Pioglitazone for primary stroke prevention in Asian patients with type 2 diabetes and cardiovascular risk factors: A retrospective study

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Abstract

Background: To date, studies assessing the efficacy of pioglitazone solely for primary stroke prevention in Asian patients with type 2 diabetes mellitus (DM) and present multiple cardiovascular (CV) risk factors are rare. Thus, we aimed to assess the effect of pioglitazone on primary stroke prevention in Asian type 2 DM patients without established CV diseases but with risk factors for CV diseases.

Methods: Between 2000 and 2012, we enrolled patients aged ≥18 years who were newly diagnosed with type 2 diabetes and had at least one of the following CV risk factors: hypertension, hyperlipidemia, proteinuria, and obesity. Patients with a history of stroke and those using insulin or glucagon-like peptide-1 agonist for more than 3 months were excluded. Patients were divided into the pioglitazone user group and non-pioglitazone user group based on their receipt of pioglitazone during the follow-up period. Propensity-score matching (1:1) was used to balance the distribution of the baseline characteristics and medications. Follow-up was terminated upon ischemic stroke development, withdrawal from the insurance system, or on December 31, 2013, whichever occurred first. The overall incidence of new-onset ischemic stroke in the two groups was subsequently compared. Subgroup analyses of ischemic stroke were conducted using different baseline features. Additionally, the effect of the pioglitazone exposure dose on the occurrence of ischemic stroke was evaluated. The chi-square test, Student's t-test, Kaplan–Meier method, and log-rank test were some of the statistical tests conducted herein.

Results: A total of 6,637 patients were included in the pioglitazone and non-pioglitazone group. Compared to patients who did not receive pioglitazone, those administered pioglitazone had a lower risk of developing ischemic stroke (adjusted hazard ratio: 0.72; 95% confidence interval: 0.57–0.9). Subgroup analyses defined by different baseline features did not reveal significant alterations to the observed effect of pioglitazone. Moreover, a significant trend regarding the decrease in ischemic stroke risk and the increase in pioglitazone dose (p-value for trend=0.03) was observed.

Conclusion: Pioglitazone use decreased the risk of new-onset ischemic stroke in Asian patients with type 2 DM and CV risk factors.

Background

Although the incidence of stroke has decreased in most regions, its incidence has increased in East Asia [1]. Stroke is the third leading cause of death in Taiwan, with ischemic stroke as the most common type [2]. Compared to the non-diabetic population, the risk of stroke is increased in patients with type 2 diabetes mellitus (DM)[3]. Additionally, it is an important contributor to stroke morbidity [2]. Pioglitazone is an oral glucose-lowering agent belonging to the drug class known as thiazolidinediones (TZD). Pioglitazone acts as an agonist of the peroxisome proliferator-activatedreceptor γ. Treatment with TZD has been demonstrated to reduce neuro-inflammation and improve the survival of neurons and glial cells [4,5]. TZD therapy has also been shown to prevent or mitigate the progression of carotid intima–media thickness, a risk factor for ischemic stroke [6,7]. Owing to this property, pioglitazone can exhibit protective

effects on the cerebrovascular system. Currently, pioglitazone is generically available and cost-effective. As a result, it is a more affordable option for cerebrovascular protection. In a subgroup analysis of patients with type 2 DM and previous stroke in the PROactive trial [8], the rate of fatal or non-fatal stroke events was significantly lower in the pioglitazone group than the placebo group (hazard ratio: 0.53; event rate 5.6% in the pioglitazone group vs 10.2% in the placebo group, 95% confidence interval: 0.34–0.85; number needed to treat = 22) [9]. In the IRIS study that included patients with insulin resistance and recent stroke or transient ischemic attack, a lower incidence of stroke or myocardial infarction (MI) was observed in patients administered pioglitazone [10]. Based on real-world data, the impact of pioglitazone on stroke varies according to the different clinical characteristics of patients and the interaction with other glucose-lowering agents [11–15]. A meta-analysis of randomized-controlled trials (RCTs) revealed that pioglitazone reduced the risk of stroke in patients with a history of established cardiovascular (CV) diseases [16]. However, as most patients with type 2 DM do not have established CV diseases, determining whether pioglitazone exerts cerebrovascular benefits in patients without established CV diseases, but present multiple risk factors, particularly those with a higher risk of ischemic stroke (e.g., patients of Asian descent), is crucial. Studies assessing the efficacy of pioglitazone solely for primary stroke prevention in Asian patients with type 2 DM and present multiple CV risk factors are rare.

Therefore, to investigate the effect of pioglitazone on primary stroke prevention in Asian patients without established CV diseases, but present risk factors for CV diseases, we conducted a population-based cohort study using the database of the Taiwan National Health Insurance (NHI) program.

Methods

Aim and Design

To assess the effect of pioglitazone on primary stroke prevention in Asian type 2 DM patients without established CV diseases but with risk factors for CV diseases, we opted to perform a retrospective study using claims data.

Data Source

The Taiwan National Health Insurance Research Database (NHIRD) contains the annual reimbursement claim data from the NHI program, which has been the universal health insurance system in Taiwan since 1996, covering approximately 99% of the Taiwanese population by 1998 [17]. The Longitudinal Health Insurance Database (LHID), which is a subset of the NHIRD, includes historical claims data for one million subjects who were randomly sampled from the entire insured population from 1996 to 2000. Prior to the release of data for research, all personal identification data in the LHID were de-identified to protect the privacy of patients by the National Health Research Institute via an anonymized number system which linked each claimant’s demographic information to the LHID. The International Classification of

Diseases, Ninth Revision, Clinical Modification (ICD–9-CM) is used by the NHIRD to categorize disease diagnoses based on outpatient and inpatient data.

Ethical approval

This study was approved by the Ethics Review Board of China Medical University (CMUH104-REC2–115-CR4), who waived the need for informed consent based on the retrospective design of the study.

Study population

Between 2000 and 2012, we enrolled patients ≥18 years-old who were newly diagnosed with type 2 diabetes (ICD–9-CM codes 250) and had at least one of the following CV risk factors: hypertension (HTN) (ICD–9-CM 401–405), hyperlipidemia (ICD–9-CM 272), proteinuria (ICD–9-CM 791), and obesity (ICD–9-CM 278). We excluded patients diagnosed with stroke (ICD–9-CM 430–438), type 1 DM (ICD–9-CM 250.x1 and 250.x3), gestational diabetes mellitus (GDM) (ICD–9-CM 648.83), using insulin or glucagon-like peptide–1(GLP–1) agonist for more than 3 months, coronary artery disease (CAD) (ICD–9-CM 414.00–414.05, 414.8, 414.9), peripheral artery occlusive disease (PAOD) (ICD–9-CM 440.0, 440.2, 440.3, 440.8, 440.9, 443, 444.0, 444.22, 444.8, 447.8, and 447.9) or with a follow-period <0.5 years. The index day was defined as the date of the first prescription of pioglitazone. Subjects were divided into the pioglitazone user group and non-pioglitazone user group according to the their receipt of pioglitazone during the follow-up period (Figure 1). Using propensity score (PS) matching, each patient without pioglitazone treatment was matched for one pioglitazone-treated patient by age, sex, the presence or absence of heart failure (HF)(ICD–9-CM codes 428), arrhythmia (ICD–9-CM codes 427), chronic renal disease (CKD)(ICD–9-CM codes 585), HTN (ICD–9-CM codes 401–405), hyperlipidemia (ICD–9-CM 272), proteinuria (ICD–9-CM 791), obesity (ICD–9-CM 278), and the administration of anti-hypertensive medication, lipid-lowering agents, anti-platelet agents, and oral glucose-lowering agents. Follow-up was terminated upon hospitalization for ischemic stroke (which was ascertained by the ICD–9-CM codes 433–435 in the first position of the hospital discharge diagnoses), a withdrawal from the insurance system, or on December 31, 2013, whichever occurred first. The overall incidence of new-onset ischemic stroke in the two groups were subsequently compared.

Statistical analysis

The chi-square test and Student's t-test were used to compare the differences in the categorical variables and continuous variables, respectively, between the groups. The incidence rate of an event was estimated using the number of events and person-years. The hazard ratio (HR) and 95% confidence interval (CI) for the risk of events were estimated using univariate and multivariate Cox proportional hazard regression models. The multivariate model was adjusted for age, sex, comorbidities, and the medications listed in

Table 1. Subgroup analyses of new-onset ischemic stroke were conducted with 12 pre-specified subgroup variables, including age, sex, HF, arrhythmia, CKD, HTN, hyperlipidemia, proteinuria, obesity, number of CV risk factors, number of anti-hypertensive agents, and number of glucose-lowering agents. We used the defined daily dose (DDD) per year to quantify the average dose of pioglitazone. Based on DDD, we established four categories of dose exposure: no exposure, low dose exposure (<100 DDD per year), intermediate dose exposure (100–250 DDD per year), and high dose exposure (>250 DDD per year) to evaluate the effect of the exposure dose on the occurrence of ischemic stroke. The cumulative incidence of new-onset ischemic stroke was assessed using the Kaplan–Meier method and differences between groups were determined by a log-rank test. All statistical analyses were performed using SAS statistical software (Version 9.4 for Windows; SAS Institute, Inc., Cary, NC, USA). Statistical significance was defined as $P<0.05$.

Results

A total of 6,637 patients treated with and without pioglitazone were matched in a 1:1 ratio. The demographic characteristics of the two cohorts were almost similar (Table 1). Most patients were aged <65 years and 50% were males. Approximately 4%, 10%, and 10% of patients in both cohorts had HF, arrhythmia, and CKD, respectively. Additionally, approximately 72%, 75%, 4%, and 5% of patients in the two groups had HTN, hyperlipidemia, proteinuria, and obesity, respectively. Forty percent of patients had one CV risk factor while 50 %had two CV risk factors. Less than 7% of patients had more than three CV risk factors. The number of patients treated with angiotensin-converting-enzyme inhibitor (ACEI), angiotensin receptor blockers (ARB), α-blocker, β-blocker, calcium channel blockers (CCB), diuretics, and other anti-hypertensive agents was similar between the two groups. Approximately 30%, 20%, and 50% of patients were treated with ≤1, 2, and ≥3 anti-hypertensive agents, respectively. Approximately 55% of patients were treated with statin and less than 1% in both groups used high intensity statin. More patients in the pioglitazone cohort used moderate intensity statin (pioglitazone cohort: 59.41%, non-pioglitazone cohort: 52.10%; $P<0.01$) while more patients in the non-pioglitazone cohort used low-intensity statin (pioglitazone cohort: 47.48%, non-pioglitazone cohort:40.21%; $P<0.01$). Approximately 35% of patients used fibrate, 35% of which were also treated with other cholesterol-lowering agents. Approximately 56% of patients in both groups used aspirin. Less than 1%, 2%,and 8% of patients in both groups used warfarin, clopidogrel, and other anti-platelet agents, respectively. More patients in the pioglitazone cohort used sulfonylureas (SU) (pioglitazone cohort: 92.89%, non-pioglitazone cohort: 47.19%; $P<0.01$), α-glucosidase inhibitor (pioglitazone cohort: 25.46%, non-pioglitazone cohort: 22.46%; $P<0.01$), and glinide (pioglitazone cohort: 15.43%, non-pioglitazone cohort: 13.95%; $P = 0.01$). However, the number of patients who used metformin and dipeptidyl peptidase 4 (DPP4) inhibitors was similar between the two groups. Approximately 13% of patients used no more than one glucose-lowering agents and 7% of patients in both groups used more than four glucose- lowering agents. More patients in the non-pioglitazone cohort used two glucose-lowering agents (pioglitazone cohort: 51.56%, non-pioglitazone cohort: 54.86%; $P<0.01$) while more patients in the pioglitazone cohort used three glucose-lowering agents (pioglitazone cohort: 27.95%, non-pioglitazone cohort: 24.36%; $P<0.01$). The mean follow-up duration was~4 years in both

cohorts but was longer in the pioglitazone cohort than the non-pioglitazone cohort (4.45±2.39 years versus 4.27±2.71 years; P<0.01).

[Insert Table 1]

As shown in Table 2, the overall incidence of ischemic stroke was 29,781 per 1,000 person-years in the pioglitazone cohort, a value lower than that found for the non-pioglitazone cohort (28,543 per 1000 person-years), with an adjusted hazard ratio (aHR) of 0.72 (95% CI = 0.57–0.9, *P*<0.01).

[Insert Table 2]

The subgroup analyses defined by the different baseline features did not disclose any significant alterations to the observed effect of pioglitazone (Table 3; all P-values for interaction>0.05).

[Insert Table 3]

Compared to non-pioglitazone users, individuals exposed to low, intermediate, or high-dose pioglitazone did demonstrate an association, with a 0.76-fold (adjusted HR 0.76, 95% CI = 0.56–1.02), 0.69-fold (adjusted HR 0.69, 95% CI = 0.48–0.96), and 0.61-fold (adjusted HR 0.61, 95% CI = 0.45–0.83) decrease in the risk of ischemic stroke, respectively (Table 4). Moreover, there was a significant trend regarding the decreased risk of ischemic stroke risk and the increase in pioglitazone dose (p-value for trend = 0.03).

[Insert Table 4]

As shown in Figure 2, the cumulative incidence of ischemic stroke was significantly lower in the pioglitazone cohort than the non-pioglitazone cohort (log-rank test, *P*<0.01).

Discussion

Based on our findings, the use of pioglitazone was associated with a decreased risk of ischemic stroke among Asian patients with type 2 diabetes but present risk factors for CV diseases. To the best of our knowledge, this is the first study to assess the efficacy of pioglitazone for primary stroke prevention alone in Asian patients with type 2 DM and no established CV diseases, but present risk factors for CV diseases.

Although pioglitazone is now generically available and more cost-effective than a sodium–glucose cotransporter 2 (SGLT2) inhibitor or a GLP–1 receptor agonist for CV protection, more clinical data may be needed to support the protective effects of pioglitazone against stroke in patients with type 2 DM and no established CV diseases. To date, RCTs assessing the effect of pioglitazone on primary stroke prevention in these patients are lacking. In 2006, the CHICAGO study (Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone) revealed that pioglitazone slowed the progression of CIMT over an 18-month treatment period in patients with type 2 DM and no prior CV disease compared to glimepiride [18]. In 2017, the Thiazolidinediones or Sulfonylureas Cardiovascular Accidents Intervention Trial

(TOSCA.IT) included patients aged 50–75 years with inadequately controlled type 2 DM with metformin monotherapy from 57 diabetes clinics in Italy [19]. Based on the findings, only 11% of patients had baseline CV disease and 1–2% of subjects had previous stroke. Nonetheless, the incidence of CV events, including non-fatal stroke, was similar to that with SUs and pioglitazone as add-on treatments to metformin [19]. Considering the large heterogeneity of patients with type 2 DM and the need for a personalized approach, a recent post hoc analysis of TOSCA.IT found that men with a urine albumin/creatinine ratio greater than 9 mg/g and body mass index >28.8 kg/m^2 presented benefits owing to pioglitazone at a hazard ratio of 0.48 (95% confidence interval, 0.25–0.76) compared to SUs [20]. In Asian type 2 DM patients without prior CV diseases, the real-world data demonstrated controversial stroke protective effects of pioglitazone. Chan et al. [21] demonstrated that compared to sulfonylurea plus metformin, pioglitazone added to metformin therapy may have fewer major CV events, including ischemic stroke in type 2 DM patients. However, another real-world study conducted by Lu et al. did not reveal the protective effects of pioglitazone on ischemic stroke prevention [22]. These conflicting results may be due to the different clinical characteristics of patients and an interaction with other glucose-lowering agents. In our study, we excluded patients who used insulin or GLP–1 agonist for more than three months and included patients with at least one or more CV risk factors. Moreover, “patients treated with pioglitazone” in our study included those who took pioglitazone during the follow-up period instead of baseline pioglitazone treatment. After PS matching was performed to match almost all baseline characteristics and adjusting for potential confounders, our study revealed that the use of pioglitazone was associated with a decreased risk of ischemic stroke. Thus, our data provided evidence that pioglitazone could be administered for the primary prevention of ischemic stroke in Asian type 2 DM patients without prior CV diseases, but present risk factors for CV diseases. Defining such group of patients with a different likelihood of benefitting from pioglitazone treatment represents an important clinical need. Further, this result was similar to the findings of a recent meta-analysis [23] that evaluated the effect of pioglitazone on the primary and secondary prevention of CV diseases in patients “with or at high risk” of type 2 DM. In this meta-analysis of 26 RCTs with 19,645 participants, although a greater reduction in non-fatal myocardial infarction, non-fatal stroke, or CV death was noted in patients with a history of established CV diseases than those without, the subgroup differences between the primary and secondary prevention were not statistically significant (p-value for subgroup heterogeneity >0.05) [23].

Previously, the relationship between pioglitazone dose and its protective effect on primary stroke prevention in patients with type 2 DM was unclear. A post hoc analysis of the IRIS study revealed that the hazard ratio of recurrent ischemic stroke could be lower for patients in the subgroup with a pioglitazone adherence ≥80% than for those in the intention-to-treat analysis [24]. According to our study, there was a significant trend regarding the decreased risk of ischemic stroke and the increasing dose of pioglitazone (p-value for trend = 0.03). Further, as fluid retention is dose-related to pioglitazone, combination therapy with pioglitazone plus an SGLT2 inhibitor might reduce the frequency of edema [25] and beneficial effects of pioglitazone on stroke could additively improve CV outcome when combined with SGLT2 inhibitors [26].

Our study had several strengths. First, the use of an administrative database prevented the underreporting of medical visits. Second, its national population-based design enabled our study to be highly representative of the general population and prevented selection bias. Third, the risk of misclassification by excluding patients who might have had other types of diabetes (patients administered insulin for more than three months) was reduced. Fourth, PS matching was employed to match almost all baseline characteristics and adjust for potential confounders during the analysis of the risk of ischemic stroke between pioglitazone and non-pioglitazone users.

Nevertheless, this study had several limitations. First, because this was an observational study, it may be affected by bias and the poor control of confounding factors. Second, the identities of patients were encrypted for privacy and data security reasons. As a result, we could not contact patients to discuss their use of pioglitazone. Third, several potential confounding factors, such as blood pressure (BP), serum glucose level, and lipid panel were not included in the database. Nonetheless, the number of antihypertensive drugs and oral glucose-lowering agents, and the intensity of initial stain therapy were PS-matched to mitigate the bias associated with different levels of BP, blood sugar, and serum lipid between the two groups. Fourth, although experts from the NHI program regularly review randomly selected medical records to confirm the diagnosis from all hospitals, bias may still arise due to miscoding. However, the diagnoses in the NHIRD have previously been validated [27,28]. Finally, as our study included only Taiwanese patients who may have been at a greater risk of developing ischemic stroke due to their Asian descent, our results may not be applicable to other populations.

Conclusions

In conclusion, the use of pioglitazone was associated with a decreased risk of new-onset ischemic stroke among Asian patients with type 2 diabetes and no established CV diseases, but present risk factors for CV diseases. Moreover, there was a significant trend regarding the decreased risk of ischemic stroke with the increase in pioglitazone dose. Further studies are thus required to determine the clinical relevance of pioglitazone on the primary prevention of stroke in type 2 DM patients.

Declarations

List of abbreviations:

Diabetes mellitus, DM

Thiazolidinediones, TZD

Myocardial infarction, MI

Randomized-controlled trials, RCTs

Cardiovascular, CV

National Health Insurance, NHI

National Health Insurance Research Database, NHIRD

Longitudinal Health Insurance Database, LHID

International Classification of Diseases, Ninth Revision, Clinical Modification, ICD–9-CM

Hypertension, HTN

Gestational diabetes mellitus, GDM

Glucagon-like peptide–1, GLP–1

Coronary artery disease, CAD

Peripheral artery occlusive disease, PAOD

Propensity score, PS

Heart failure, HF

Hazard ratio, HR

Confidence interval, CI

Defined daily dose, DDD

Calcium channel blockers, CCB

Sulfonylureas, SUs

Dipeptidyl peptidase 4, DPP4

Sodium–glucose cotransporter 2, SGLT2

Thiazolidinediones or Sulfonylureas Cardiovascular Accidents Intervention Trial, TOSCA.IT

Blood pressure, BP

Ethics approval and consent to participate:

This study was approved by the Ethics Review Board of China Medical University (CMUH104-REC2–115-CR4). Owing to the retrospective nature of the study, informed consent was waived.

Consent for publication:

Not applicable

Availability of data and material:

The Taiwan National Health Insurance Research Database (NHIRD) collects the annual reimbursement claim data from the National Health Insurance program, which has been the universal health insurance system in Taiwan since 1996 (by 1998, the program covered almost 99% of the Taiwanese population) [17].

Competing interests:

The authors declare that they have no competing interests.

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Authors’ contributions:

Yi-Chih Hung: study design, writing of the manuscript, data interpretation, revision, and approval of the manuscript

Lu-Ting Chiu: data analysis and interpretation

Hung-Yu, Huang: critical discussion

Da-Tian Bau: revision and approval of the manuscript

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None

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Tables

Due to technical limitations, Tables 1 - 4 are only available for download from the Supplementary Files section.

Figures

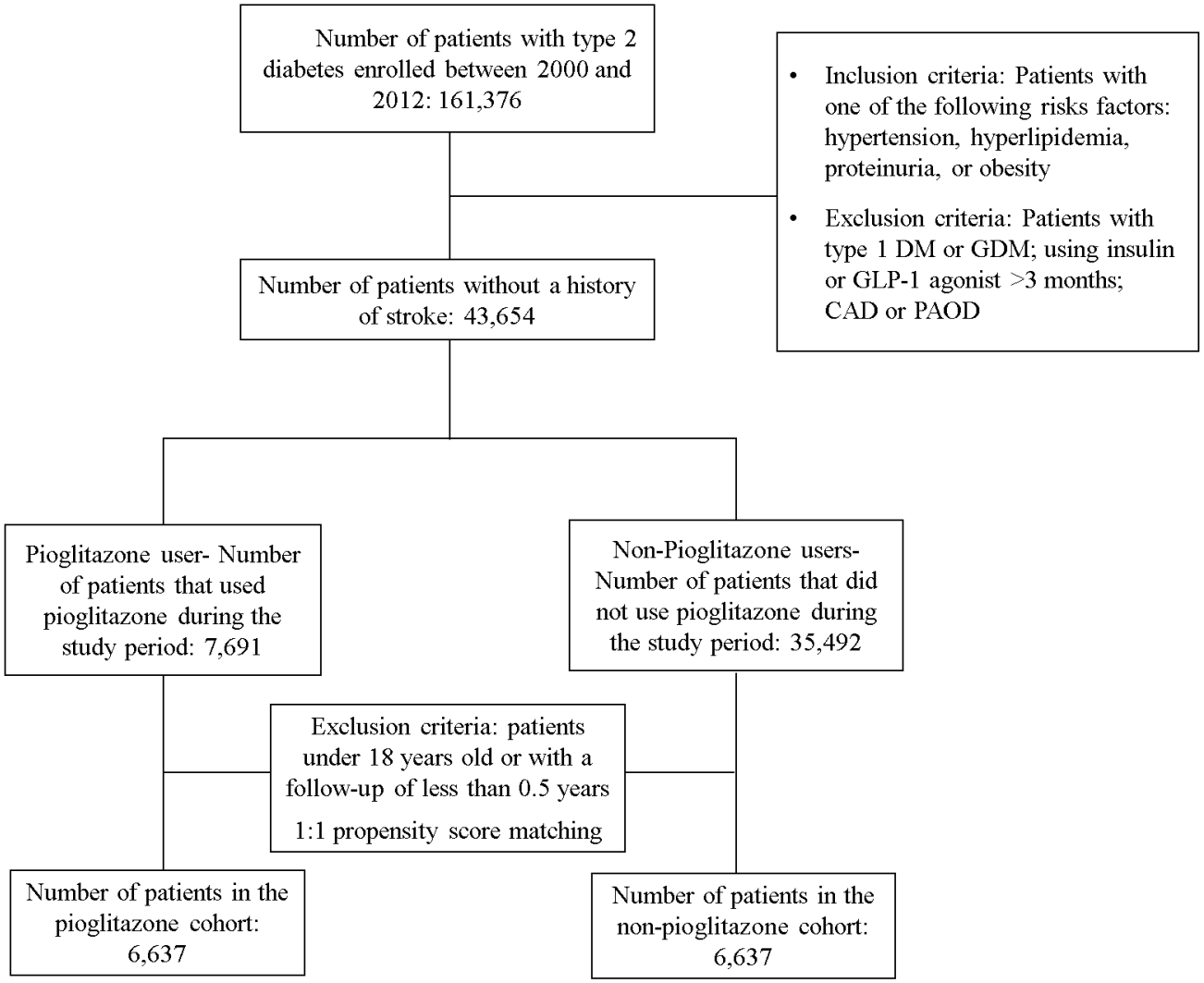

Figure 1

Flow-chart for cohort selection.

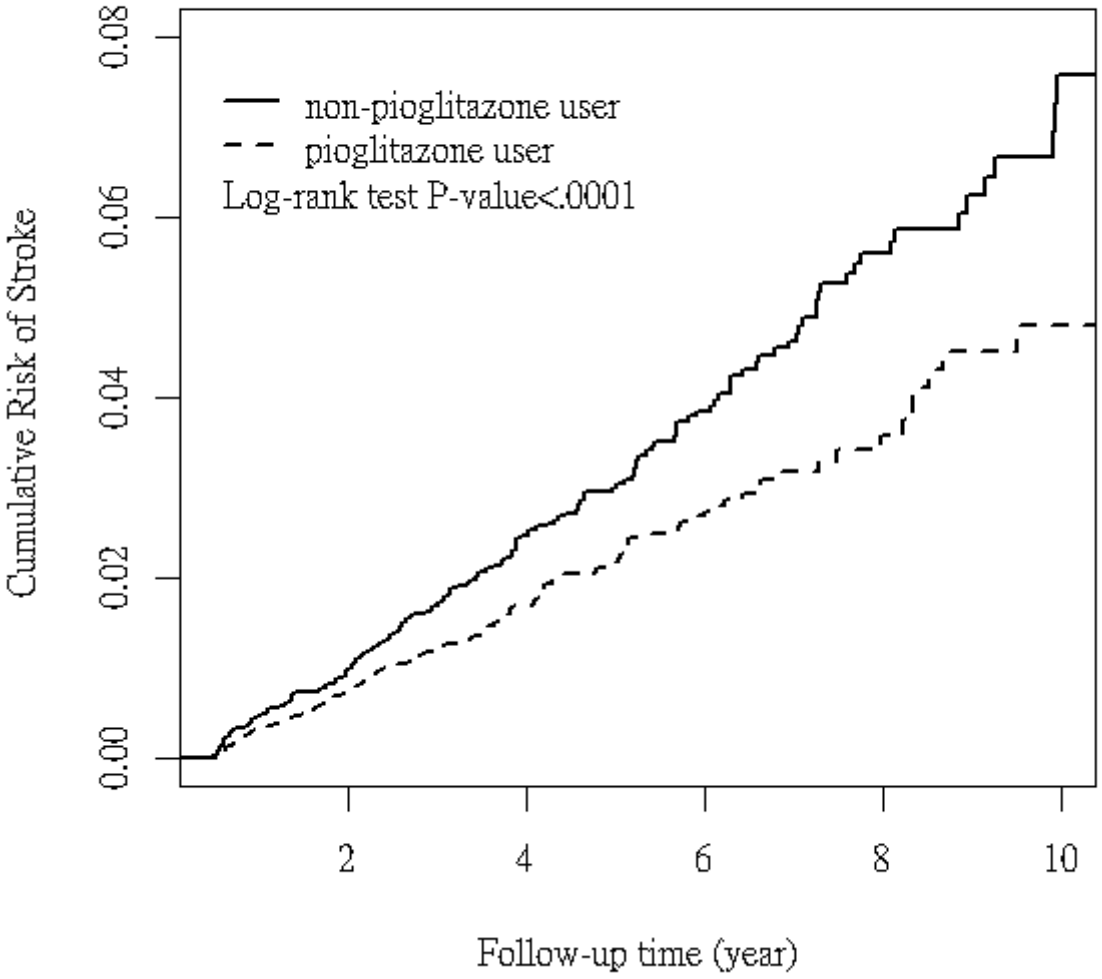

Figure 2

Cumulative incidence of ischemic strokein pioglitazone (solid line) and non-pioglitazone (dashed line) users

Supplementary Files

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- Tables14.docx