Impact of treatment with pioglitazone on stroke outcomes: a real world database analysis.

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Abstract

Aims Randomised controlled trials have reported an association between pioglitazone and reduced incidence of stroke in type 2 diabetic (T2DM) and insulin-resistant populations. We investigated this association within a real-world database.

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Materials and methods T2DM patients initiating pioglitazone between 2000-2012 were extracted from the Clinical Practice Research Datalink (CPRD); a UK routine. Two non-exposed control cohorts were matched on age, gender, HbA1c, diabetes duration, stroke history, co-morbidities and prior T2DM regimen. Control cohort-1 comprised patients initiating a new T2DM therapy as their respective case initiated pioglitazone. Control cohort-2 remained on the same T2DM regimen as their respective case prior to the case initiating pioglitazone. The primary outcome was incident stroke; other outcomes included mortality, hospital length of stay and stroke recurrence.

Results 4,234 pioglitazone patients matched to controls in cohort-1 and 3,604 in cohort-2. For the primary outcome there were significantly reduced hazard ratios (HRs) for cases:controls. Cohort 1, the HR was 0.627 (95% CI, 0.404-0.972) during the therapy period and 0.640 (0.485-0.843) over the entire observation period; respective HRs were 0.516 (0.336-0.794) and 0.773 (0.611-0.978) for cohort 2. There was no significant difference in 30-day mortality rate or rate of recurrent stroke. For hospitalised stroke events there was a significant difference in length of stay for patients discharged to usual residence (median 3.0 days versus 7.0 days; p=0.008) for control cohort-2 whilst on-treatment.

Conclusions In support of evidence from two large randomized trials, these observational data show that pioglitazone has a potent effect in reducing stroke events in patients with type 2 diabetes.

Introduction

Type 2 diabetes in an increasing public health concern with an estimated prevalence of 4.5% in the United Kingdom[1] and approximately 8.0% in the United States.[2] Type 2 diabetes is known to increase the risk of stroke relative to the non-diabetic population.[3,4] Insulin resistance, which is a predictor of the future development of type 2 diabetes, also appears to be a strong stroke risk factor. This metabolic state is reported in approximately half of all stroke patients without diabetes.[5] The treatment of insulin resistance in those at high risk of stroke, regardless of diabetes status, could therefore offer potential benefit for high-risk patients.[6]

Glucose-lowering drugs of the thiazolidinedione (TZD) class increase peripheral sensitivity to insulin, thereby reducing insulin resistance and hyperinsulinemia.[7] The TZD pioglitazone has properties that may improve other risk factors associated with cerebrovascular disease, such as dyslipidaemia,[8] blood pressure,[9] and inflammation. The drug may also have direct anti-atherosclerotic effects via PPAR-γ, the nuclear transcription factor activated by this class of drugs. In the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) study, pioglitazone therapy was associated with a markedly reduced incidence of stroke in patients with type 2 diabetes and prior stroke.[10,11] Recent data on insulin-resistant, but non-diabetic patients with a prior history of stroke or transient ischemic attack (TIA) from the Insulin Resistance Intervention after Stroke (IRIS) trial[12,13,14] also indicate a benefit in reducing recurrent stroke and myocardial infarction.

Whilst prospective randomised trials may be considered a gold standard that allow for the equalisation of differences between groups, the inclusion/exclusion criteria applied can reduce the study population to a non-representative sub-set of those that will receive the therapy in real-life clinical practice. The aim of this study therefore is to determine whether the reduced incidence of stroke associated with pioglitazone is observed within a retrospective UK database derived from day-to-day primary care practice.

Methods

Data source

The study was conducted using data from the Clinical Practice Research Datalink (CPRD)[15]. The core dataset within CPRD is CPRD GOLD which comprises anonymised, longitudinal data from approximately 700 primary care practices from the United Kingdom. Available data includes patient demographics, diagnoses, prescription history for prescriptions emanating in primary care and laboratory test results. For a sub-cohort of those primary care practices based in England, linkage to other data sources has been undertaken. The linked data sources used within this study were the Health Episodes Statistics (HES);[16] providing details of inpatient hospital contacts, and Office of National Statistics (ONS)[17] mortality dataset.

Patient selection

Patients eligible for linkage to HES and ONS, and of acceptable research quality as defined by CPRD, were selected for this study. Patients with type 2 diabetes were identified by previously used algorithms[18] that select patients based on diagnostic codes and treatment history. A wash-in period of at least 90 days from the later of the patient's registration date and the practice's up-to-standard date to the patient's first recorded diagnosis of diabetes was required to allow selection from an approximate type 2 diabetes incident population.

From this pool of patients, those initiating pioglitazone between 1st January 2000 and 31st December 2012 were selected. Patients with a prior history of heart failure were excluded since the drug is contraindicated in this group. Date of first prescription for pioglitazone was defined as the case index date. The duration of treatment was defined as from index date to the date of the last prescription in the regimen, (that is prior to change of any regimen component) augmented by the estimated duration of that prescription. If the duration could not be calculated a default value of 28 days was used.

Pioglitazone exposed patients were matched to two cohorts controls at ratios of 1:1. The pool of control patients comprised those with an incident diagnosis of type 2 diabetes, no history of heart failure, and no history of receiving a TZD at any point in their patient record.

The first control cohort was comprised of those individuals on the same previous glucose-lowering regimen as their respective case and who changed to a different (i.e., non-TZD) glucose-lowering therapy within 180 days of the case index date. The index date for the

controls was defined as the date of medication change. The second control cohort included those who remained on the same glucose-lowering regimen as their respective case prior to the case initiating pioglitazone. The index date for these controls was defined as the date of the controls initiation with that therapy plus the duration on the regimen of their respective case prior to the addition of pioglitazone.

For both control cohorts the following matching criteria was used: age (+/- 3 years), gender, HbA1c (+/- 1%), duration of diagnosed diabetes (+/- 1 year), history of stroke prior to index date, Charlson co-morbidity index matching on scores of 1, 2 or 3+, and same glucose-lowering drug class combination immediately prior to index date.

Outcomes

The primary outcome was time to first stroke post index date. Incident stroke events were defined by Read code within the CPRD GOLD database or ICD-10 code in either the HES or ONS datasets.

Secondary outcomes were:

- the proportion of first stroke events that resulted in death within 28 days (fatal stroke).
- the inpatient length of stay following hospital admission for stroke
- recurrence of stroke

Statistical analysis

Baseline characteristics were compared using the chi-squared test for categorical variables and t-test for continuous variables. All analyses were performed twice; firstly with follow-up restricted to on-treatment, that is the time the patient remained on the index regimen defined as date of last prescription + 90 days and secondly for the entire follow-up period within the database.

For the primary outcome, time to first stroke was evaluated using the Cox proportional hazards model (CPHM). Hazard ratios (HRs) were calculated with 95% confidence intervals and adjusted for age, sex, body mass index (BMI), duration of diabetes, systolic blood pressure, HbA1c, total cholesterol, lipid-lowering therapy, antihypertensive therapy, antiplatelet therapy, Charlson comorbidity index, the number of primary care contacts in the year prior to index date, smoking status, prior history of atrial fibrillation and prior history of stroke. For BMI, total cholesterol and systolic blood pressure values observed in the 30 days prior to index date were used. If no readings were available in this time-frame, values in the

30 days subsequent to index date were used. If values were still missing then the nearest value to the index date within the preceding 365 days was used.

The proportion of stroke events resulting in 28-day death was compared between treatment groups using a logistic regression model adjusting for age, gender and Charlson index. The Mann-Whitney U test was used to compare the length of stay in hospital following stroke. Logistic regression was used to investigate the likelihood of discharge to usual place of residence.

Studies using CPRD are covered by ethics approval granted by Trent Multicentre Research Ethics Committee (Reference 05/MRE04/87). CPRD Independent Scientific Advisory Committee approval was granted for this study (ISAC 16-292). CPRD studies which do not include patient identifiable data do not require patient consent. Patients are able to opt-out of CPRD; such that their data is not extracted from their particular primary care practice.

Results

Identified patients and baseline characteristics

7,577 patients initiated with pioglitazone met the initial study inclusion criteria. Of these pioglitazone patients, 4,234 (55.9%) could be matched at a ratio of 1:1 to the first control cohort and 3,604 (47.6%) could be matched to the second. Baseline characteristics for each matched cohort are shown in Tables 1 and 2, respectively. Compared with control cohort-1, cases had significantly higher BMI (32.2 versus 31.7 kg/m^2), were more likely to have received lipid lowering therapy (81.7% versus 77.8%) and less likely to have a history of atrial fibrillation in their patient record (3.4% versus 4.4%). The most common index regimen for cases was metformin and pioglitazone (49.3%) and for controls was metformin and sulfonylurea (43.9%) (supplementary tables 1 and 2).

Compared with control cohort-2, cases had a greater number of primary care contacts in the 12 months prior to index date (10.4 versus 9.6), a significantly higher mean BMI (32.3 versus 31.6 kg/m^2), lower cholesterol (4.3 versus 4.5 mmol/l) and more likely to receive lipid lowering (82.7% versus 75.0%), anti-hypertensive (72.7% versus 69.4%), and anti-platelet therapies (45.5% versus 41.1%). The most common index regimen for cases was metformin and pioglitazone (52.0%) and for controls was metformin and sulfonylurea (33.5%) (supplementary tables 1 and 2)

Primary outcome.

In comparison with control cohort-1, the rate of stroke events whilst on-treatment was 5.0 per 1,000 person years (kpy) exposure for cases (pioglitazone) versus 7.5 per kpy for controls; a crude relative risk of 0.662 (0.462-0.952), Table 3. After adjusting for co-variates in the CPHM, the hazard ratio (HR) was 0.666 (0.466-0.952, Figure 1). Over the duration of the entire follow-up period, the crude event rate was 7.5 versus 9.9 events per kpy exposure; a crude relative risk of 0.761 (0.622-0.930) and HR of 0.750 (0.612-0.919).

In comparison with control cohort-2 the crude event rates on-treatment were 3.9 versus 7.0 events per kpy exposure, respectively, a crude relative risk of 0.551 (0.362-0.827). The adjusted hazard ratio was 0.516 (0.336-0.794) (Figure 1). For the analysis that followed patients for the entire follow-up period, the respective rates were 7.2 versus 8.5 events per

kpy exposure (crude relative rate 0.844, 0.672-1.060, Table 3). The HR was 0.773 (0.611-0.978) (Figure 1).

Supplementary table 3 reports the hazard ratios for patient with and without prior history of stroke.

Secondary outcomes

Stroke recurrence and mortality

There was no difference between cases and controls in the 30-day mortality rate following the index stroke event. For events observed during the on-treatment period, the proportion of deaths was 12.0% versus 12.7% (p=0.444) for control cohort-1 and 8.8% versus 10.1% (p=0.358) for control cohort-2. Following patients until the end of the observed period, the respective figures were 10.3% versus 12.3% (p=0.121) and 11.1% versus 11.8% (p=0.832); (Table 4).

There was also no significant difference in the rate of recurrent strokes in each control cohort over either follow-up period. For control cohort-1, the HR was 0.558 (0.104-2.978) for patients during the therapy period and 0.921(0.504-1.683) over the entire observed period. For control cohort-2 the respective figures were 0.298 (0.033-2.679) and 0.761(0.399-1.451) (Supplementary table 4).

Hospital outcomes

For those incident stroke events resulting in hospital admission, there was no significant difference in overall length of stay for control cohort 1 over either the on-treatment follow-up period (4.0 days versus 5.0; p=0.419) or over the entire follow-up period (7.0 versus 6.0; p=0.417). There was also no significant difference when considering those admissions that resulted in discharge to the patient's usual place of residence: 3.0 days versus 3.0 (p=0.645) and 6.0 versus 3.0 (p=0.196), respectively (Table 5).

For cohort 2, however, there was a significant difference in length of stay for the incident stroke admission during the on-treatment period (3.0 days versus 8.0; p=0.002) but no significant difference over the entire follow-up period (6.0 days versus 7.0; p=0.941). For those admissions resulting in discharge to the patient's usual place of residence, there was a significant difference for those events occurring during the therapy period (3.0 versus 7.0; p=0.008). For the entire follow-up period, there was no significant difference, however (5.0 versus 6.0 days p=0.485), (Table 5).

Discussion

In this study, we have shown a significantly reduced risk of incident stroke in patients treated with pioglitazone compared with matched controls using other glucose lowering agents for T2DM. This was observed for both control sets and over both follow-up periods. Interestingly, the hazard ratios were lower during the period on-treatment compared with over the entire follow-up period in both control sets. If the association we find is related causally to pioglitazone treatment, this observation suggests attenuation of treatment effect over time, as suggested in long-term follow-up of the original PROactive cohort.[14]

There was no difference in the secondary outcomes of proportion of incident strokes resulting in death or time to recurrent stroke between cases and controls in either control cohort or over either follow-up period. In each however, the odds ratio was below unity with wide confidence limits, likely due to small numbers. For strokes resulting in hospitalisation there was no significant difference in length of stay overall or for patients discharged to their usual place of residence for patients in control set 1 over either the on-treatment or entire follow-up periods. For those patients in control set 2, length of stay was significantly lower for pioglitazone patients whilst on-treatment overall (median 3.0 versus 8.0 days) and for admissions resulting in discharge to the patient's usual residence (median 3.0 versus 7.0 days). There was no significant difference over the entire follow-up period, however.

For the primary outcome, the adjusted hazard ratios we observed on-treatment (HR = 0.627 (0.404-0.972) and 0.516 (0.336-0.794) for cohorts 1 and 2 respectively) were more favourable to pioglitazone than those observed for the overall stroke outcome in the PROactive trial (0.81 [0.61-1.07]) although there was considerable overlap of the 95% confidence intervals.[11] In a sub-analysis comparing patients enrolled with prior stroke, the PROactive investigators reported a hazard ratio for stroke of 0.53 (0.34–0.85). It should be noted that that trial was conducted in a population (N=5,238) with pre-existing macrovascular disease, whereas this was not an inclusion criteria in our study. The IRIS trial involved 3,876 non-diabetic patients with insulin resistance with prior stroke or TIA. Active therapy with pioglitazone reduced the time to a composite cardiovascular outcome of fatal or nonfatal myocardial infarction and stroke (HR 0.74 [0.62-0.93] vs. placebo. The specific HR for stroke alone in IRIS was 0.82 (0.61-1.10.) using the original definition of stroke at the trial's conception. In a pre-specified analysis, however, using the updated 2013 consensus criteria for ischemic stroke, the HR was 0.75 (0.60-0.94) in favour of pioglitazone, interestingly precisely the same as that obtained for the entire observation period in cohort 1 and very

close to that in cohort 2.

Two meta-analyses have reported a similar reduced relative risk of stroke for patients treated with pioglitazone to the PROactive study, perhaps not surprisingly, as both were numerically dominated by that trial. Lincoff and colleagues reported a relative risk of 0.80 (0.62-1.04)[19] in patients with type 2 diabetes whereas Liao and colleagues reported 0.78 (0.60- 1.02)[20] in studies that also included data from IRIS.

The precise mechanism that could explain these results is not clear. It is known that, in addition to its impact on insulin sensitivity, pioglitazone affects other risk factors for cerebrovascular disease. In the IRIS trial, for example, the profile of a range of risk factors including blood glucose, blood pressure, certain lipids and the inflammatory marker, C-reactive protein, were improved[12]. Similar observations have also been reported in other investigations.[9,21,22,] There may also be direct salutary effects via activation of PPAR-γ on the vascular endothelium, thrombotic factors, as well as cellular elements involved in the development of atheroma.[23]

To provide comparable controls, we matched patients directly on a broad range of demographic, treatment and clinical characteristics. As a result, we were able to match approximately 50% (4,234 (55.9%) to the first control cohort and 3,604 (47.6%) to the second of our original pioglitazone pool, this reduced the power of the study especially for those outcomes related to occurrence of strokes such as mortality and length of stay and also risk of recurrent stroke. Similar studies using routine data from different cohorts would be of interest to confirm the magnitude of our findings.

We used two cohorts of control for this study. The purpose of this was to partly address issues of confounding by indication inherent in pharmaco-epidemiolgical studies. Control cohort-1 were patients who had their regimen changed at the same time as their control and thus to some extent were at a similar stage of the treatment pathway. However, it should be noted that for reasons of physician preference, contra-indication or other factors they were not prescribed pioglitazone, and thus confounding by indication may remain. For example, given the drug's salt-retaining properties and contraindication in heart failure, patients with suspected left ventricular dysfunction (without diagnosed heart failure, which was an exclusion), who may have been an inherently higher risk for stroke, may have been prescribed other agents.

Control cohort-2 were not constrained to being prescribed any additional therapy, i.e. changing regimen at the same time as the index case, but continued on the same treatment as

their respective case prior to the addition of pioglitazone. The direction of confounding by indication may therefore be considered to be 'against' the case group, in that their therapy was intensified possibly due to a perceived treatment failure or progression of disease. However, there is also the possibility that the intensification of treatment may proxy other elements such as closer monitoring or greater awareness of the patient and/or their physician. It should be noted that in the baseline characteristics of this group (Table 2), cases were more likely to be prescribed lipid lowering, anti-platelet and anti-hypertensive medication which may be indicative of potential differences between the management of these groups – some of which may not have be accounted for in our multivariable model.

There are other limitations to this study. Patient ethnicity, known to impact on diabetes progression and outcome, is not systematically recorded within the CPRD dataset and so was excluded as a potential confounding variable. However, we do not believe that there would be significant differences between prescription rates of pioglitazone by ethnic group. Furthermore, exposure to the regimens can only be taken as an intention-to-treat on the part of the prescriber. From the data source it is not possible to determine whether the patient collected the prescription of whether they took the treatment at the prescribed dosage. Due to different side-effects between different therapies it is possible that adherence rates between treatment groups may have been different.

Unlike a trial situation, real-world observational studies may not contain key information recorded at baseline or at subsequent follow-up periods. As such, missing data is inevitable. It is likely that data would not be missing at random but will instead reflect the number of health contacts a person has, and therefore can be considered a proxy for morbidity. Within this study we categorized key variables with 'missing' included as a category in order to maximize patient numbers but may have lost some of the granularity of this data. It is therefore important to consider this in the interpretation of results.

The quality of coding of outcomes in routine data has been questioned but within CPRD and HES the data quality is considered reasonably robust.[24,25,26] Whilst some events may be misdiagnosed, incorrectly transcribed or omitted, we do not consider it likely that there would be a differential bias in error rates between the cohorts and thus whilst the absolute number of events may be questioned, the relative difference between treatment arms should persist.

Conclusion

In conclusion, this study found a significant reduction in incident stroke for patients treated with pioglitazone compared with other glucose lowering strategies, matched to controls in two analysis cohorts and over two follow-up periods. There was no clear effect, however, on stroke mortality, recurrent stroke or hospital length of stay. These data support the findings from PROactive in patients with type 2 diabetes and established macrovascular disease and also from IRIS in patients with insulin resistance but without diabetes. Further study is warranted into the beneficial effects of this insulin sensitizing drug in patients with or at risk for cerebrovascular disease. As a result of the consistency of the findings across randomized trials and observational data sets, guideline committees should now consider a recommendation to use pioglitazone, barring contraindications, in secondary stroke prevention, at least in patients with type 2 diabetes.

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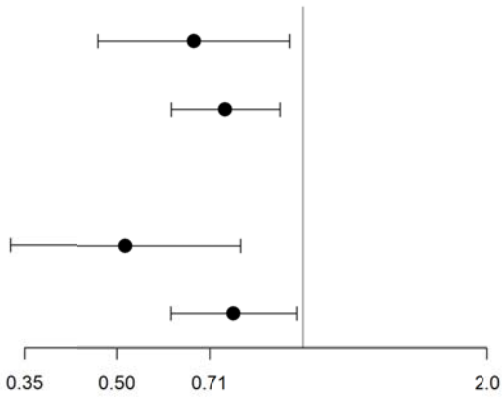
Disclosures

Christopher Morgan, Sara Jenkins-Jones and Craig Currie are employees of Pharmatelligence who received funding from Takeda to conduct the study. Jorge Puelles in an employee of Takeda. Silvio Inzucchi is a consultant advisor to Sanofi/Lexicon, Janssen, Merck, vTv Pharmaceuticals, Alere; a clinical trial steering/executive committee member to AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo Eisai (TIMI Study Group) and Novo Nordisk and a data monitoring committee member for Intarcia.

Figure 1

Adjusted hazard ratio for incident stroke for patients initiated with pioglitazone and matched controls.



	Hazard Ratio	95% CI
Control cohort-1		
On-treatment	0.666	(0.466-0.952)
Until end of follow up	0.750	(0.612-0.919)
Control cohort-2		
On-treatment	0.516	(0.336-0.794)
Until end of follow up	0.773	(0.611-0.978)

Table 1.

Baseline characteristics of patients initiated with pioglitazone and matched controls – control cohort-1

	Case		Control		p-value
Number	4,234		4,234		
Gender*	1,665	(39.3%)	1,665	(39.3%)	1.000
Age, years**	61.4	(10.8)	61.5	(10.8)	0.837
Follow-up on therapy, years**	2.4	(2.1)	2.5	(2.3)	0.025
Follow-up to end of study, years**	5.5	(2.9)	5.1	(2.8)	<0.001
Charlson index **	2.1	(1.4)	2.1	(1.4)	0.667
Primary care contacts in prior year **	10.4	(8.3)	10.7	(9.2)	0.145
Duration of diabetes, years **	4.4	(3.1)	4.4	(3.1)	0.607
Body Mass Index, **	32.2	(6.1)	31.7	(6.3)	0.001
HbA1c, DCCT, % **	7.1	(12.6)	7.0	(12.6)	0.811
Systolic blood pressure, mmHg **	136.1	(14.7)	135.7	(15.3)	0.254
Total cholesterol, mmol/L **	4.4	(1.1)	4.4	(1.1)	0.045
Serum creatinine umol/L **	85.4	(24.1)	85.1	(25.7)	0.551
Lipid lowering therapy *	3,459	(81.7%)	3294	(77.8%)	<0.001
Anti-hypertensives *	3,056	(72.2%)	3055	(72.2%)	1.000
Anti-platelet therapy *	1,889	(44.6%)	1853	(43.8%)	0.444
History of prior stroke *	86	(2.0%)	86	(2.0%)	1.000
History of atrial fibrillation *	145	(3.4%)	185	(4.4%)	0.028
Smoking history					0.328
Never smoked (%)	1,656	(39.1%)	1697	(39.3%)	
Ex-smoker (%)	1,892	(44.7%)	1823	(39.3%)	
Current smoker (%)	686	(16.2%)	711	(39.3%)	

* n (%), ** mean (standard deviation).

Table 2.

Baseline characteristics of patients initiated with pioglitazone and matched controls – control cohort-2

	Case		Control		p-value
Number	3,604		3,604		
Gender*	1367	(37.9%)	1367	(37.9%)	1.000
Age, years**	61.0	(10.9)	61.0	(11.0)	0.828
Follow-up on therapy, years**	2.4	(2.1)	2.7	(2.4)	<0.001
Follow-up to end of study, years**	5.6	(2.9)	5.0	(3.0)	<0.001
Charlson index **	2.1	(1.4)	2.1	(1.4)	0.564
Primary care contacts in prior year **	10.4	(8.2)	9.6	(7.6)	<0.001
Duration of diabetes, years **	4.4	(3.1)	4.4	(3.1)	0.690
Body Mass Index, **	32.3	(6.1)	31.6	(6.2)	<0.001
HbA1c, DCCT, % **	6.8	(13.5)	6.6	(13.5)	0.427
Systolic blood pressure, mmHg **	135.7	(14.7)	136.1	(14.9)	0.220
Total cholesterol, mmol/L **	4.3	(1.0)	4.5	(1.1)	<0.001
Serum creatinine umol/L **	84.7	(22.6)	84.5	(22.1)	0.690
Lipid lowering therapy *	2981	(82.7%)	2702	(75.0%)	<0.001
Anti-hypertensives *	2621	(72.7%)	2502	(69.4%)	0.002
Anti-platelet therapy *	1641	(45.5%)	1480	(41.1%)	<0.001
History of prior stroke *	85	(2.4%)	85	(2.4%)	1.000
History of atrial fibrillation *	118	(3.3%)	156	(4.3%)	0.023
Smoking history					<0.001
Never smoked (%)	1392	(38.6%)	1536	(42.6%)	
Ex-smoker (%)	1630	(45.2%)	1442	(40.0%)	
Current smoker (%)	582	(16.1%)	625	(17.3%)	

* n (%), ** mean (standard deviation).

Table 3

Number, crude rate and crude relative risk for incident stroke for patients initiated with pioglitazone and matched controls.

	Case		Control		Crude relative risk (95% CI)	
Control cohort-1	Events	Rate*	Events	Rate*		
On-treatment	50	5.0	79	7.5	0.662	(0.462-0.941)
Until end of follow up	174	7.5	211	9.9	0.761	(0.622-0.930)
Control cohort-2						
On-treatment	34	3.9	69	7.0	0.551	(0.362-0.827)
Until end of follow up	144	7.2	152	8.5	0.844	(0.672-1.060)

* Rate per 1,000 person years.

Table 4

Number and proportion of stroke events resulting in 30-day mortality for patients initiated with pioglitazone and matched controls.

	Cases		Controls		Odds ratio	p-value*
	n	**Deaths (%)**	**n**	**Deaths (%)**		
Control cohort-1						
On-treatment	50	6 (12.0%)	79	10 (12.7%)	0.891 (0.286-2.776)	0.843
Until end of follow up	174	18 (10.3%)	211	26 (12.3%)	0.744 (0.387-1.43)	0.375
Control cohort-2						
On-treatment	34	3 (8.8%)	69	7 (10.1%)	0.931 (0.215-4.025)	0.924
Until end of follow up	144	16 (11.1%)	152	18 (11.8%)	0.912 (0.441-1.884)	0.803

*Adjusted for age, gender, Charlson index

Table 5

Destination on discharge and associated length of stay for patients initiated with pioglitazone and matched controls.

	Case			Control			
	Number	**Median LOS (IQR)**		**Number**	**Median LOS (IQR)**		
Cohort 1							
On-treatment							
Usual residence	31	3	(1-8)	51	3	(2-11)	0.645
Death	5	5	(1-11)	9	3	(3-6)	0.687
Nursing home	1	42	(42-42)	1	45	(45-45)	1.000
Transfer to acute unit	5	3	(3-30)	10	17	(7-21)	0.713
Other	0			1	19	(19-19)	****
All admissions	42	4	(1-11)	72	5	(2-15)	0.419
End of follow up							
Usual residence	113	6	(2-15)	128	3	(2-11)	0.196
Death	20	13	(5-51)	21	5	(3-25)	0.120
Nursing home	2	56	(42-69)	1	45	(45-45)	1.000
Transfer	17	9	(5-29)	30	21	(7-41)	0.090
Other	0				15	(10-19)	****
All admissions	152	7	(2-20)	182	6.0	(2-17)	0.417
Cohort 2							
On-treatment							
Usual residence	20	3	(1-8)	42	7	(3-18)	0.008
Death	3	5	(1-14)	7	7	(6-41)	0.209
Nursing home				1	91	(91-91)	****
Transfer to acute unit	4	17	(2-45)	5	13	(8-17)	0.624
Other	1	3	(3-3)	2	63	(14-111)	0.221
All admissions	28	3	(1-8)	57	8	(5-20)	0.002
End of follow up							
Usual residence	85	5	(1-15)	97	6	(2-11)	0.485
Death	19	14	(5-51)	15	6	(4-21)	0.211
Nursing home	1	69	(69-69)	2	72	(53-91)	1.000
Transfer	17	11	(6-32)	16	15	(8-36)	0.929
Other	1	3	(3-3)	2	63	(14-111)	0.221
All admissions	123	6	(2-20)	132	7	(3-16)	0.941

*Adjusted for age and gender

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