

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

Junghee Ha, MD, PhD,\* Dong-Woo Choi, PhD,\* Kwang Joon Kim, MD, PhD, Keun You Kim, MD, Chung Mo Nam, PhD, and Eosu Kim, MD, PhD

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## Correspondence

Dr. Kim  
kimeosu@yuhs.ac

## Abstract

### Background and Objectives

Previous studies have reported the protective effect of pioglitazone on dementia in patients with type 2 diabetes mellitus (DM). 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 patients with DM 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 multistate 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 nonuse (adjusted hazard ratio [aHR] = 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 (aHR = 0.46, 95% CI 0.24–0.90; aHR = 0.57, 95% CI 0.38–0.86, respectively). The incidence of stroke was also reduced by pioglitazone use (aHR = 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 (aHR = 1.27, 95% CI 0.80–2.04).

### Discussion

Pioglitazone use is associated with a lower risk of dementia in patients with DM, 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 patients with DM.

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\*These authors contributed equally to this work as first authors.

From the Department of Psychiatry (J.H., K.Y.K., E.K.), Institute of Behavioral Science in Medicine, and Division of Geriatrics (K.J.K.), Department of Internal Medicine, and Department of Preventive Medicine (C.M.N.), and Graduate School of Medical Science (E.K.), Brain Korea 21 FOUR Project for Medical Science, Yonsei University College of Medicine, Seoul, Republic of Korea; Cancer Big Data Center (D.-W.C.), National Cancer Control Institute, National Cancer Center, Gyeonggi-do, Republic of Korea; and Department of Psychiatry (K.Y.K.), Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul, Republic of Korea.

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## Glossary

**AD** = Alzheimer disease; **aHR** = adjusted hazard ratio; **APOE** = apolipoprotein E; **cDDD**s = cumulative defined daily doses; **DM** = diabetes mellitus; **HR** = hazard ratio; **NHIS** = National Health Insurance Service; **NHSP** = National Health Screening Program; **PSM** = propensity score-matching; **sIPTW** = stabilized inverse probability of treatment weighting.

Type 2 diabetes mellitus (DM) increases the risk of aging-associated cognitive decline and dementia.<sup>1</sup> DM and Alzheimer disease (AD) share pathogenic mechanisms, such as insulin resistance and microvascular dysfunction,<sup>2</sup> 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.<sup>3</sup> Pioglitazone is a peroxisome proliferation-activated receptor  $\gamma$  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 ( $A\beta$ ) and inflammation, inhibiting tau hyperphosphorylation, and enhancing synaptic plasticity.<sup>4,5</sup> Previous studies have found that pioglitazone has a role in primary and secondary stroke prevention.<sup>6,7</sup> These findings raise expectations concerning the protective role of pioglitazone against dementia because DM and stroke are considered among the most common conditions that predisposed to dementia in old age.<sup>8,9</sup>

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.<sup>10</sup> A recent large clinical trial also failed to demonstrate its efficacy against AD development in a group of nondiabetic participants prescreened as at high risk of cognitive decline.<sup>11</sup> 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  $A\beta_{40}/A\beta_{42}$  ratio, compared with the control group, suggesting that the disease was being stabilized.<sup>12</sup> Promising results have also been reported in a previous cohort study, although the proportion of patients with DM was relatively small.<sup>13</sup>

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.<sup>11,12</sup> 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 before using pioglitazone and incident stroke while using it, in that stroke

and DM could substantially affect the relationship between pioglitazone use and dementia risk.<sup>8,9</sup>

## Methods

### Data Source

The Korean National Health Insurance Service (NHIS)-DM cohort between 2002 and 2017 were used. These datasets included 400,000 patients with type 2 DM accounting for approximately 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 checkup 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, and so forth.<sup>14</sup> 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 because of de-identified data.

### Selection of Participants

A total of 191,507 newly diagnosed patients with DM (ICD-10 code E11-E14) who had received health checkup between 2004 and 2012 were selected from the cohort. Finally, 91,218 newly diagnosed patients with DM without dementia were enrolled, and follow-up data were reviewed until December 2017 (eFigure 1, [links.lww.com/WNL/C637](https://links.lww.com/WNL/C637)). The following ICD-10 codes were used to identify dementia: F00, F01, F02, F03, G30, and G31. Patients with 2 or more prescriptions for any of the 4 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 previous studies.<sup>15,16</sup> ICD-10 code I63 was used to diagnose ischemic stroke.<sup>17,18</sup> To ensure accuracy of diagnosis, an ischemic stroke was considered only if the primary diagnosis code was I63 at admission. We excluded (1) patients aged <50 years ( $n = 61,093$ ), (2) those who had not used antidiabetic medications ( $n = 35,498$ ), (3) those who had taken insulin

more than a month ( $n = 4,338$ ), (4) those with a history of dementia or antidementia medication use before DM diagnosis ( $n = 917$ ), (5) those diagnosed with dementia within 4 years after DM diagnosis ( $n = 3,462$ ), or (6) 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.<sup>19</sup>

In this study, a pioglitazone user was defined as a person with a total cumulative defined daily doses (cDDD) of 90 or greater after initiation of DM treatment as previously described.<sup>7</sup> 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 World Health Organization. The degree of pioglitazone exposure was expressed in the following 3 ways: previous user (vs 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, preexisting 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 the DM diagnosis. As described in our previous study,<sup>7</sup> 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/wk, moderate: 1–4 times/wk, and heavy: 5–7 times/wk), and physical activity (yes:  $\geq 1$  time/wk, 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.<sup>20,21</sup> Specifically, certain index time points are chosen, and survival analysis and follow-up are performed only on patients who 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.<sup>20,22</sup> To address these limitations, sensitivity analyses were performed using alternative landmark times (eTable 1, [links.lww.com/WNL/C637](https://links.lww.com/WNL/C637)), and detailed outcome characteristics of those excluded within 4 years of the onset of diabetes were added to the supplementary section

(eTable 2, [links.lww.com/WNL/C637](https://links.lww.com/WNL/C637)). To balance baseline characteristics between pioglitazone users and nonusers, 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 cotransporter-2 inhibitors, and insulin), body mass 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 2 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% CIs for dementia risk between pioglitazone users and nonusers. To further assess heterogeneity of preexisting 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  $\geq 180$  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 multistate models with 3 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.<sup>23</sup> In eFigure 2 ([links.lww.com/WNL/C637](https://links.lww.com/WNL/C637)), 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 transitioned 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 multistate 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 multistage 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

**Table 1** Demographics and Characteristics of the Participants at Baseline

Variables	Before sIPTW			After sIPTW		
	Pioglitazone never users (n = 87,751) n (%)	Pioglitazone users (n = 3,467) n (%)	SMD	Pioglitazone never users (n = 87,758) n (%)	Pioglitazone users (n = 3,218) n (%)	SMD
Age (y)	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 (d) <sup>a</sup>	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 (kg/m <sup>2</sup> )	—	—	0.026	—	—	0.027
<18.5	761 (0.9)	26 (0.7)	—	757 (0.9)	21 (0.7)	—
18.5–22.9	17,965 (20.5)	719 (20.7)	—	17,975 (20.5)	647 (20.1)	—
23–25	22,306 (25.4)	849 (24.5)	—	22,277 (25.4)	808 (25.1)	—
≥25	46,719 (53.2)	1,873 (54.0)	—	46,750 (53.3)	1,742 (54.1)	—
Fasting blood glucose (mg/dL) <sup>b</sup>	137.4 (49.2)	152.7 (61.7)	0.276	138.0 (50.0)	142.0 (51.7)	0.080
BP (mm Hg) <sup>b</sup>	—	—	—	—	—	—
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) <sup>b</sup>	205.9 (42.1)	205.8 (43.3)	0.002	205.9 (42.2)	205.4 (42.4)	0.010
Creatinine (mg/dL) <sup>b</sup>	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	7,670 (8.7)	276 (8.6)	0.006
Heart failure	3,103 (3.5)	95 (2.7)	0.046	3,077 (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

Continued

**Table 1** Demographics and Characteristics of the Participants at Baseline (continued)

Variables	Before sIPTW		SMD	After sIPTW		SMD
	Pioglitazone never users (n = 87,751) n (%)	Pioglitazone users (n = 3,467) n (%)		Pioglitazone never users (n = 87,758) n (%)	Pioglitazone users (n = 3,218) n (%)	
<b>Hemorrhagic stroke</b>	324 (0.4)	8 (0.2)	0.025	319 (0.4)	12 (0.4)	0.001
<b>Depression</b>	3,059 (3.5)	95 (2.7)	0.043	3,034 (3.5)	113 (3.5)	0.003
<b>CCI</b>	—	—	0.083	—	—	0.017
<b>0</b>	22,149 (25.2)	780 (22.5)	—	22,058 (25.1)	790 (24.6)	—
<b>1</b>	23,110 (26.3)	871 (25.1)	—	23,070 (26.3)	838 (26.0)	—
<b>2</b>	42,492 (48.4)	1,816 (52.4)	—	42,630 (48.6)	1,590 (49.4)	—
<b>Medication</b>						
<b>Statin</b>	45,326 (51.7)	2,179 (62.8)	0.228	45,707 (52.1)	1,767 (54.9)	0.056
<b>Aspirin</b>	19,723 (22.5)	663 (19.1)	0.083	19,612 (22.3)	695 (21.6)	0.017
<b>Antiplatelet<sup>c</sup></b>	1,995 (2.3)	62 (1.8)	0.034	1,979 (2.3)	79 (2.5)	0.014
<b>Anticoagulant</b>	420 (0.5)	8 (0.2)	0.042	34,270 (39.1)	1,206 (37.5)	0.038
<b>Antihypertensive agents</b>	34,402 (39.2)	1,221 (35.2)	0.083	412 (0.5)	24 (0.8)	0.032
<b>Antiarrhythmic agents</b>	3,276 (3.7)	124 (3.6)	0.008	3,271 (3.7)	115 (3.6)	0.009
<b>Antidiabetic medication</b>						
<b>Biguanide</b>	56,561 (64.5)	2,939 (84.8)	0.480	57,250 (65.2)	2,404 (74.7)	0.208
<b>Alpha-glucosidase inhibitors</b>	4,551 (5.2)	221 (6.4)	0.051	4,592 (5.2)	205 (6.4)	0.048
<b>DPP- IV inhibitors</b>	9,314 (10.6)	573 (16.5)	0.173	9,515 (10.8)	406 (12.6)	0.055
<b>Insulin</b>	11,683 (13.3)	613 (17.7)	0.121	11,833 (13.5)	515 (16.0)	0.071
<b>SGLT-2 inhibitors</b>	108 (0.1)	10 (0.3)	0.036	110.3 (0.1)	9.2 (0.3)	0.035
<b>Sulfonylurea</b>	51,447 (58.6)	2,704 (78.0)	0.426	52,103 (59.4)	2,118 (65.8)	0.133
<b>Smoking</b>			0.082			0.027
<b>None</b>	58,242 (66.4)	2,166 (62.5)		58,115 (66.2)	2,092 (65.0)	
<b>Past</b>	12,165 (13.9)	533 (15.4)		12,217 (13.9)	458 (14.2)	
<b>Current</b>	17,344 (19.8)	768 (22.2)		17,426 (19.9)	668 (20.8)	
<b>Alcohol use</b>	—	—	0.012	—	—	0.020
<b>Low</b>	64,962 (74.0)	2,548 (73.5)	—	64,949 (74.0)	2,375 (73.8)	—
<b>Moderate</b>	17,548 (20.0)	706 (20.4)	—	17,562 (20.0)	663 (20.6)	—
<b>Heavy</b>	5,241 (6.0)	213 (6.1)	—	5,247 (6.0)	181 (5.6)	—
<b>Physical activity</b>						
<b>Yes (≥1 time per wk)</b>	63,205 (72.0)	2,539 (73.2)	0.027	63,251 (72.1)	2,350 (73.0)	0.021
<b>Year of type 2 diabetes mellitus onset</b>	—	—	0.481	—	—	0.077
<b>2004</b>	14,014 (16.0)	171 (4.9)	—	13,646 (15.5)	440 (13.7)	—
<b>2005</b>	15,025 (17.1)	344 (9.9)	—	14,785 (16.8)	509 (15.8)	—
<b>2006</b>	11,778 (13.4)	498 (14.4)	—	11,809 (13.5)	430 (13.4)	—
<b>2007</b>	10,848 (12.4)	552 (15.9)	—	10,969 (12.5)	420 (13.1)	—

Continued



**Table 1** Demographics and Characteristics of the Participants at Baseline (continued)

Variables	Before sIPTW		SMD	After sIPTW		SMD
	Pioglitazone never users (n = 87,751)	Pioglitazone users (n = 3,467)		Pioglitazone never users (n = 87,758)	Pioglitazone users (n = 3,218)	
	n (%)	n (%)		n (%)	n (%)	
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)	—

Abbreviations: BMI = body mass index; BP = blood pressure; CCI = Charlson Comorbidity Index; DPP-IV = dipeptidyl peptidase IV; SGLT-2 = sodium-glucose cotransporter 2; sIPTW = stabilized inverse probability of treatment weighting; SMD = standardized mean difference.

Data are presented as n (%), unless stated otherwise.

<sup>a</sup> Median and the interquartile range (1st quartile and 3rd quartile).

<sup>b</sup> Mean and SD of continuous independent variables in this study.

<sup>c</sup> Except for aspirin.

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. In addition, we applied cause-specific hazard model to address the competing event (death). Last, we used the 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) and R version 3.6 (The R Foundation, 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 because of 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 online (nhiss.nhis.or.kr) and requires a study proposal and ethics approval from the institutional review board.

## Results

### Study Population

In total, 91,218 patients with new-onset type 2 DM without a history of dementia were finally selected. Of these patients, 3,467 pioglitazone users and 87,751 nonusers were identified (eFigure 1). 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 nonusers were less than 10%, except for those who used biguanide and sulfonylurea (eFigure 3, links.lww.com/WNL/C637). We further adjusted these 2 factors for the final models. For each pioglitazone user and nonuser, information on multiple uses of antidiabetic drugs was separately described (eTable 3, links.lww.com/WNL/C637).

### 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 nonusers 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 nonusers (Figure 1). Of patients using pioglitazone, 286 (8.3%) developed dementia, whereas 8,755 nonusers (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 nonuse. As shown in 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 nonusers, 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 4 years, compared with nonusers (HR [CI] = 0.56 [0.38–0.81], eTable 2). The results of the sensitivity analyses using an alternative landmark point were in line with those of the main analysis (eTable 4, links.lww.com/WNL/C637). After PSM, the risk of dementia remained significantly reduced in pioglitazone users, with an aHR of 0.85 (0.72–1.00) (eTables 5 and 6, links.lww.com/WNL/C637).

**Table 2** Reduced Dementia Risk Associated With Pioglitazone Use in Patients With Diabetes Mellitus

	Before sIPTW		After sIPTW <sup>a</sup>		Crude HR (95% CI)	sIPTW aHR (95% CI)	p for trend
	Dementia		No (n = 81,954)	Yes (n = 9,022)			
	No (n = 82,139)	Yes (n = 9,079)					
<b>Pioglitazone use</b>							0.006
Never user	78,924 (88.8)	8,827 (11.2)	79,003 (90.0)	8,755 (10.0)	1.00	1.00	—
Users	3,215 (92.2)	252 (7.8)	2,950 (91.7)	268 (8.3)	0.84 (0.74–0.95)	0.84 (0.75–0.95)	—
<b>Cumulative dose of use</b>							0.0249
Never user	78,924 (88.8)	8,827 (11.2)	79,003 (90.0)	8,755 (10.0)	1.00	1.00	—
<b>Ever user</b>							
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)	—
<b>Duration of use (d, quartile)</b>							0.0058
<b>Ever user</b>							
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)	—
<b>Duration of use (y)</b>							0.0066
<b>Ever user</b>							
<1 y	1,022 (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 y	1,090 (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 y	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 y	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)	—

Abbreviations: aHR = adjusted hazard ratio; CCI = Charlson Comorbidity Index; cDDD = cumulative defined daily doses; HR = hazard ratio; sIPTW = stabilized inverse probability of treatment weighting.

<sup>a</sup> 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 cotransporter-2 inhibitors, insulin), BMI, alcohol and smoking habits, and physical activity, and year of type 2 diabetes mellitus onset.

### The Protective Effect of Pioglitazone on Dementia in Patients with Diabetes Mellitus With a History of Stroke or Ischemic Heart Disease

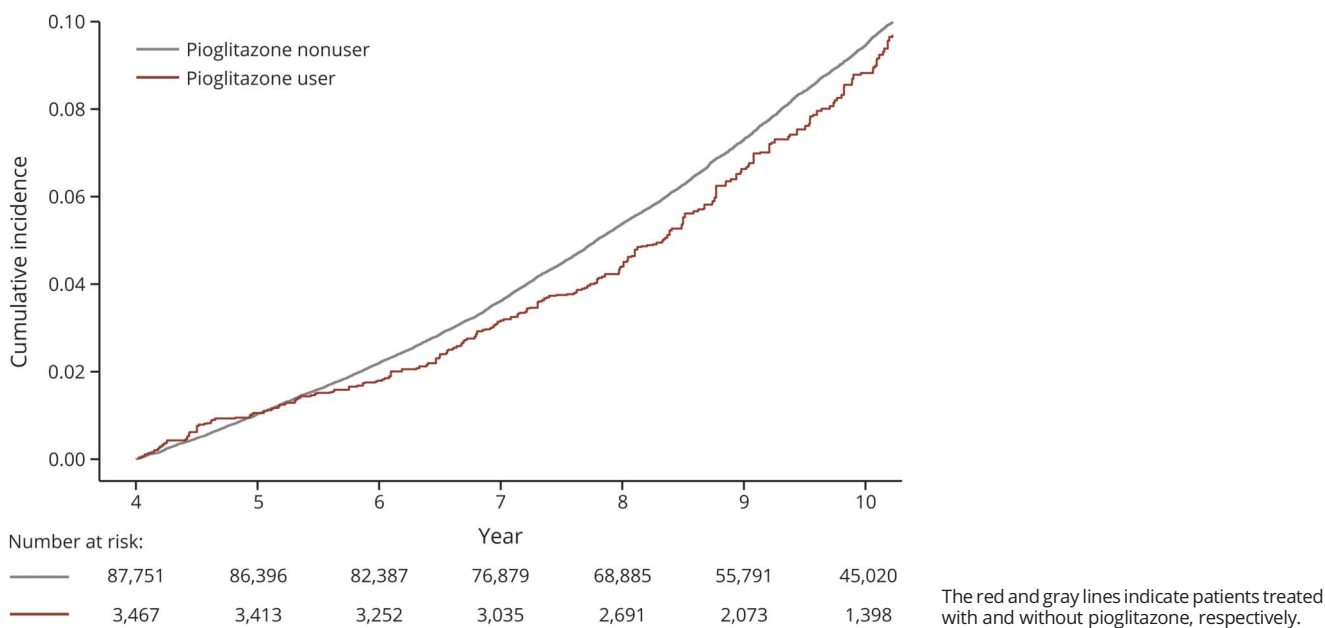
In a subsequent subgroup analysis, the association between pioglitazone and dementia risk were further evaluated (Table 3). Pioglitazone use showed heterogeneities of association with a lower risk of dementia according to subgroups of conditions, such as hypertension, ischemic heart disease, atrial fibrillation, 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 patients with DM 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

**Figure 1** Kaplan–Meier Cumulative Incidence of Dementia in Patients With Newly Diagnosed Type 2 Diabetes Mellitus



potential intermediate clinical event between pioglitazone exposure and the development of dementia. Multistate 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 nonuse (eFigure 2). 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: (1) pioglitazone use was significantly associated with a reduced risk of dementia in patients with DM, (2) the association between pioglitazone and dementia was more pronounced among patients with a history of ischemic heart disease or stroke, and (3) 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 patients with dementia with DM. To our knowledge, this is the first study to demonstrate 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.<sup>24</sup> Because dementia, particularly AD, has a long latency period or prodromal stage before diagnosis,<sup>25</sup> 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<sup>13</sup>; 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.<sup>26</sup> However, the investigators did not find a significant association between pioglitazone use and major risk factors for dementia. This adverse finding is likely because of the smaller sample size and shorter observation period (1,825 days) in that study compared with our study (3,512 days).



**Table 3** Hazard Ratios for Dementia in Different Subgroups in the Overall Population

Subgroups	Pioglitazone use	Dementia		aHR (95% CI) <sup>a</sup>	p for interaction
		No (n = 81,954)	Yes (n = 9,022)		
<b>Hypertension</b>					0.4505
<b>No</b>	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)	
<b>Yes</b>	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)	
<b>Ischemic heart disease</b>					0.0484
<b>No</b>	Never user	72,398 (90.4)	7,690 (9.6)		
	Users	2,698 (91.7)	244 (8.3)	0.88 (0.78–1.00)	
<b>Yes</b>	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)	
<b>Atrial fibrillation</b>					0.4538
<b>No</b>	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)	
<b>Yes</b>	Never user	615 (84.3)	115 (15.7)	1.00	
	Users	26 (90.5)	3 (9.5)	0.54 (0.16–1.76)	
<b>Heart failure</b>					0.9723
<b>No</b>	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)	
<b>Yes</b>	Never user	2,506 (81.4)	571 (18.6)	1.00	
	Users	86 (85.6)	15 (14.4)	0.84 (0.50–1.41)	
<b>Dyslipidemia</b>					0.0561
<b>No</b>	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)	
<b>Yes</b>	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)	
<b>Hemorrhagic stroke</b>					0.0130
<b>No</b>	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)	
<b>Yes</b>	Never user	268 (35.2)	493 (64.8)	1.00	
	Users	8 (47.1)	9 (52.9)	3.26 (1.13–9.41)	
<b>Ischemic stroke</b>					0.0686
<b>No</b>	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)	
<b>Yes</b>	Never user	2,060 (80.7)	493 (19.3)	1.00	
	Users	85 (89.6)	9 (9.4)	0.46 (0.24–0.90)	
<b>Depression</b>					0.6512
<b>No</b>	Never user	76,478 (90.3)	8,246 (9.7)	1.00	

Continued

**Table 3** Hazard Ratios for Dementia in Different Subgroups in the Overall Population (*continued*)

Subgroups	Pioglitazone use	Dementia		aHR (95% CI) <sup>a</sup>	p for interaction
		No (n = 81,954)	Yes (n = 9,022)		
	Users	2,851 (91.8)	254 (8.2)	0.85 (0.75–0.96)	
<b>Yes</b>	Never user	2,526 (83.2)	509 (16.8)	1.00	
	Users	100 (87.9)	14 (12.1)	0.75 (0.44–1.28)	

Abbreviations: aHR = adjusted hazard ratio; CCI = Charlson Comorbidity Index; LDL = low-density lipoprotein; sIPTW = stabilized inverse probability of treatment weighting.

<sup>a</sup> 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 cotransporter-2 inhibitors, insulin), BMI, alcohol and smoking habits, and physical activity, and year of type 2 diabetes mellitus onset.

The pathophysiologic 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,<sup>27</sup> blocking the synthesis of proinflammatory cytokines and promoting the differentiation of myeloid cells into an immunosuppressive state.<sup>28</sup> In addition to increasing cerebral glucose utilization,<sup>29</sup> pioglitazone also reduces oxidative stress,<sup>30</sup> blocks the synthesis of A $\beta$  by transcriptional suppression of beta-site amyloid precursor protein cleaving enzyme-1,<sup>31</sup> and regulates the phagocytic clearance of A $\beta$  by microglia.<sup>32</sup> Recent studies have highlighted that defective mitochondrial bioenergetics influences neurodegeneration,<sup>33</sup> and these changes may precede the accumulation of A $\beta$  and tau.<sup>34</sup> Pioglitazone could be beneficial by enhancing adenosine triphosphate production through mitochondria in neurons without augmenting reactive oxygen species (ROS) production.<sup>35</sup> Of interest, 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.<sup>36</sup> 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 on pioglitazone treatment<sup>37</sup> and studies showing that fluid retention or weight gain can be controlled by combining other drugs or reducing the drug dose.<sup>38,39</sup>

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.<sup>11</sup> 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.<sup>12</sup> 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 because it improves the atherogenic lipid profile in patients with DM by upregulating hepatic low-density lipoprotein receptor-related protein 1.<sup>40</sup> In a randomized control study, pioglitazone therapy added to either metformin or sulfonylurea, significantly decreased triglycerides, and increased high-density lipoprotein cholesterol.<sup>41</sup> Reducing ROS production and reducing endothelial dysfunction in both cerebrovascular and neural cells<sup>42</sup> 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.<sup>43</sup> However, a previous clinical trial reported no association with the risk of hemorrhagic stroke in pioglitazone users.<sup>44</sup> Moreover, previous findings that pioglitazone exerted a protective effect against neuronal damage caused by toxic blood degradation products and reduced brain edema after intracerebral hemorrhage may suggest that it could also have a positive role in patients with a history of hemorrhagic stroke.<sup>45</sup> 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.<sup>13</sup> demonstrated that social selection in pioglitazone treatment might influence the results. Therefore, we included socioeconomic status information and other lifestyle variables in our study.<sup>35</sup> However, our study has some limitations that needed to be discussed. Because this was a population-based study using claims data, drug compliance of patients could not be guaranteed, and exposure may have been overestimated. Second, the results should be interpreted carefully, and we cannot infer causality because of 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.<sup>16</sup> 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 mild cognitive impairment 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. Because APOE is a major genetic risk factor for AD and a modifier of the association between hypoglycemic agents and cognitive decline,<sup>47,48</sup> 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.<sup>46</sup> Thus, studies with an independent cohort containing more thorough clinical information should address this issue across the various forms of dementia. Last, we did not pay attention to the potential side effects of pioglitazone,

that is, weight gain and heart failure that could be relevant to dementia risk.<sup>36</sup> Notably, it has been shown that far smaller than usual doses used in DM treatment are effective in reducing A $\beta$  pathology and protecting cognition through low-density lipoprotein receptor-related protein.<sup>40,49</sup> 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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## Appendix Authors

Name	Location	Contribution
<b>Junghee Ha, MD, PhD</b>	Department of Psychiatry, Institute of Behavioral Science in Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
<b>Dong-Woo Choi, PhD</b>	Cancer Big Data Center, National Cancer Control Institute, National Cancer Center, Gyeonggi-do, Republic of Korea	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data

Continued

## Appendix (continued)

Name	Location	Contribution
<b>Kwang Joon Kim, MD, PhD</b>	Division of Geriatrics, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea	Drafting/revision of the manuscript for content, including medical writing for content; and analysis or interpretation of data
<b>Keun You Kim, MD</b>	Department of Psychiatry, Institute of Behavioral Science in Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea; Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul, Republic of Korea	Study concept or design
<b>Chung Mo Nam, PhD</b>	Department of Preventive Medicine (C.M.N.), Yonsei University College of Medicine, Seoul, Republic of Korea	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
<b>Eosu Kim, MD, PhD</b>	Department of Psychiatry, Institute of Behavioral Science in Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea; Graduate School of Medical Science, Brain Korea 21 FOUR Project for Medical Science, Yonsei University College of Medicine, Seoul, Republic of Korea	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; and analysis or interpretation of data

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