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Pioglitazone Use and Reduced Risk of Dementia in Patients With Diabetes Mellitus With a History of Ischemic Stroke

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Abstract

Background and objectives: Previous studies have reported the protective effect of pioglitazone on dementia in type 2 diabetic mellitus (DM) patients. Recent studies have shown that pioglitazone also lowers the risk of primary and recurrent stroke. Understanding the characteristics of patients particularly associated with the benefits of pioglitazone would facilitate its personalized use by specifying subpopulations during routine clinical care. The aim of this study was to examine the effects of pioglitazone use on dementia in consideration of stroke occurrence.

Methods: Using nationwide longitudinal data of DM patients from the Korean National Health Insurance Service DM cohort (2002–2017), we investigated the association of pioglitazone use with incident dementia in patients with new-onset type 2 DM. The heterogeneity of the treatment effect was examined using exploratory analyses. Using a multi-state model, we assessed the extent to which incident stroke affects the association between pioglitazone use and dementia.

Results: Pioglitazone use was associated with a reduced risk of dementia, compared with non-use (adjusted hazard ratio (HR) = 0.84, 95% CI, 0.75-0.95); the risk reduction in

dementia was greater among patients with a history of ischemic heart disease or stroke before DM onset (adjusted HR = 0.46, 95% CI, 0.24-0.90, adjust HR = 0.57, 95% CI, 0.38-0.86, respectively). The incidence of stroke was also reduced by pioglitazone use (adjusted HR = 0.81, 95% CI, 0.66-1.00). However, when the stroke developed during the observation period of pioglitazone use, such lowered risk of dementia was not observed (adjusted HR = 1.27, 95% CI, 0.80-2.04).

Discussion: Pioglitazone use is associated with a lower risk of dementia in DM patients, particularly in those with a history of stroke or ischemic heart disease, suggesting the possibility of applying a personalized approach when choosing pioglitazone to suppress dementia in DM patients.

Introduction

Type 2 diabetes mellitus (DM) increases the risk of aging-associated cognitive decline and dementia[1]. DM and Alzheimer's disease (AD) share pathogenic mechanisms, such as insulin resistance and microvascular dysfunction[2], prompting investigations to examine the possibility of using antidiabetic drugs to prevent or ameliorate cognitive decline in patients at risk of or who already have dementia[3]. Pioglitazone is a peroxisome proliferation-activated receptor γ agonist and a potent insulin-sensitizing antidiabetic drug. In addition to its action on glycemic control, pioglitazone may exert neuroprotective effects by reducing the levels of beta-amyloid (Aβ) and inflammation, inhibiting tau hyperphosphorylation, and enhancing synaptic plasticity[4, 5]. Previous studies have found that pioglitazone has a role in primary and secondary stroke prevention[6, 7]. These findings raise expectations concerning the protective role of pioglitazone against dementia, as DM and stroke are considered among the most common conditions that predisposed to dementia in old age[8, 9].

Despite these expectations, clinical studies of pioglitazone use have shown mixed effects on dementia. In a pilot clinical trial for patients with AD without DM, no significant cognitive improvement was observed after 18 months of treatment with pioglitazone[10]. A recent large clinical trial also failed to demonstrate its efficacy against AD development in a group of non-diabetic participants pre-screened as at high risk of cognitive decline[11]. On the other hand, a randomized clinical trial in Japan in patients with AD and type 2 DM has shown that pioglitazone not only improved regional cerebral blood flow in this group but also delayed the increase in the Aβ40/Aβ42 ratio, compared with the control group, suggesting that the disease was being stabilized[12]. Promising results have also been reported in a previous cohort study, although the proportion of patients with DM was relatively small[13].

Based on these findings, it is likely that a critical factor affecting the effectiveness of pioglitazone in alleviating dementia risk may be the presence of DM in the target population to whom the drug was administered[11, 12]. Testing this hypothesis would provide valuable information on who can or cannot benefit from pioglitazone use for dementia prevention. Without this information, we may lose the opportunity or cause unnecessary delay in implementing a new effective approach at least in a defined population in routine clinical practice. Hence, we aimed to examine the effects of pioglitazone use on the risk of dementia among patients with DM and examine whether the effect of the drug would differ according to patient characteristics. Mainly, we considered a history of stroke prior to using pioglitazone and incident stroke while using it, in that stroke and DM could substantially affect the relationship between pioglitazone use and dementia risk[8, 9].

Methods

Data source

The Korean National Health Insurance Service (NHIS)-DM cohort between 2002 and 2017 were used. These datasets included 400,000 type 2 DM patients, accounting for about 23% of all type 2 DM population in South Korea. It consists of inpatient and outpatient medical insurance reimbursement claims data including prescription of drugs, primary and secondary diagnostic codes, procedures, and treatment that each patient received. The National Health Screening Program (NHSP) dataset was also available, and it is a biennial general health check-up for all NHIS beneficiaries. The NHSP includes anthropometric measurements, lifestyle and health behavior-related self-reported questionnaire, blood pressure, and laboratory tests including hemoglobin, fasting glucose, and cholesterol levels, etc.[14]. The claims record database of the Korean NHIS includes diagnoses based on ICD-10 codes.

Standard protocol approvals, registrations, and patient consents

This research was approved by the Institutional Review Board at Yonsei University Health system (4-2021-0127) and the requirement for informed consent was waived due to de-identified data.

Selection of participants

A total of 191,507 newly diagnosed DM patients (ICD-10 code E11-E14) who had received health check-up between 2004 and 2012 were selected from the cohort. Finally, 91,218 newly diagnosed DM patients without dementia were enrolled, and follow-up data were reviewed until December 2017 (eFigure 1 in the Supplement). The following ICD-10

codes were used to identify dementia: F00, F01, F02, F03, G30, and G31. Patients with two or more prescriptions for any of the four antidementia drugs (donepezil, rivastigmine, galantamine, and memantine) within 1 year of diagnosis using the dementia codes were classified into a dementia group. The validity of this diagnostic approach has been verified through prior studies[15, 16]. ICD-10 code I63 was used to diagnose ischemic stroke[17, 18]. To ensure accuracy of diagnosis, an ischemic stroke was considered only if the primary diagnosis code was I63 at admission. We excluded (i) patients aged <50 years (n = 61,093), (ii) those who had not used antidiabetic medications (n = 35,498), (iii) those who had taken insulin more than a month (n = 4,338), (iv) those with a history of dementia or antidementia medication use before DM diagnosis (n = 917), (v) those diagnosed with dementia within 4 years after DM diagnosis (n = 3,462), or (vi) those who were prescribed with rosiglitazone during the study period (n = 3,448). Rosiglitazone was removed from the market for potential cardiovascular risk, and therefore, rosiglitazone users were withdrawn from study to avoid the confounding effect [19].

In the present study, a pioglitazone user was defined as a person with a total cumulative defined daily dose (cDDDs) of 90 or greater after initiation of DM treatment as previously described[7]. The same definition applies to other diabetes medications. To determine each patient's DDD, all pioglitazone prescriptions made within the landmark period after DM diagnosis were summed and converted to the corresponding number of cDDDs as defined by the WHO. The degree of pioglitazone exposure was expressed in the following three ways: previous user (versus no use), cDDD, and duration of the prescription. We used inpatient and outpatient hospital diagnostic records to obtain information on selected comorbidities. Ischemic heart disease, heart failure, pre-existing hypertension, dyslipidemia, arterial fibrillation, and ischemic and hemorrhagic stroke were examined 2 years before DM diagnosis. The Charlson Comorbidity Index (CCI) score was calculated by using the

diagnosis within 1 year before DM diagnosis. As described in our previous study[7], the following parameters were measured at a time point closest to the date of DM diagnosis; fasting blood glucose level, systolic blood pressure, diastolic blood pressure, total cholesterol level, creatinine level, body mass index, smoking status (none, past, and current), alcohol consumption (low: < 1 time/week, moderate: 1–4 times/week, and heavy: 5–7 times/week), and physical activity (yes: ≥ 1 time/week, no: never).

Statistical analyses

We used the landmark method to explore the association of extended pioglitazone use with long-term dementia risk. Landmark analysis is a form of survival analysis that takes a sequence of follow-up evaluations based on survival, by selecting a fixed time as the landmark[20, 21]. Specifically, certain index time points are chosen, and survival analysis and follow-up are performed only on patients that remain event-free at those index times. Thus, the time-varying nature of exposure is controlled for by conditioning its status only up to the selected landmark time, and the following exposure-outcome analyses are free from immortal time bias. In our analysis, we defined a landmark time of 4 years to measure pioglitazone exposure from the onset of DM, and the study outcome was dementia incidence during the follow-up period. However, there is a limitation as well. Arbitrarily choosing a landmark time and omitting events that occur before the landmark could lead to selection bias[20, 22]. To address these limitations, sensitivity analyses was performed using alternative landmark times (eTable 1 in the Supplement), and detailed outcome characteristics of those excluded within 4 years of the onset of diabetes were added to the supplementary section (eTable 2). To balance baseline characteristics between pioglitazone users and non-users, stabilized inverse probability of treatment weighting (sIPTW) was used with propensity scores. We used multivariable logistic regression models to calculate propensity scores for pioglitazone users,

with potential confounders such as hypertension, atrial fibrillation, dyslipidemia, heart failure, ischemic heart disease, ischemic stroke, hemorrhagic stroke, CCI, fasting blood glucose levels, blood pressure, levels of total cholesterol and creatinine, statin use, use of cardiovascular medications (aspirin, statin, anticoagulant, antiplatelet, and antihypertension drugs), use of other antidiabetic medications (biguanide, sulfonylurea, dipeptidyl peptidase-4 inhibitors, alpha-glucosidase inhibitors, sodium-glucose co-transporter-2 inhibitors, insulin), body max index, alcohol consumption, smoking status, physical activity, and the year of type 2 diabetes onset. Each drug use was included in the regression model. We compared baseline characteristics in two groups using standardized mean differences; values above 0·1 indicate potential imbalances in the distribution of covariates between groups. Cox-proportional hazard regression with sIPTW was performed to examine the association of pioglitazone use with dementia risk. Patients who deceased during the follow-up period were censored at their transition time. Outcomes are presented as crude hazard ratios (HRs), adjusted HRs (aHRs), and 95% confidence intervals (CIs) for dementia risk between pioglitazone users and non-users. To further assess heterogeneity of pre-existing risk factors for dementia, such as hypertension, atrial fibrillation, ischemic heart disease, heart failure, dyslipidemia, ischemic stroke, and hemorrhagic stroke, we analyzed the patient's data separately according to the presence or absence of risk factors.

Sensitivity analyses were performed using alternative landmark time points ranging from 1 to 7 years to assess whether the selected landmark time point affected the study results. Furthermore, we conducted Cox-proportional hazard regression by redefining the exposure group to the group taking ≥ 180 cDDDs of pioglitazone after the onset of DM treatment to determine if the main result could be altered according to how drug exposure was defined. We analyzed multi-state models with three states: stroke-free was named state 1, ischemic stroke was named state 2, and dementia was named state 3, after the onset of type 2

DM[23]. In eFigure 2 in the Supplement, boxes represent each state and arrows indicate possible transitions. All patients with DM commenced in state 1, some of them moved to state 2 (ischemic stroke; transition 1), and some patients transited directly to state 3 (dementia; transition 2). Moving from ischemic stroke to dementia (transition 3) is also possible. The statistical quantities of interest in a multi-state model are the transition intensities, or transit-specific hazard rates based on the Cox-proportional hazard model with sIPTW. Each probability model describes the path of individual shifting through a sequence of states in a multi-stage process. We assumed that each transition was associated with a separate baseline hazard, and we stratified the data according to each transition. From the baseline state to an incident ischemic state (a), the event time was calculated as the time from the baseline point to event date (onset of ischemic stroke). Patients with ischemic stroke onset were censored from the baseline state to incident dementia (c). From incident stroke to incident dementia (b), the event time was left-truncated from baseline to ischemic stroke onset in patients with DM. Participants whose event of interest did not occur until the end of the study or lost to follow-up were censored. Also, we applied cause-specific hazard model to address the competing event (death). Lastly, we used propensity score-matching (PSM) analysis to adjust for covariate imbalances by the nearest matching method with the baseline covariates in a 1:2 ratio. All statistical analyses were conducted using SAS software, version 9·4 (Cary, NC, USA) and R version 3.6 (The R Foundation, www.R-project.org). Significance was set at a *p*-value <0·05.

Data Availability

The datasets analyzed in this study are not open to the public due to the NHIS restrictions and are stored on separated servers managed by NHIS. NHIS require an interested party to apply for accessing data. The applications are submitted on-line (https://nhiss.nhis.or.kr) and

requires a study proposal and ethics approval from the institutional review board.

Results

Study population

In total, 91,218 new onset type 2 DM patients without history of dementia were finally selected. Of these patients, 3,467 pioglitazone users and 87,751 non-users were identified (eFigure 1 in the Supplement). Table 1 shows unweighted and weighted baseline characteristics of eligible patients stratified according to the use of pioglitazone within the 4-year landmark period. In unweighted comparison, both groups showed significant difference in age, duration of DM, and use of other oral antidiabetic medications. After sIPTW adjustment, weighted comparisons showed that standardized differences between pioglitazone users and non-users were less than 10%, except for those who used biguanide and sulfonylurea (eFigure 3). We further adjusted these two factors for the final models. For each pioglitazone user and non-user, information on multiple uses of antidiabetic drugs was separately described (eTable 3).

Pioglitazone use and all-cause dementia

The associations of pioglitazone use with incident all-cause dementia were evaluated using the Cox-proportional hazard model with sIPTW (Table 2). The mean follow-up time was 3,736 days (SD: ± 876·0) in non-users and 3,512 days (SD: ± 760·8) in pioglitazone users. The 4-year conditional landmark Kaplan–Meier curves showed that the overall dementia risk was lower in pioglitazone users than in non-users (Figure 1). Of patients using pioglitazone, 286 (8·3%) developed dementia, while 8,755 non-users (10·0%) developed dementia. In the univariate analysis, pioglitazone use was associated with a lower risk of dementia (HR [CI], 0·84 [0·74–0·95]), compared with non-use. As shownin Table 2, a dose-response relationship was found for reduced risk of dementia in pioglitazone user, [aHR (95% CI) for the first

cDDD quartile: 1·00 (0·81–1·23); second quartile: 0·83 (0·66–1·06); third quartile: 0·79 (0·61–1·03); and highest quartile: 0·72 (0·55–0·94)]. The reduced risk of dementia was more pronounced in patients who used pioglitazone for 4 years than in non-users, with an aHR of 0·63 (0·44–0·90). Further sensitivity analysis using a different definition of pioglitazone user, (180 cDDDs) consistently showed that the risk of dementia was significantly reduced in the group treated for four years, compared with non-users (HR [CI], 0·56 [0·38–0·81], eTable 2 in the Supplement). The results of the sensitivity analyses using an alternative landmark point were in line with those of the main analysis (eTable 4). After PSM, the risk of dementia remained significantly reduced in pioglitazone users, with an aHR of 0·85 (0·72–1·00) (eTable 5 and 6).

The protective effect of pioglitazone on dementia in diabetes mellitus patients with a history of stroke or ischemic heart disease

In subsequent subgroup analysis, the association between pioglitazone and dementia risk were further evaluated (Table 3). Pioglitazone use showed heterogeneities of association with a lower risk of dementia according to subgroups of conditions, such as hypertension, ischemic heart disease, atrial fibrillation, heart failure, dyslipidemia, hemorrhagic stroke, ischemic stroke, and depression. Notably, there were statistically significant subgroup differences in patients with ischemic stroke and ischemic heart disease (*p* for interaction: 0·048 and 0·069, respectively). The reduced risk of dementia was more significant in DM patients with a history of stroke (aHR [95% CI], 0·46 [0·24–0·90]) or ischemic heart disease (aHR [95% CI] 0·57 [0·38–0·86]), than in those who had no such history. These findings indicate that the association of pioglitazone use with reduced dementia risk is more evident in patients with DM with higher levels of ischemic burden.

Role of ischemic stroke in the association between pioglitazone use and dementia

Given our findings that previous ischemic injury may interact with the effect of pioglitazone on dementia (Table 3), we further defined the impact of incident ischemic stroke as a potential intermediate clinical event between pioglitazone exposure and the development of dementia. Multi-state models showed that pioglitazone use was associated with a 0·81-times decrease in the risk of incident stroke (95% CI, 0·66–1·00), compared with non-use (eFigure 2 in the Supplement). The association between pioglitazone and incident dementia was observed before an incident ischemic stroke occurred (aHR = 0·85, 95% CI = 0·75–0·96). However, the protective effect of pioglitazone on dementia was not observed in patients who experienced ischemic stroke after starting pioglitazone treatment (aHR = 1·27, 95% CI = 0·80–2·04).

Discussion

In this national, longitudinal population-based cohort study, our main findings are as follows: (i) pioglitazone use was significantly associated with a reduced risk of dementia in DM patients, (ii) the association between pioglitazone and dementia was more pronounced among patients with history of ischemic heart disease or stroke, and (iii) the association of pioglitazone use with reduced risk of dementia was maintained among those who experienced no stroke incidence before dementia. These findings collectively suggest that pioglitazone has a preventive effect on dementia patients with DM. To the extent of our knowledge, this is the first study to demonstrates a reduction in dementia risk with pioglitazone in newly diagnosed patients with type 2 DM, with stroke as a potential intermediate clinical event.

Dementia presents many challenges to our society. The risk of developing dementia is doubled in patients with DM[24]. Since dementia, particularly AD, has a long latency period or prodromal stage before diagnosis[25], there might be an opportunity for intervention. Preventive and personalized approaches, especially for patients with DM, would be beneficial for individuals at high risk of dementia, such as those with a history of ischemia. Identifying risk modifiers in these populations can improve their quality of life while saving on healthcare expenses.

A retrospective study in Germany, using public health insurance company records, found that pioglitazone use was associated with a 47% reduction in the incidence of dementia in patients with DM, compared with those without DM[13]; long-term pioglitazone users had a lower risk of dementia, whereas short-term users had no such preventive benefits. However, that study was based on a selected sample from an insurance company claims database, and the study population may not reflect the characteristics of the general population. In addition, only 40% of the total population had DM, the proportion of people using pioglitazone in the total population was only 5%, and the DM duration and its severity were not considered at baseline. To overcome these limitations, we used a diabetes cohort in which all participants had DM, and we recruited newly diagnosed patients with type 2 DM to compensate for possible confounding factors for dementia risk. Our findings suggest that pioglitazone could be used as a personalized treatment approach for dementia prevention in diabetic patients with a history of stroke or ischemic heart disease. In agreement with our findings, another population-based study in Taiwan showed that long-term pioglitazone exposure reduced the risk of dementia[26]. However, the investigators did not find a significant association between pioglitazone use and major risk factors for dementia. This adverse finding is likely due to the smaller sample size and shorter observation period (1,825 days) in that study compared with our study (3,512 days).

The pathophysiological mechanism between pioglitazone use and the low incidence of dementia has not been elucidated. The neuroprotective effects of pioglitazone can be explained in several ways. Pioglitazone treatment is known to suppress the expression of proinflammatory genes in patients with impaired glucose tolerance[27], blocking the synthesis of proinflammatory cytokines and promoting the differentiation of myeloid cells into an immunosuppressive state[28]. In addition to increasing cerebral glucose utilization[29], pioglitazone also reduces oxidative stress[30], blocks the synthesis of Aβ by transcriptional suppression of beta-site amyloid precursor protein cleaving enzyme-1[31], and regulates the phagocytic clearance of Aβ by microglia[32]. Recent studies have highlighted that defective mitochondrial bioenergetics influences neurodegeneration[33], and these changes may precede the accumulation of Aβ and tau[34]. Pioglitazone could be beneficial by enhancing adenosine triphosphate (ATP) production through mitochondria in neurons without augmenting reactive oxygen species (ROS) production[35]. Interestingly, pioglitazone reversed maternal high fat diet-induced impaired astrocytic metabolism and oxidative phosphorylation in the female rat offspring. Overall, pioglitazone may exert its neuroprotective effects against dementia by protecting against ischemic stroke, balancing neuronal energy through the mitochondria, and enhancing glucose metabolism.

On the other hand, there are concerns about the side effects associated with pioglitazone that includes edema, weight gain, bone loss, and congestive heart failure[36]. The clinical use of pioglitazone could be limited because of these concerns. However, there have been recent reports that the risk of congestive heart failure was not significantly increased upon pioglitazone treatment[37], and studies showing that fluid retention or weight gain can be controlled by combining other drugs or reducing the drug dose[38-39].

Recently, a phase-3 randomized, double-blind, placebo-controlled trial conducted among patients with a genetically high risk of AD concluded that pioglitazone was unlikely to

delay the onset of cognitive impairment[11]. However, that study did not evaluate the delay of the onset of dementia progression in the population with DM, and most of the study participants were metabolically healthy. In contrast, another randomized controlled study reported cognitive and functional improvement in patients with mild AD accompanied by DM, evidenced by an improved regional cerebral blood flow in the parietal lobe[12]. Given that DM is a major risk factor for dementia, selecting personalized DM medication for patients at risk of dementia may also be beneficial for dementia prevention. Particularly, we found that the effect of pioglitazone on dementia risk was more pronounced in people who previously had ischemic stroke or heart disease before starting the medication. The use of pioglitazone may be more beneficial for patients with ischemic burden since it improves the atherogenic lipid profile in patients with DM by upregulating hepatic LDL receptor-related protein 1 (LRP1)[40]. In a randomized control study, pioglitazone therapy added to either metformin or sulfonylurea, significantly decreased triglycerides and increased high-density lipoprotein cholesterol[41]. Reducing ROS production and reducing endothelial dysfunction in both cerebrovascular and neural cells[42] may be another mechanism underlying the protective effect of pioglitazone in patients with ischemic burden.

However, a protective effect against dementia was not found in pioglitazone users with incident stroke during the observational period. There are several possible explanations for this discrepancy. The number of stroke events in pioglitazone users after DM diagnosis was small (n = 3,214), and the results might be distorted because of the possibility of a crossover between the pioglitazone user group and the non-user group after stroke occurrence. Further follow-up studies are required to explore whether a significant dementia-preventing effect can be maintained, even in patients who experienced a stroke event in the pioglitazone-treated group.

As shown in Table 3, an increased dementia risk was observed in the pioglitazone users with previous hemorrhagic stroke (aHR (95% CI), 3.26 (1.13–9.41). Although, this result should be interpreted with caution because of the small number of the incident (n = 8), there was a report that long-term use of pioglitazone may affect the coagulation factor profile in patients with type 2 diabetes and inhibit platelet function[43]. However, a previous clinical trial reported no association with the risk of hemorrhagic stroke in pioglitazone users[44]. Moreover, previous findings that pioglitazone exerted a protective effect against neuronal damage caused by toxic blood degradation products and reduced brain edema following intracerebral hemorrhage may suggest that it could also have a positive role in patients with a history of hemorrhagic stroke[45]. Therefore, further investigation is needed to identify whether our finding of increased risk of dementia in persons with previous hemorrhagic strokes indeed reflects the cause-and-effect relationship, residual confounding, or reverse causality.

A strength of this study is that we used well-established nationwide longitudinal data of type 2 DM population from 2002 to 2017. The database also represents the entire Korean population with sufficient lifestyle, socioeconomic, and clinical information to facilitate rigorous statistical analysis including adjustments. Heneka et al.[13] demonstrated that social selection in pioglitazone treatment might influence the results. Therefore, we included socioeconomic status information and other lifestyle variables in our study[35]. However, our study has some limitations needed to be discussed. Since this was a population-based study using claims data, drug compliance of patients could not be guaranteed, and exposure may have been over-estimated. Second, the results should be interpreted carefully, and we cannot infer causality, due to the nature of observational study. A potential of selection bias should be taken seriously. In a sense, our subjects are those who were originally 'selected' to receive pioglitazone for some unidentifiable reasons. We cannot entirely exclude the possibility that such characteristics of the group, rather than of the drugs, may have led to our results. Third,

using administrative database for clinical study is liable to measurement errors caused by inaccuracy in diagnostic coding. To minimize such errors, we defined dementia by the way which had been validated in a previous study using the Korean NHIS cohort[16]. In the study, positive predictive value for dementia diagnosis were reported as 94.7%. However, there is a possibility of underdiagnosis of dementia by misclassification of patients who did not seek treatment as health controls. In addition, people with MCI could have been included based on the inclusion criteria of dementia medication use; therefore, overdiagnosis could have occurred. Fourth, there is no information on apolipoprotein E (APOE) in this NHIS database. Since APOE is a major genetic risk factor for AD and a modifier of the association between hypoglycemic agents and cognitive decline[47, 48], this should be considered in a future study. Fifth, we only addressed all-cause dementia as a main outcome, not specific types of dementia. Distinguishing subtypes of dementia based on ICD codes without information on autopsy or imaging biomarkers would bring inevitable misclassification. Moreover, patients with diabetes are likely to suffer from mixed dementia[46]. Thus, studies with an independent cohort containing more thorough clinical information should address this issue across the various forms of dementia. Lastly, we did not pay attention to the potential side effects of pioglitazone, i.e., weight gain, and heart failure that could be relevant to dementia risk[36]. Notably, it has been shown that far smaller than usual doses used in DM treatment are effective in reducing Aβ pathology and protecting cognition through low-density lipoprotein receptor-related protein[40, 49]. Further studies are required to identify if there is an optimal dose that minimizes side effects while maintaining the benefits of dementia pathology. A large prospective cohort study would be required to confirm the long-term drug safety and the preventive effect of pioglitazone against dementia among patients with DM.

In conclusion, pioglitazone use was associated with lower risk of dementia in patients with type 2 DM, and such association was more robust in those with a history of

stroke or ischemic heart disease. However, the protective effect on dementia was not significant in stroke patients after commencing treatment with pioglitazone. Further studies are required to determine the role of stroke in the association between pioglitazone and dementia.

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References

1. Umegaki H. Type 2 diabetes as a risk factor for cognitive impairment: current insights. *Clin Interv Aging*. 2014;9:1011-1019.

2. Akter K, Lanza EA, Martin SA, Myronyuk N, Rua M, Raffa RB. Diabetes mellitus and Alzheimer's disease: shared pathology and treatment? *Br J Clin Pharmacol*. 2011;71:365-376.

3. Yarchoan M, Arnold SE. Repurposing diabetes drugs for brain insulin resistance in Alzheimer disease. *Diabetes*. 2014;63:2253-2261.

4. Combs CK, Bates P, Karlo JC, Landreth GE. Regulation of β-amyloid stimulated proinflammatory responses by peroxisome proliferator-activated receptor α. *Neurochemistry international*. 2001;39:449-457.

5. Searcy JL, Phelps JT, Pancani T, et al. Long-term pioglitazone treatment improves learning and attenuates pathological markers in a mouse model of Alzheimer's disease. *J Alzheimers Dis*. 2012;30:943-961.

6. Spence JD, Viscoli CM, Inzucchi SE, et al. Pioglitazone Therapy in Patients With Stroke and Prediabetes: A Post Hoc Analysis of the IRIS Randomized Clinical Trial. *JAMA Neurology*. 2019;76:526-535.

7. Ha J, Choi DW, Kim KY, Nam CM, Kim E. Pioglitazone use associated with reduced

risk of the first attack of ischemic stroke in patients with newly onset type 2 diabetes: a nationwide nested case-control study. *Cardiovasc Diabetol*. 2021;20:152.

8. Kuźma E, Lourida I, Moore SF, Levine DA, Ukoumunne OC, Llewellyn DJ. Stroke and dementia risk: A systematic review and meta-analysis. Alzheimer's & dementia : *Alzheimer's & Dementia*. *The Journal of the Alzheimer's Assocation.* 2018;14:1416-1426.

9. Luchsinger JA, Tang M-X, Stern Y, Shea S, Mayeux R. Diabetes Mellitus and Risk of Alzheimer's Disease and Dementia with Stroke in a Multiethnic Cohort. *Am J Epidemiology*. 2001;154:635-641.

10. Geldmacher DS, Fritsch T, McClendon MJ, Landreth G. A Randomized Pilot Clinical Trial of the Safety of Pioglitazone in Treatment of Patients With Alzheimer Disease. *Arch Neurol.* 2011;68:45-50.

11. Burns DK, Alexander RC, Welsh-Bohmer KA, et al. Safety and efficacy of pioglitazone for the delay of cognitive impairment in people at risk of Alzheimer's disease (TOMORROW): a prognostic biomarker study and a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet Neurol.* 2021;20:537-547.

12. Sato T, Hanyu H, Hirao K, Kanetaka H, Sakurai H, Iwamoto T. Efficacy of PPAR-γ agonist pioglitazone in mild Alzheimer disease. *Neurobiol Aging.* 2011;32:1626-1633.

13. Heneka MT, Fink A, Doblhammer G. Effect of pioglitazone medication on the incidence of dementia. *Ann Neurol*. 2015;78:284-294.

14. Shin DW, Cho J, Park JH, Cho B. National General Health Screening Program in Korea: history, current status, and future direction. *Precis Future Med.* 2022;6:9-31.

15. Park B, Sung J, Park K, Seo S, Kim S. Report of the evaluation for validity of discharged diagnoses in Korean Health Insurance database. Seoul: Seoul National University 2003:19-52.

16. Kim D, Yang P-S, Lip GYH, Joung B. Atrial Fibrillation Increases the Risk of Early-

Onset Dementia in the General Population: Data from a Population-Based Cohort. *J Clin Med*. 2020;9:3665.

17. McCormick N, Bhole V, Lacaille D, Avina-Zubieta JA. Validity of Diagnostic Codes for Acute Stroke in Administrative Databases: A Systematic Review. *PLoS One.* 2015;10:e0135834.

18. Park J-K, Kim K-S, Lee T-Y, et al. The accuracy of ICD codes for cerebrovascular diseases in medical insurance claims. *J Prev Med Public Health*. 2000;33:76-82.

19. Nissen SE, Wolski K. Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes. *NEJM*. 2007;356:2457-2471.

20. Dafni U. Landmark analysis at the 25-year landmark point. *Circ Cardiovasc Qual Outcomes*. 2011;4:363-371.

21. Morgan CJ. Landmark analysis: A primer. *J Nucl Cardiol*. 2019;26:391-393.

22. Giobbie-Hurder A, Gelber RD, Regan MM. Challenges of guarantee-time bias. *J Clin Oncol.* 2013;31:2963-2969.

23. Meira-Machado L, de Uña-Alvarez J, Cadarso-Suárez C, Andersen PK. Multi-state models for the analysis of time-to-event data. *Stat Methods Med Res*. 2009;18:195-222.

24. Ott A, Stolk RP, van Harskamp F, Pols HA, Hofman A, Breteler MM. Diabetes mellitus and the risk of dementia: The Rotterdam Study. *Neurology*. 1999;53:1937-1942.

25. Vermunt L, Sikkes SAM, van den Hout A, et al. Duration of preclinical, prodromal, and dementia stages of Alzheimer's disease in relation to age, sex, and APOE genotype. *Alzheimers Dement.* 2019;15:888-898.

26. Chou PS, Ho BL, Yang YH. Effects of pioglitazone on the incidence of dementia in patients with diabetes. *J Diabetes Complicat.* 2017;31:1053-1057.

27. Zhang W-Y, Schwartz EA, Permana PA, Reaven PD. Pioglitazone Inhibits the Expression of Inflammatory Cytokines From Both Monocytes and Lymphocytes in Patients

With Impaired Glucose Tolerance. *Arterioscler Thromb Vasc Biol*. 2008;28:2312-2318.

28. Bouhlel MA, Derudas B, Rigamonti E, et al. PPARγ Activation Primes Human Monocytes into Alternative M2 Macrophages with Anti-inflammatory Properties. *Cell Metab*. 2007;6:137-143.

29. Dello Russo C, Gavrilyuk V, Weinberg G, et al. Peroxisome Proliferator-activated Receptor γ Thiazolidinedione Agonists Increase Glucose Metabolism in Astrocytes. *J Biol Chem.* 2003;278:5828-5836.

30. Dobrian AD, Schriver SD, Khraibi AA, Prewitt RL. Pioglitazone Prevents Hypertension and Reduces Oxidative Stress in Diet-Induced Obesity. *Hypertens.* 2004;43:48-56.

31. Lin N, Chen LM, Pan XD, et al. Tripchlorolide Attenuates β-amyloid Generation via Suppressing PPARγ-Regulated BACE1 Activity in N2a/APP695 Cells. *Mol Neurobiol*. 2016;53:6397-6406.

32. Camacho IE, Serneels L, Spittaels K, Merchiers P, Dominguez D, De Strooper B. Peroxisome-proliferator-activated receptor gamma induces a clearance mechanism for the amyloid-beta peptide. *J Neurosci.* 2004;24:10908-10917.

33. Rossi A, Rigotto G, Valente G, et al. Defective Mitochondrial Pyruvate Flux Affects Cell Bioenergetics in Alzheimer's Disease-Related Models. *Cell Rep.* 2020;30:2332-2348.e2310.

34. Swerdlow RH, Khan SM. A “mitochondrial cascade hypothesis” for sporadic Alzheimer's disease. *Med Hypotheses*. 2004;63:8-20.

35. Izawa Y, Takahashi S, Suzuki N. Pioglitazone enhances pyruvate and lactate oxidation in cultured neurons but not in cultured astroglia. *Brain Res*. 2009;1305:64-73.

36. Shah P, Mudaliar S. Pioglitazone: side effect and safety profile. *Expert Opin Dr Saf.* 2010;9:347-354.

37. Young LH, Viscoli CM, Schwartz GG, et al. Heart Failure After Ischemic Stroke or Transient Ischemic Attack in Insulin-Resistant Patients Without Diabetes Mellitus Treated With Pioglitazone. *Circulation.* 2018;138:1210-1220.

38. Adachi H, Katsuyama H, Yanai H. The low dose (7.5mg/day) pioglitazone is beneficial to the improvement in metabolic parameters without weight gain and an increase of risk for heart failure. *Int J Cardiol.* 2017;227:247-248.

39. Rosenstock J, Vico M, Wei L, Salsali A, List JF. Effects of dapagliflozin, an SGLT2 inhibitor, on HbA(1c), body weight, and hypoglycemia risk in patients with type 2 diabetes inadequately controlled on pioglitazone monotherapy. *Diabetes Care.* 2012;35:1473-1478.

40. Moon JH, Kim HJ, Kim HM, et al. Upregulation of hepatic LRP1 by rosiglitazone: a possible novel mechanism of the beneficial effect of thiazolidinediones on atherogenic dyslipidemia. *J Mol Endocrinol.* 2012;49:165-174.

41. Betteridge DJ, Vergès B. Long-term effects on lipids and lipoproteins of pioglitazone versus gliclazide addition to metformin and pioglitazone versus metformin addition to sulphonylurea in the treatment of type 2 diabetes. *Diabetologia.* 2005;48:2477-2481.

42. Sourij H, Zweiker R, Wascher TC. Effects of Pioglitazone on Endothelial Function, Insulin Sensitivity, and Glucose Control in Subjects With Coronary Artery Disease and New-Onset Type 2 Diabetes. *Diabetes Care.* 2006;29:1039-1045.

43. Perriello G, Pampanelli S, Brunetti P, di Pietro C, Mariz S. Long-term effects of pioglitazone versus gliclazide on hepatic and humoral coagulation factors in patients with type 2 diabetes. *Diab Vasc Dis Res.* 2007;4:226-230.

44. Yaghi S, Furie KL, Viscoli CM, et al. Pioglitazone Prevents Stroke in Patients With a Recent Transient Ischemic Attack or Ischemic Stroke. *Circulation*. 2018;137:455-463.

45. Zhao X, Sun G, Zhang J, et al. Hematoma resolution as a target for intracerebral hemorrhage treatment: Role for peroxisome proliferator-activated receptor γ in

microglia/macrophages. *Ann Neurol*. 2007;61:352-362.

46. Secnik J, Cermakova P, Fereshtehnejad S-M, et al. Diabetes in a Large Dementia Cohort: Clinical Characteristics and Treatment From the Swedish Dementia Registry. *Diabetes Care*. 2017;40:1159-1166.

47. Shinohara M, Tashiro Y, Suzuki K, Fukumori A, Bu G, Sato N. Interaction between APOE genotype and diabetes in cognitive decline. *Alzheimers Dement (Amst)* 2020;12:e12006.

48. Irie F, Fitzpatrick AL, Lopez OL, et al. Enhanced Risk for Alzheimer Disease in Persons With Type 2 Diabetes and APOE ε4: The Cardiovascular Health Study Cognition Study. *Arch Neurol* 2.008;65:89-93.

49. Seok H, Lee M, Shin E, et al. Low-dose pioglitazone can ameliorate learning and memory impairment in a mouse model of dementia by increasing LRP1 expression in the hippocampus. *Sci Rep.* 2019;9:441.

Tables

Table 1. Demographics and characteristics of the participants at baseline

	Before sIPTW			After sIPTW		
Variables	Pioglitazone never users (n = 87,751)	Pioglitazone users (n = 3,467)	SMD	Pioglitazone never users (n = 87,758)	Pioglitazone users (n = 3,218)	SMD
	n (%)	n (%)		n (%)	n (%)	
Age (years)	60.5 (7.3)	59.5 (7.1)	0.145	60.5 (7.3)	60.0 (7.1)	0.063
Women	41,642 (47.5)	1,504 (43.4)	0.082	41,510 (47.3)	1,521 (47.3)	0.001
Diabetes mellitus duration (days) †	3,691 (3,015-4,434)	3,475 (2,977-4,030)	0.273	3,677 (3,013-4,415)	3,649 (2,994-4,387)	0.042
Income			0.068			0.021
0	2,645 (3.0)	135 (3.9)		2,675 (3.0)	103 (3.2)	
Q1	13,519 (15.4)	503 (14.5)		13,491 (15.4)	512 (15.9)	
Q2	12,284 (14.0)	528 (15.2)		12,326 (14.0)	458 (14.2)	
Q3	15,230 (17.4)	597 (17.2)		15,226 (17.4)	550 (17.1)	
Q4	19,326 (22.0)	774 (22.3)		19,336 (22.0)	695 (21.6)	
Q5	24,747 (28.2)	930 (26.8)		24,704 (28.1)	900 (28.0)	
Insurance						
National Health Insurance	86,537 (98.6)	3,390 (97.8)	0.063	86,516 (98.6)	3,169 (98.5)	0.008
Medicaid	1,214 (1.4)	77 (2.2)		1,242 (1.4)	49 (1.5)	
Region			0.084			0.018
1	17,144 (19.5)	668 (19.3)		17,136 (19.5)	649 (20.2)	

2	22,187 (25.3)	761 (21.9)		22,077 (25.2)	814 (25.3)	
3	48,420 (55.2)	2,038 (58.8)		48,545 (55.3)	1,754 (54.5)	
BMI			0.026			0.027
<18.5 kg/m^2	761 (0.9)	26 (0.7)		757 (0.9)	21 (0.7)	
18.5–22.9 kg/m^2	17,965 (20.5)	719 (20.7)		17,975 (20.5)	647 (20.1)	
23–25 kg/m^2	22,306 (25.4)	849 (24.5)		22,277 (25.4)	808 (25.1)	
≥25 kg/m^2	46,719 (53.2)	1,873 (54.0)		46,750 (53.3)	1,742 (54.1)	
Fasting blood glucose (mg/dL) ††	137.4 (49.2)	152.7 (61.7)	0.276	138.0 (50.0)	142.0 (51.7)	0.080
BP (mmHg) ††						
Systolic	132.0 (17.2)	131.0 (16.3)	0.057	131.9 (17.2)	131.39 (16.7)	0.033
Diastolic	80.9 (10.7)	80.6 (10.2)	0.026	80.8 (10.7)	80.79 (10.4)	0.004
Total cholesterol (mg/dL) ††	205.9 (42.1)	205.8 (43.3)	0.002	205.9 (42.2)	205.4 (42.4)	0.010
Creatinine (mg/dL) ††	1.00 (0.93)	1.03 (1.01)	0.023	1.0 (0.9)	1.0 (1.0)	0.014
Hypertension	40,088 (45.7)	1,402 (40.4)	0.106	39,915 (45.5)	1,403 (43.6)	0.038
Atrial fibrillation	741 (0.8)	18 (0.5)	0.040	730 (0.8)	29 (0.9)	0.007
Ischemic heart disease	7,749 (8.8)	224 (6.5)	0.089	7670 (8.7)	276 (8.6)	0.006
Heart failure	3,103 (3.5)	95 (2.7)	0.046	3077 (3.5)	100 (3.1)	0.022
Dyslipidemia	15,318 (17.5)	531 (15.3)	0.058	15,248 (17.4)	570 (17.7)	0.009
Ischemic stroke	3,940 (4.5)	123 (3.5)	0.048	2,553 (2.9)	93 (2.9)	0.001
Hemorrhagic stroke	324 (0.4)	8 (0.2)	0.025	319 (0.4)	12 (0.4)	0.001
Depression	3,059 (3.5)	95 (2.7)	0.043	3,034 (3.5)	113 (3.5)	0.003
CCI			0.083			0.017
0	22,149	780 (22.5)		22,058	790 (24.6)	

	(25.2)			(25.1)		
1	23,110 (26.3)	871 (25.1)		23,070 (26.3)	838 (26.0)	
2	42,492 (48.4)	1,816 (52.4)		42,630 (48.6)	1,590 (49.4)	
Medication						
Statin	45,326 (51.7)	2,179 (62.8)	0.228	45,707 (52.1)	1,767 (54.9)	0.056
Aspirin	19,723 (22.5)	663 (19.1)	0.083	19,612 (22.3)	695 (21.6)	0.017
Antiplatelet*	1,995 (2.3)	62 (1.8)	0.034	1,979 (2.3)	79 (2.5)	0.014
Anticoagulant	420 (0.5)	8 (0.2)	0.042	34,270 (39.1)	1,206 (37.5)	0.038
Antihypertensive agents	34,402 (39.2)	1,221 (35.2)	0.083	412 (0.5)	24 (0.8)	0.032
Antiarrhythmic agents	3,276 (3.7)	124 (3.6)	0.008	3,271 (3.7)	115 (3.6)	0.009
Antidiabetic medication						
Biguanide	56,561 (64.5)	2,939 (84.8)	0.480	57,250 (65.2)	2,404 (74.7)	0.208
Alpha-glucosidase inhibitors	4,551 (5.2)	221 (6.4)	0.051	4592 (5.2)	205 (6.4)	0.048
DPP- IV inhibitors	9,314 (10.6)	573 (16.5)	0.173	9,515 (10.8)	406 (12.6)	0.055
Insulin	11,683 (13.3)	613 (17.7)	0.121	11,833 (13.5)	515 (16.0)	0.071
SGLT-2 inhibitors	108 (0.1)	10 (0.3)	0.036	110.3 (0.1)	9.2 (0.3)	0.035
Sulfonylurea	51,447 (58.6)	2,704 (78.0)	0.426	52,103 (59.4)	2,118 (65.8)	0.133
Smoking			0.082			0.027
None	58,242 (66.4)	2,166 (62.5)		58,115 (66.2)	2,092 (65.0)	
Past	12,165	533 (15.4)		12,217	458 (14.2)	

	(13.9)			(13.9)		
Current	17,344 (19.8)	768 (22.2)		17,426 (19.9)	668 (20.8)	
Alcohol use			0.012			0.020
Low	64,962 (74.0)	2,548 (73.5)		64,949 (74.0)	2,375 (73.8)	
Moderate	17,548 (20.0)	706 (20.4)		17,562 (20.0)	663 (20.6)	
Heavy	5,241 (6.0)	213 (6.1)		5,247 (6.0)	181 (5.6)	
Physical activity						
Yes (≥1 time per week)	63,205 (72.0)	2,539 (73.2)	0.027	63,251 (72.1)	2,350 (73.0)	0.021
Year of type 2 diabetes mellitus onset			0.481			0.077
2004	14,014 (16.0)	171 (4.9)		13,646 (15.5)	440 (13.7)	
2005	15,025 (17.1)	344 (9.9)		14,785 (16.8)	509 (15.8)	
2006	11,778 (13.4)	498 (14.4)		11,809 (13.5)	430 (13.4)	
2007	10,848 (12.4)	552 (15.9)		10,969 (12.5)	420 (13.1)	
2008	10,557 (12.0)	713 (20.6)		10,844 (12.4)	415 (12.9)	
2009	12,688 (14.5)	614 (17.7)		12,798 (14.6)	470 (14.6)	
2010	6,459 (7.4)	296 (8.5)		6,500 (7.4)	268 (8.3)	
2011	3,880 (4.4)	166 (4.8)		3,892 (4.4)	158 (4.9)	
2012	2,502 (2.9)	113 (3.3)		2,516 (2.9)	109 (3.4)	

Data are presented as n (%), unless stated otherwise. †Median and the interquartile range (1st quartile and 3rd quartile). ††Mean and standard deviation (SD) of continuous independent variables in this study. BP, blood pressure; CCI, Charlson Comorbidity Index; DPP-IV, dipeptidyl peptidase IV; SGLT-2, sodium-glucose cotransporter 2; SMD, standardized mean difference; sIPTW, stabilized inverse probability of treatment weighting. * Except for aspirin.

Table 2. Reduced dementia risk associated with pioglitazone use in patients with diabetes mellitus

	Before sIPTW		After sIPTW		Crude	sIPTW	P for trend
	Dementia						
	No (n = 82,139)	Yes (n = 9,079)	No (n = 81,954)	Yes (n = 9,022)	HR (95% CI)	aHR (95% CI)	
Pioglitazone use							0.006
Never user	78924 (88.8)	8827 (11.2)	79003 (90.0)	8755 (10.0)	1.00	1.00	
Users	3215 (92.2)	252 (7.8)	2950 (91.7)	268 (8.3)	0.84 (0.74–0.95)	0.84 (0.75–0.95)	
Cumulative dose of use							0.0249
Never user	78924 (88.8)	8827 (11.2)	79003 (90.0)	8755 (10.0)	1.00	1.00	
Ever user							
Q1	789 (91.2)	76 (8.8)	762 (89.5)	90 (10.5)	0.95 (0.76–1.20)	1.00 (0.81–1.23)	
Q2	799 (92.3)	67 (7.7)	735 (91.5)	69 (8.5)	0.86 (0.68–1.09)	0.83 (0.66–1.06)	
Q3	800 (92.9)	61 (7.1)	671 (92.3)	56 (7.7)	0.83 (0.64–1.06)	0.79 (0.61–1.03)	
Q4	827 (94.5)	48 (5.5)	784 (93.6)	53 (6.4)	0.70 (0.53-0.93)	0.72(0.55–0.94)	
Duration of use (days, quartile)							0.0058
Ever user							
Q1	788 (91.0)	78 (9.0)	741.9 (89.1)	91.0 (10.9)	0.99 (0.80–1.24)	1.07 (0.87–1.31)	
Q2	805 (92.8)	62 (7.2)	750.8 (92.1)	64.2 (7.9)	0.79 (0.62–1.01)	0.76 (0.59–0.96)	
Q3	801 (92.4)	66 (7.6)	679.6 (91.7)	61.9 (8.3)	0.88 (0.69–1.13)	0.86 (0.67–1.10)	
Q4	821 (94.7)	46 (5.3)	778.5 (93.9)	50.5 (6.1)	0.67 (0.50–0.90)	0.68 (0.51–0.89)	
Duration of use (years)							0.0066
Ever user							
<1 year	1022 (91.2)	99 (8.8)	976.8 (89.3)	116 (10.7)	0.97 (0.80–1.18)	1.03 (0.86–1.24)	
1-2 years	1090 (92.3)	91 (7.7)	971.3 (92.1)	83 (7.9)	0.86 (0.70–1.06)	0.78 (0.62–0.96)	
2-3 years	615 (94.9)	33 (5.1)	512.6 (92.9)	39 (7.1)	0.62 (0.44–0.87)	0.78 (0.57–1.07)	
4 years	488 (94.4)	29 (5.6)	490.1 (94.4)	29 (5.6)	0.73 (0.51–1.05)	0.63 (0.44–0.90)	

cDDDs, cumulative defined daily doses; aHR, adjusted hazard ratio; CI, confidence interval; sIPTW, stabilized inverse probability of treatment weighting.

* Analysis was adjusted sIPTW which was calculated using propensity scores by the following covariates: hypertension, dyslipidemia, atrial fibrillation, heart failure, ischemic heart disease, ischemic stroke, hemorrhagic stroke, CCI, fasting blood glucose levels, systolic blood pressure, diastolic blood pressure, total cholesterol levels, creatinine levels, statin use, use of cardiovascular medications (aspirin, statin, anticoagulant, antiplatelet, antiarrhythmic agents, and antihypertension drugs), use of other antidiabetic medications (biguanide, sulfonylurea, dipeptidyl peptidase-4 inhibitors, alpha-glucosidase inhibitors, sodium-glucose co-transporter-2inhibitors, insulin), BMI, alcohol and smoking habits, and physical activity., and year of type 2 diabetes mellitus onset.

Table 3. Hazard ratios for dementia in different subgroups in the overall population

Subgroups	**Pioglitazone use**	**Dementia**		**aHR (95% CI)**	***P* for interaction**
		No (n = 81,954)	Yes (n = 9,022)		
Hypertension					0.4505
No	Never user	43,876 (91.7)	3,968 (8.3)	1.00	
	Users	1,692 (93.2)	123 (6.8)	0.81 (0.68–0.97)	
Yes	Never user	35,128 (88.0)	4,787(12.0)	1.00	
	Users	1,259 (89.7)	144 (10.3)	0.89 (0.75–1.05)	
Ischemic heart disease					0.0484
No	Never user	72,398 (90.4)	7,690 (9.6)		
	Users	2,698 91.7)	244 (8.3)	0.88 (0.78–1.00)	
Yes	Never user	6,606 (86.1)	1,065 (13.9)	1.00	
	Users	252 (91.3)	24 (8.7)	0.57 (0.38–0.86)	
Atrial fibrillation					0.4538
No	Never user	78,388 (90.1)	8,640 (9.9)	1.00	
	Users	2,924 (91.7)	265 (8.3)	0.85 (0.75–0.96)	
Yes	Never user	615 (84.3)	115 (15.7)	1.00	
	Users	26 (90.5)	3 (9.5)	0.54 (0.16–1.76)	

Heart failure					0.9723
No	Never user	76,498 (90.3)	8,184 (9.7)	1.00	
	Users	2,864 (91.9)	253 (8.1)	0.85 (0.75–0.96)	
Yes	Never user	2,506 (81.4)	571 (18.6)	1.00	
	Users	86 (85.6)	15 (14.4)	0.84 (0.50–1.41)	
Dyslipidemia					0.0561
No	Never user	65,275 (90.0)	7,235 (10.0)	1.00	
	Users	2,440 (92.2)	208 (7.8)	0.80 (0.69–0.91)	
Yes	Never user	13,728 (90.0)	1,520 (10.0)	1.00	
	Users	510 (89.5)	60 (10.5)	1.06 (0.82–1.37)	
Hemorrhagic stroke					0.0130
No	Never user	78,735 (90.5)	8,262 (9.5)	1.00	
	Users	2,942 (91.9)	259 (8.1)	0.84 (0.74–0.94)	
Yes	Never user	268 (35.2)	493 (64.8)	1.00	
	Users	8 (47.1)	9 (52.9)	3.26 (1.13–9.41)	
Ischemic stroke					0.0686
No	Never user	76,943(90.3)	8,262 (9.7)	1.00	
	Users	2,866 (91.7)	259 (8.3)	0.87 (0.76–0.98)	
Yes	Never user	2,060 (80.7)	493 (19.3)	1.00	

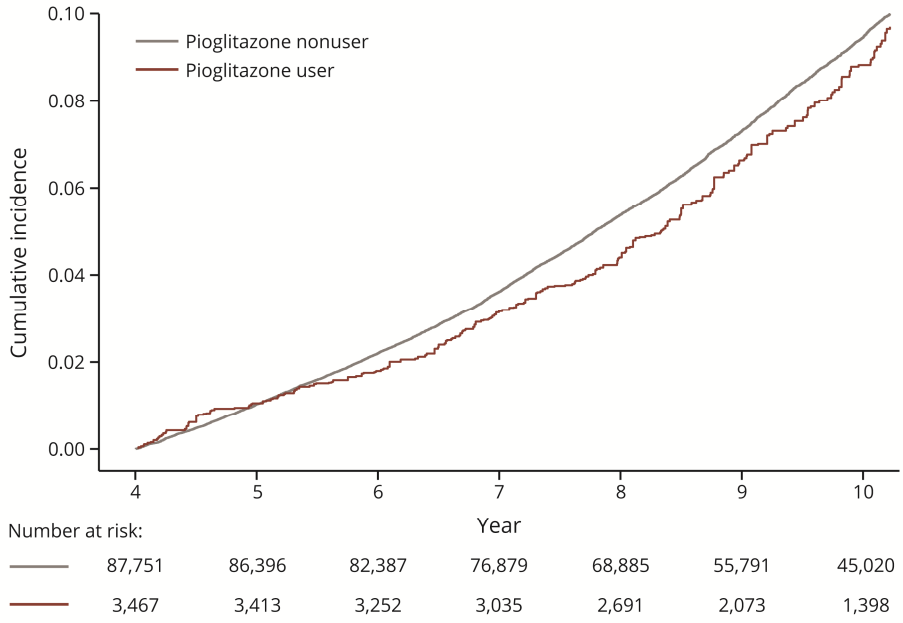
	Users	85 (89.6)	9 (9.4)	0.46 (0.24–0.90)	
Depression					0.6512
No	Never user	76,478 (90.3)	8,246 (9.7)	1.00	
	Users	2,851 (91.8)	254 (8.2)	0.85 (0.75–0.96)	
Yes	Never user	2,526 (83.2)	509 (16.8)	1.00	
	Users	100 (87.9)	14 (12.1)	0.75 (0.44–1.28)	

aHR, adjusted hazard ratio.

* Analysis was adjusted sIPTW which was calculated using propensity scores by the following covariates: hypertension, dyslipidemia, atrial fibrillation, heart failure, ischemic heart disease, ischemic stroke, hemorrhagic stroke, CCI, fasting blood glucose levels, systolic blood pressure, diastolic blood pressure, total cholesterol levels, creatinine levels, statin use, use of cardiovascular medications (aspirin, statin, anticoagulant, antiplatelet, antiarrhythmic agents, and antihypertension drugs), use of other antidiabetic medications (biguanide, sulfonylurea, dipeptidyl peptidase-4 inhibitors, alpha-glucosidase inhibitors, sodium-glucose co-transporter-2 inhibitors, insulin), BMI, alcohol and smoking habits, and physical activity., and year of type 2 diabetes mellitus onset.

Figure Legends

Figure 1. Kaplan–Meier cumulative incidence of dementia in patients with newly diagnosed type 2 diabetes mellitus.



The red and gray lines indicate patients treated with and without pioglitazone, respectively