer; [3]including renal dialysis and transplant

1.4 **Outcomes**

Table 1.4.1 General characteristics of bladder cancer patients

				Ever pioglitazone exposed **N =** n (%)	**Never pioglitazone exposed** **N =** n (%)
Age at diagnosis (years)					
40-<50					
50-<60					
60-<70					
≥70					
Gender					
Male					
Female					
Staging					
Unknown					
Stage 0a	Ta	N0	M0		
Stage 0is	Tis	N0	M0 (in situ)		
Stage I	T1	N0	M0		
Stage II	T2a	N0	M0		
	T2b	N0	M0		
Stage III	T3a	N0	M0		
	T3b	N0	M0		
	T4a	N0	M0		
Stage IV	T4b	N0	M0		
	Any T	N1-3	M0		
	Any T	Any N	M1		
Histologic tumour grade					
Unknown					
GX Grade cannot be assessed					
G1 Well differentiated					
G2 Moderately differentiated					
G3 Poorly differentiated					
G4 Undifferentiated					
Morphology*					
Unknown					
Adenocarcinomas					
Squamous cell carcinomas					
Transitional cell urothelial tumours					
Others					
Initial treatment					
Surgery					
Intravesical therapy					
Chemotherapy					
Radiation therapy					

*only tumor types mentioned in the sensitivity analyses section of the protocol are included in this overview, pertaining morphology codes ICD-O-3 are listed in table below

ICD-O-3 morphology codes	
TRANSITIONAL CELL CARCINOMA	
8120/2	Transitional cell carcinoma in situ
8120/3	Transitional cell carcinoma, NOS
8120/3	Transitional cell carcinoma, NOS
8121/3	Schneiderian carcinoma
8122/3	Trans. cell carcinoma, spindle cell
8123/3	Basaloid carcinoma
8124/3	Cloacogenic carcinoma
8130/2	Papillary trans. cell carcinoma, non-invasive
8130/3	Papillary trans. cell carcinoma
8131/3	Transitional cell carcinoma, micropapillary
ADENOCARCINOMA	
8140/2	Adenocarcinoma in situ
8140/3	Adenocarcinoma, NOS
8141/3	Scirrhous adenocarcinoma
8143/3	Superficial spreading adenocarcinoma
8147/3	Basal cell adenocarcinoma
8260/3	Papillary adenocarcinoma, NOS
8261/2	Adenocarcinoma in situ in villous adenoma
8261/3	Adenocarcinoma in villous adenoma
8310/3	Clear cell adenocarcinoma, NOS
8480/3	Mucinous adenocarcinoma
8481/3	Mucin-producing adenocarcinoma
8440/3	Cystadenocarcinoma, NOS
8560/3	Adenosquamous carcinoma
8562/3	Epithelial-myoepithelial carcinoma
SQUAMOUS CELL CARCINOMA	
8073/3	Sq. cell carcinoma, sm. cell, non-ker.
8074/3	Sq. cell carcinoma, spindle cell
8075/3	Squamous cell carcinoma, adenoid
8076/2	Sq. cell carc. in situ with question. stromal invas.
8076/3	Sq. cell carcinoma, micro-invasive
8078/3	Squamous cell carcinoma with horn formation
OTHER	
any other code	

Table 1.4.2 Antidiabetic exposure characteristics of bladder cancer patients

	Ever pioglitazone exposed **N =** n (%)	**Never pioglitazone exposed** **N =** n (%)
Duration of pioglitazone exposure (months)		
40-<50		
50-<60		
60-<70		
≥70		
Cumulative dose of pioglitazone (mg)		
Male		
Female		
Unknown		
Stage 0a Ta N0 M0		
Time since last pioglitazone exposure (months)		
Stage 0is Tis N0 M0 (in situ)		
Ever exposure to insulin		
Yes		
Duration of insulin exposure (years)		
<1year		
1-<2 years		
2-<4 years		
>=4 years		
Ever exposure to metformin n(%)		
Yes		
Ever exposure to SU n (%)		
Yes		
Ever exposure to other non-insulin AD (%)		
Yes		

Table 1.4.3 Sensitivity endpoints

	Ever pioglitazone exposed **N =** n (%)	**Never pioglitazone exposed** **N =** n (%)
Bladder neoplasms In situ bladder cancer Bladder cancer Neoplasm of uncertain or unknown behaviour		

1.5 Validation of bladder cancer (PHARMO and CPRD-HES datasets only)

Table 1.5.1 Validation of bladder cancer cases using a subcohort with cancer registry data

Data source	Patients subcohort[1] N	True positive n	True negative n	False positive n	False negative n	Sensitivity	Specificity	PPV %	NPV %
Overall									
GP									
Hospital									
Mortality register[2]									
Ever pioglitazone exposed									
GP									
Hospital									
Mortality register[2]									
Never pioglitazone exposed									
GP									
Hospital									
Mortality register[2]									

[1] Number of patients available in subcohort with cancer registry data

[2] only UK, cause of death may be bladder cancer, but cancer registry may not have been notified

In discussion of validation it may be useful to use treatment of cancer as explanation why a proportion of cancers is not found in the hospital datasets.

2. Statistical analyses

2.1 Bladder cancer - primary analyses

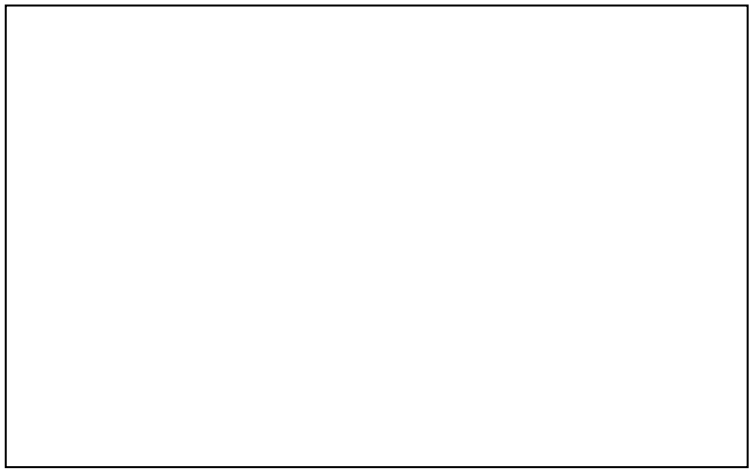


Figure 2.1.1 Kaplan Meier curves for bladder cancer

Survival curves stratified by ever vs. never pioglitazone exposed

T_0 = cohort entry

Table 2.1.1 Crude incidence rates for bladder cancer stratified by ever and never pioglitazone exposed

	Never pioglitazone exposed				Ever pioglitazone exposed			
	$N_{at\ risk}$	PY	n_{events}	IR[1] (95% CI)	$N_{at\ risk}$	PY	n_{events}	IR[1] (95% CI)
Total								
Gender								
female								
male								
Age (years)								
40-<50								
50-<60								
60-<70								
≥70								
Year of cohort entry								
2000-2003								
2004-2007								
2007-2010								
Duration of treated diabetes mellitus[1]								
<1year								
1-<2 years								
2-<4 years								
4-<6 years								
>=6 years								
Previous antidiabetic treatment								
metformin only								
SU only								
metformin and SU								
insulin only								
other								
no treatment								

	Never pioglitazone exposed				Ever pioglitazone exposed			
	$N_{at\ risk}$	PY	n_{events}	IR[1] (95% CI)	$N_{at\ risk}$	PY	n_{events}	IR[1] (95% CI)
Other medication use								
statin								
ARB								
ACE								
BPH drugs								
Diabetic complications								
diabetic retinopathy								
lower limb severe complications								
diabetic renal complications								
proteinuria assessment [1]								
missing								
positive								
negative								
ketoacidosis								
hyperosmolar/ketoacidotic coma								
Other comorbidities								
other urinary tract cancer[2]								
other cancer[3]								
MI or stroke								
congestive heart failure								
COPD								
Bladder comorbidities								
urinary incontinence								
urinary tract infection								
pyelonephritis								
urolithiasis								
haematuria								
urinary retention								
neurogenic bladder								
catheterization								

PY: person years; IR: incidence rate; CI: confidence interval; COPD: chronic obstructive pulmonary disease; MI: myocardial infarction; ACE: angiotensine I converting enzyme; ARB: angiotensine II receptor blocker; BPH: benign prostatic hyperplasia; [1] per 10,000 PY; All variables assessed before CED

Table 2.1.2 Crude incidence rates for bladder cancer stratified by duration of exposure

Person time is divided over periods. All patients are included in the first period, consecutive periods only contain patients for which pioglitazone exposure extends into that period. Only the person time and bladder cancer diagnoses in that period are used in the calculation of incidence rates.

	<12 months pioglitazone exposure				12-<24 months pioglitazone exposure				24-<48 months pioglitazone exposure				≥48 months pioglitazone exposure			
	$N_{at\ risk}$	PY	n_{events}	IR[1] (95% CI)	$N_{at\ risk}$	PY	n_{events}	IR[1] (95% CI)	$N_{at\ risk}$	PY	n-events	IR[1] (95% CI)	$N_{at\ risk}$	PY	n-events	IR[1] (95% CI)
Total																
Gender																
male																
female																
Age (years)																
40-<50																
50-<60																
60-<70																
≥70																
Year of cohort entry																
2000-2003																
2004-2007																
2007-2010																
Duration of treated diabetes mellitus[1]																
<1year																
1-<2 years																
2-<4 years																
4-<6 years																
>=6 years																
Previous antidiabetic treatment																
metformin only																
SU only																
metformin and SU																
insulin only																
Other																
no treatment																

	<12 months pioglitazone exposure				12-<24 months pioglitazone exposure				24-<48 months pioglitazone exposure				≥48 months pioglitazone exposure			
	$N_{at\ risk}$	PY	n_{events}	IR[1] (95% CI)	$N_{at\ risk}$	PY	n_{events}	IR[1] (95% CI)	$N_{at\ risk}$	PY	n-events	IR[1] (95% CI)	$N_{at\ risk}$	PY	n-events	IR[1] (95% CI)
Other medication use																
statin																
ARB																
ACE																
BPH drugs																
Diabetic complications																
diabetic retinopathy																
lower limb severe complications																
diabetic renal complications																
proteinuria assessment [1]																
missing																
positive																
negative																
Ketoacidosis																
hyperosmolar/ketoacidotic coma																
Other comorbidities																
other urinary tract cancer[2]																
other cancer[3]																
MI or stroke																
congestive heart failure																
COPD																
Bladder comorbidities																
urinary incontinence																
urinary tract infection																
pyelonephritis																
urolithiasis																
haematuria																
urinary retention																
neurogenic bladder																
cathetarization																

PY: person years; IR: incidence rate; CI: confidence interval; COPD: chronic obstructive pulmonary disease; MI: myocardial infarction; ACE: angiotensine I converting enzyme; ARB: angiotensine II receptor blocker; BPH: benign prostatic hyperplasia; [1] per 10,000 PY; All variables assessed before CED

Table 2.1.3 Crude incidence rates for bladder cancer stratified by cumulative dose amongst pioglitazone exposed patients

	1-10,500mg pioglitazone exposure				10,501-28,000mg pioglitazone exposure				>28,000mg pioglitazone exposure			
	$N_{at\ risk}$	PY	n_{events}	IR[1] (95% CI)	$N_{at\ risk}$	PY	n_{events}	IR[1] (95% CI)	$N_{at\ risk}$	PY	n_{events}	IR[1] (95% CI)
Total												
Gender												
male												
female												
Age (years)												
40-<50												
50-<60												
60-<70												
≥70												
Year of cohort entry												
2000-2003												
2004-2007												
2007-2010												
Duration of treated diabetes mellitus[1]												
<1year												
1-<2 years												
2-<4 years												
4-<6 years												
>=6 years												
Prior use of TZD other than pioglitazone in known history												
No												
Yes												
Previous antidiabetic treatment												
metformin only												
SU only												
metformin and SU												
insulin only												
other												
no treatment												

	1-10,500mg pioglitazone exposure				10,501-28,000mg pioglitazone exposure				>28,000mg pioglitazone exposure			
	$N_{at\ risk}$	PY	n_{events}	IR[1] (95% CI)	$N_{at\ risk}$	PY	n_{events}	IR[1] (95% CI)	$N_{at\ risk}$	PY	n_{events}	IR[1] (95% CI)
Other medication use												
statin												
ARB												
ACE												
BPH drugs												
Diabetic complications												
diabetic retinopathy												
lower limb severe complications												
diabetic renal complications												
proteinuria assessment [1]												
missing												
positive												
negative												
Ketoacidosis												
hyperosmolar/ketoacidotic coma												
Other comorbidities												
other urinary tract cancer[2]												
other cancer[3]												
MI or stroke												
congestive heart failure												
COPD												
Bladder comorbidities												
urinary incontinence												
urinary tract infection												
pyelonephritis												
urolithiasis												
haematuria												
urinary retention												
neurogenic bladder												
catheterization												

PY: person years; IR: incidence rate; CI: confidence interval; COPD: chronic obstructive pulmonary disease; MI: myocardial infarction; ACE: angiotensine I converting enzyme; ARB: angiotensine II receptor blocker; BPH: benign prostatic hyperplasia; [1] per 10,000 PY; All variables assessed before CED

Table 2.1.4 Crude incidence rates for bladder cancer stratified by time since last exposure amongst pioglitazone patients

	Current exposure				<1 years since last pioglitazone exposure				1-<2 years since last pioglitazone exposure			
	$N_{at\ risk}$	PY	n_{events}	IR[1] (95% CI)	$N_{at\ risk}$	PY	n_{events}	IR[1] (95% CI)	$N_{at\ risk}$	PY	n_{events}	IR[1] (95% CI)
Total												
Gender)												
male												
female												
Age (years)												
40-<50												
50-<60												
60-<70												
≥70												
Year of cohort entry												
2000-2003												
2004-2007												
2007-2010												
Duration of treated diabetes mellitus[1]												
<1 year												
1-<2 years												
2-<4 years												
4-<6 years												
>=6 years												
Prior use of TZD other than pioglitazone in known history												
no												
yes												
Previous antidiabetic treatment												
metformin only												
SU only												
metformin and SU												
insulin only												
other												
no treatment												

	Current exposure				<1 years since last pioglitazone exposure				1-<2 years since last pioglitazone exposure			
	$N_{at\ risk}$	PY	n_{events}	IR[1] (95% CI)	$N_{at\ risk}$	PY	n_{events}	IR[1] (95% CI)	$N_{at\ risk}$	PY	n_{events}	IR[1] (95% CI)
Other medication use												
statin												
ARB												
ACE												
BPH drugs												
Diabetic complications												
diabetic retinopathy												
lower limb severe complications												
diabetic renal complications												
proteinuria assessment [1]												
missing												
positive												
negative												
ketoacidosis												
hyperosmolar/ketoacidotic coma												
Other comorbidities												
other urinary tract cancer[2]												
other cancer[3]												
MI or myocardial infarction												
congestive heart failure												
COPD												
Bladder comorbidities												
urinary incontinence												
urinary tract infection												
pyelonephritis												
urolithiasis												
haematuria												
urinary retention												
neurogenic bladder												
catheterization												

PY: person years; IR: incidence rate; CI: confidence interval; COPD: chronic obstructive pulmonary disease; MI: myocardial infarction; ACE: angiotensine I converting enzyme; ARB: angiotensine II receptor blocker; BPH: benign prostatic hyperplasia; [1] per 10,000 PY; All variables assessed before CED

Table 2.1.4 Crude incidence rates for bladder cancer stratified by time since last exposure (continued)

	2-<3 years since last pioglitazone exposure				3-<4 years since last pioglitazone exposure				≥4 years since last pioglitazone exposure			
	$N_{at\ risk}$	PY	n_{events}	IR[1] (95% CI)	$N_{at\ risk}$	PY	n_{events}	IR[1] (95% CI)	$N_{at\ risk}$	PY	n_{events}	IR[1] (95% CI)
Total												
Age (years)												
40-<50												
50-<60												
60-<70												
≥70												
Year of cohort entry												
2000-2003												
2004-2007												
2007-2010												
Duration of treated diabetes mellitus[1]												
<1year												
1-<2 years												
2-<4 years												
4-<6 years												
>=6 years												
Prior use of TZD other than pioglitazone in known history												
No												
Yes												
Previous antidiabetic treatment												
metformin only												
SU only												
metformin and SU												
insulin only												
other												
no treatment												

	2-<3 years since last pioglitazone exposure				3-<4 years since last pioglitazone exposure				≥4 years since last pioglitazone exposure			
	$N_{at\ risk}$	PY	n_{events}	IR[1] (95% CI)	$N_{at\ risk}$	PY	n_{events}	IR[1] (95% CI)	$N_{at\ risk}$	PY	n_{events}	IR[1] (95% CI)
Other medication use												
statin												
ARB												
ACE												
BPH drugs												
Diabetic complications												
diabetic retinopathy												
lower limb severe complications												
diabetic renal complications												
proteinuria assessment [1]												
missing												
positive												
negative												
ketoacidosis												
hyperosmolar/ketoacidotic coma												
Other comorbidities												
other urinary tract cancer[2]												
other cancer[3]												
MI or myocardial infarction												
congestive heart failure												
COPD												
Bladder comorbidities												
urinary incontinence												
urinary tract infection												
pyelonephritis												
urolithiasis												
haematuria												
urinary retention												
neurogenic bladder												
catheterization												

PY: person years; IR: incidence rate; CI: confidence interval; COPD: chronic obstructive pulmonary disease; MI: myocardial infarction; ACE: angiotensine I converting enzyme; ARB: angiotensine II receptor blocker; BPH: benign prostatic hyperplasia; [1] per 10,000 PY; All variables assessed before CED

Table 2.1.5 Crude and adjusted Hazard Ratios for bladder cancer per pioglitazone exposure group

	Crude HR (95%CI)	Base model HR (95%CI)	Adjusted HR (95%CI)
Pioglitazone exposure			
Never[1]	Reference	Reference	Reference
ever			
Duration of pioglitazone exposure (months)[1]			
<12			
12-24			
>24			
Cumulative pioglitazone dose (mg)[1]			
1-10,500mg			
10,501-28,000mg			
>28,000 mg			
Time since last exposure (years)[1]			
current use[2]			
< 1			
1-<2			
2-<3			
3-<4			
>4			

HR: Hazard ratio; CI: confidence interval; [1] Never use of pioglitazone will be the reference group for the calculation of the HR associated with ever use of pioglitazone and duration, dose and time since last exposure; [2] the current use category includes all patients up to the time they stop using pioglitazone

- Need to report what variables were adjusted for in each model in a footnote or a note below the table

2.2 Bladder cancer -additional stratified analsyses

Table 2.2.1 Crude and adjusted Hazard Ratios for bladder cancer per additional stratification group

	Crude IR (95%CI)	Crude HR (95%CI)	Base model HR (95%CI)	Adjusted HR (95%CI)
Pioglitazone exposure				
Never[1]		Reference	Reference	Reference
Ever				
Duration of treated diabetes prior to CED (years)[1]				
<1				
1-<2				
2-<4				
4-<6				
>=6				
Prior use of other TZD than pioglitazone prior to CED				
No				
Yes				
History of diabetic renal complications at CED				
No				
Yes				
History of micro- or macroproteinuria at CED				
No				
Yes				
No measurement				

HR: Hazard ratio; CI: confidence interval; [1] Never use of pioglitazone will be the reference group for the calculation of the HR associated with ever use of pioglitazone and duration, dose and time since last exposure; [2] the current use category includes all patients up to the time they stop using pioglitazone

- Need to report what variables were adjusted for in each model in a footnote or a note below the table

2.3 All-cause mortality

Figure 2.3.1 Kaplan Meier curves for all cause mortality

Survival curves for ever vs. never pioglitazone exposed patients with and without bladder cancer

T_0 = cohort entry

Figure 2.3.2 Kaplan Meier curves for all cause mortality within patients diagnosed with bladder cancer

Survival curves for ever vs. never pioglitazone exposed patients with bladder cancer

T_0 = diagnosis of bladder cancer

Table 2.3.1 Crude incidence rates for all-cause mortality stratified by ever and never pioglitazone exposed

Table 2.3.2 Crude incidence rates for all-cause mortality stratified by duration of exposure

Table 2.3.3 Crude incidence rates for all-cause mortality stratified by cumulative dose

Table 2.3.4 Crude incidence rates for all-cause mortality stratified by time since last exposure

Table 2.3.5 Crude and adjusted Hazard Ratios for all-cause mortality per pioglitazone exposure group

2.4 Bladder cancer mortality

Figure 2.4.1 Kaplan Meier curves for bladder cancer mortality

Survival curves for ever vs. never pioglitazone exposed patients with or without bladder cancer

T_0 = cohort entry

Figure 2.4.2 Kaplan Meier curves for bladder cancer mortality within patients diagnosed with bladder cancer

Survival curves for ever vs. never pioglitazone exposed patients with bladder cancer

T_0 = diagnosis of bladder cancer

Table 2.4.1 Crude incidence rates for bladder cancer mortality stratified by ever and never pioglitazone exposed

Table 2.4.2 Crude incidence rates for bladder cancer mortality stratified by duration of exposure

Table 2.4.3 Crude incidence rates for bladder cancer mortality stratified by cumulative dose

Table 2.4.4 Crude incidence rates for bladder cancer mortality stratified by time since last exposure

Table 2.4.5 Crude and adjusted Hazard Ratios for bladder cancer mortality per pioglitazone exposure group

3. Sensitivity analyses

3.1 Impact of exclusion unmatched pioglitazone patients

This analysis will only be performed if >2.5% of pioglitazone users have no match. Incidence density sampling to determine cohort entry date for unmatched patients: select a random date from the possible matching dates of the reference patient.

Table 3.1.1 General characteristics at cohort entry using an unmatched cohort analysis

Table 3.1.2 Clinical parameters at cohort entry using an unmatched cohort analysis

Table 3.1.3 Antidiabetic and other treatment characteristics before and at cohort entry using an unmatched cohort analysis

Table 3.1.4 Treatment changes at cohort entry using an unmatched cohort analysis

Table 3.1.5 History of diabetic complications, other comorbidities and bladder comorbidities before cohort entry using an unmatched cohort analysis

Table 3.1.6 Crude incidence rates for bladder cancer stratified by ever and never pioglitazone exposed using an unmatched cohort analysis

Table 3.1.7 Crude and adjusted Hazard Ratios for bladder cancer stratified by ever and never pioglitazone exposed using an unmatched cohort analysis

HR estimates from the propensity score matched cohort analyses will be compared with the HR estimates from an unmatched cohort analyses where propensity score or individual matching variables will be included as baseline covariates in the risk model

3.2 Impact of cancer latency period

Table 3.2.1 Crude and adjusted Hazard Ratios for bladder cancer stratified by ever and never pioglitazone exposed excluding cases within 12 months after CED

3.3 Risk within transitional cell urothelial tumours

Table 3.3.1 Crude and adjusted Hazard Ratios for bladder cancer stratified by ever and never pioglitazone exposed excluding cases of adeno- and squamous cell carcinoma

3.4 Impact of follow-up time censoring after first gap of 4 months between two pioglitazone prescriptions

Analysis limited to Finland and Sweden

Table 3.4.1 Crude and adjusted Hazard Ratios for bladder cancer stratified by ever and never pioglitazone exposed censoring follow-up at first gap of 4 months between two prescriptions

3.5 Impact of (not) adjusting for smoking status, BMI and HbA1c (NL and UK only)

Table 3.5.1 Crude and adjusted Hazard Ratios for bladder cancer stratified by ever and never pioglitazone exposed adjusted for smoking, BMI and HbA1C

Table 3.5.2 Crude and adjusted Hazard Ratios per for bladder cancer stratified by ever and never pioglitazone exposed not adjusted for smoking, BMI and HbA1C

3.6 Impact of imputing smoking and BMI

Finland excluded from analyses (no data).

Table 3.6.1 Crude and adjusted Hazard Ratios for bladder cancer stratified by ever and never pioglitazone exposed adjusted for smoking, BMI and HbA1C when including missings as category

Table 3.6.2 Crude and adjusted Hazard Ratios for bladder cancer stratified by ever and never pioglitazone exposed not adjusted for smoking, BMI and HbA1C when imputing missing values

3.7 Incident users (patients with at least 12 months prescription database membership before first diabetes treatment)

Finland excluded from analyses (all patients have at least 12 months membership).

Table 3.7.1 Crude and adjusted Hazard Ratios for bladder cancer stratified by ever and never pioglitazone exposed among incident diabetes subcohort

3.8 Cumulative duration of insulin

Table 3.8.1 Crude and adjusted Hazard Ratios for bladder cancer stratified by ever and never pioglitazone exposed with cumulative duration of insulin added to the adjusted model

3.9 Change pioglitazone exposure definition to at least 2prescribing/dispensing dates within a 6 months period

Table 3.9.1 Crude and adjusted Hazard Ratios for bladder cancer stratified by ever and never pioglitazone exposed using at least 2 pioglitazone prescribing dates for ever exposure

3.10 Impact of including neoplasms of uncertain or unknown behavior in definition of bladder cancer

Table 3.10.1 Crude and adjusted Hazard Ratios for bladder cancer including neoplasms of uncertain or unknown behavior stratified by ever and never pioglitazone exposed