RESEARCH ARTICLE

WILEY

# The impact of sodium-glucose co-transporter-2 inhibitors on dementia and cardiovascular events in diabetic patients with atrial fibrillation

Yun-Yu Chen[1,2,3] | Hao-Chih Chang[4,5] | Yenn-Jiang Lin[2,4] | Kuo-Liong Chien[6] | Yu-Cheng Hsieh[1,7] | Fa-Po Chung[2,4] | Ching-Heng Lin[1] | Gregory Y. H. Lip[8,9] | Shih-Ann Chen[1,4,7]

[1]Department of Medical Research, Taichung Veterans General Hospital, Taichung, Taiwan

[2]Heart Rhythm Center, Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan

[3]Department of Post-Baccalaureate Medicine and College of Life Sciences, National Chung Hsing University, Taichung, Taiwan

[4]Faculty of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan

[5]Department of Medicine, Taipei Veterans General Hospital Taoyuan Branch, Taoyuan, Taiwan

[6]Institute of Epidemiology and Preventive Medicine College of Public Health, National Taiwan University, Taipei, Taiwan

[7]Cardiovascular Center, Taichung Veterans General Hospital, Taichung, Taiwan

[8]Liverpool Centre for Cardiovascular Science at University of Liverpool, Liverpool John Moores University and Liverpool Heart & Chest Hospital, Liverpool, UK

[9]Danish Center for Clinical Health Services Research, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

**Correspondence**
Yenn-Jiang Lin, Division of Cardiology, Taipei Veterans General Hospital, 201 Sec. 2, Shih-Pai Road, Taipei, Taiwan.
Email: linyennjiang@gmail.com

## Abstract

**Aims:** The effectiveness of sodium-glucose co-transporter-2 inhibitors (SGLT2i) on incident dementia in patients with diabetes and atrial fibrillation (AF) remains unknown. This study aimed to investigate the association between SGLT2i and the risk of incident dementia in diabetic patients with AF, and to explore the interactions with oral anticoagulants or dipeptidyl peptidase-4 inhibitors (DPP4i).

**Materials and Methods:** We conducted a cohort study using Taiwan's National Health Insurance Research Database. Patients with diabetes and AF without a prior history of established cardiovascular diseases, were identified. Using propensity score matching, 810 patients receiving SGLT2i were matched with 1620 patients not receiving SGLT2i. The primary outcome was incident dementia, and secondary outcomes included composite cardiovascular events and mortality.

**Results:** After up to 5 years of follow-up, SGLT2i use was associated with a significantly lower risk of incident dementia (hazard: 0.71, 95% confidence interval: 0.51–0.98), particularly vascular dementia (HR: 0.44, 95% CI: 0.24–0.82). SGLT2i was related to reduced risks of AF-related hospitalisation (HR: 0.72, 95% CI: 0.56–0.93),

Yenn-Jiang Lin, Gregory Y. H. Lip and Shih-Ann Chen joint senior authors.

Yun-Yu Chen and Hao-Chih Chang contributed equally to this work.

stroke (HR: 0.75, 95% CI: 0.60–0.94), and all-cause death (HR: 0.33, 95% CI: 0.24–0.44). The protective effects were consistent irrespective of the concurrent use of non-vitamin K antagonist oral anticoagulants (NOACs) or DPP4i.

**Conclusions:** In diabetic patients with AF, SGLT2i was associated with reduced risks of incident dementia, AF-related hospitalisation, stroke, and all-cause death. The protective effects were independent of either concurrent use of NOACs or DPP4i.

KEYWORDS
atrial fibrillation, cardiovascular events, dementia, diabetes mellitus, sodium-glucose cotransporter-2 inhibitors

## 1 | INTRODUCTION

Patients with atrial fibrillation (AF) are associated with a higher risk for cognitive decline and progression to dementia.[1–3] The prevalence of AF and dementia will continue to grow with the ageing population, causing a substantial burden to the global health system. Since AF and dementia may have shared risk factors such as diabetes mellitus, AF patients with diabetes have an even greater risk of incident dementia compared to those without diabetes.[4] Although previous studies have suggested a protective effect of oral anticoagulation on cognitive outcomes in patients with AF,[5,6] those considered low risk or do not have a clear indication for anticoagulation remain at risk of cognitive decline. A recently published meta-analysis suggested the beneficial effects of newer glucose-lowering drugs, including sodium-glucose co-transporter-2 inhibitors (SGLT2i) and dipeptidyl peptidase-4 inhibitors (DPP4i), in protecting humans against cognitive decline.[7] Recent observational studies have reported that the uses of SGLT2i are associated with an even lower dementia risk among diabetic patients as compared with DPP4i.[8,9] However, there is limited data on whether SGLT2i reduces new-onset cognitive dysfunction, especially in Asian patients with diabetes.[7,10]

In addition, whether SGLT2i also reduces the risk of new-onset cognitive dysfunction among AF patients with diabetes and whether the benefits of SGLTi2 can be modified by the concurrent use of oral anticoagulants or DPP4i remain unclear. Therefore, this study aimed to investigate the association between SGLT2i and the risks of incident dementia among AF patients with diabetes and also to evaluate its interaction (s) with the use of oral anticoagulants or DPP4i in a nationwide cohort study.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design

We conducted a nationwide population-based cohort study using the data from the National Health Insurance Research Database (NHIRD) in Taiwan, covering more than 99% of the country's population and including demographics, hospital visits, and prescribed medications. This study was approved by the Institutional Review Board (IRB) of

Taipei Veterans General Hospital (IRB number: 2021-09-014BC) and informed consent from participants was not deemed necessary. Additionally, permission has been obtained from the National Health Research Institute and the Health Promotion Administration of the Ministry of Health and Welfare of Taiwan to conduct this research.

### 2.2 | Study population and data source

Patients with AF and diabetes mellitus were identified using the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) codes from the NHIRD in 2016 (Table S1). The validity of ICD codes in the NHIRD in Taiwan has been previously validated.[11,12] To improve the precision of coding, the diagnoses were confirmed only if the patients had at least one hospitalisation or three consecutive outpatient visits.[13,14] Patients aged <55 or >85 years with a history of heart failure, stroke, or myocardial infarction were excluded from analyses (Figure 1). Co-morbidities were also identified using the ICD-10-CM codes. The $CHA_2DS_2$-VASc score, integral for evaluating stroke risk in patients with AF, is calculated based on several key factors including heart failure, hypertension, age, diabetes, history of stroke, vascular diseases, and gender.[15] Additionally, the Charlson comorbidity index (CCI), a widely recognized tool for predicting long-term mortality risk, including a wide range of comorbidities, was identified based on the ICD-10-CM codes.[16] Prescribed medications during 2016–2021 were identified using the Anatomical Therapeutic Chemical (ATC) Classification. To ensure sufficient exposure, it was necessary to prescribe SGLT2i (ATC codes: A10BK01, A10BK03, and A10BA02) for more than 90 days.

### 2.3 | Study endpoints

The primary outcome was incident dementia, defined as a composite of Alzheimer's disease or senile dementia, vascular dementia, or other/mixed dementia. The secondary outcomes were a composite of cardiovascular events, including hospitalizations for AF, stroke, heart failure, myocardial infarction, cardiovascular death, and all-cause death. All the study endpoints were determined by linking to the
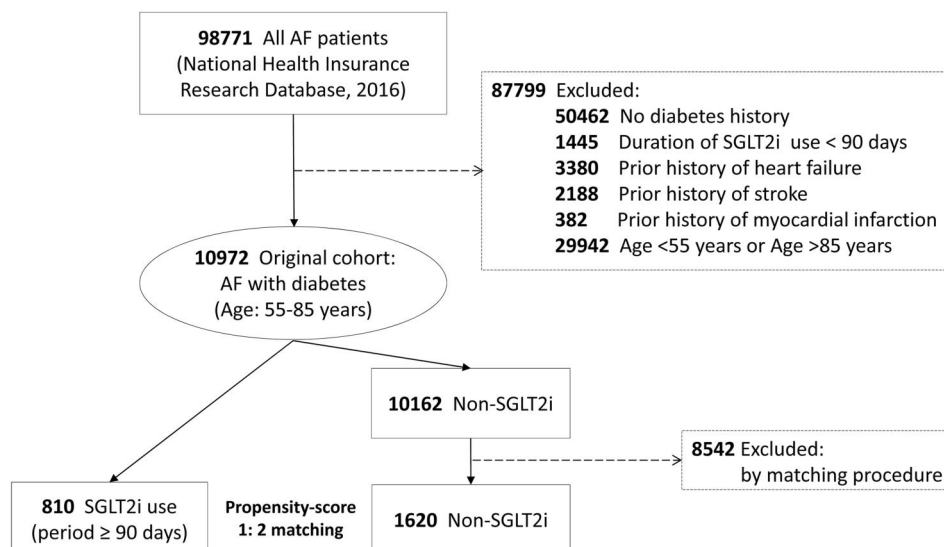
**98771** All AF patients
(National Health Insurance Research Database, 2016)

**87799** Excluded:
**50462** No diabetes history
**1445** Duration of SGLT2i use < 90 days
**3380** Prior history of heart failure
**2188** Prior history of stroke
**382** Prior history of myocardial infarction
**29942** Age <55 years or Age >85 years

**10972** Original cohort:
AF with diabetes
(Age: 55-85 years)

**10162** Non-SGLT2i

**8542** Excluded:
by matching procedure

**810** SGLT2i use
(period ≥ 90 days)

**Propensity-score
1: 2 matching**

**1620** Non-SGLT2i

**FIGURE 1** Flowchart of the study population.

corresponding ICD codes in the NHIRD as defined in Table S1. Death events and the primary cause of death were identified by linking to the National Death Registry. All participants were followed up until the occurrence of the above events or until the administrative censoring date on 31 December 2021.

## 2.4 | Statistical analysis

Continuous and categorical variables were expressed as mean $\pm$ standard deviation (SD) and absolute numbers with proportions, respectively. Comparison between groups was performed using Student's $t$-test for continuous variables and Chi-square test for categorical variables. The details of the methods used for the propensity score (PS) technique and the balance assessment are provided in the Supplementary methods. The main analyses were performed in analogy to the intention to treat principle according to the treatment at baseline regardless of subsequent changes.

Incidence rates were calculated as the number of events per 1000 person-years, along with 95% confidence intervals (CIs). Time-to-event was analysed using the Kaplan-Meier survival analysis, and statistical significance was determined using the log-rank test. The cumulative incidence function (CIF) via the Fine-Grey sub-distribution hazard model was used to estimate the probability of competing events for various sub-type of dementia.[17,18] Hazard ratios (HRs) for the major outcomes were compared using ~~univariable and multivariable effects based on~~ the conditional Cox proportional hazards regression analysis and the Fine and Grey's method of competing risk model to analyse the sub-distribution hazard ratios for events. Subgroup analyses were conducted to evaluate the interaction between SGLT2i and warfarin, non-vitamin K antagonist oral anticoagulants (NOACs), or DPP4i to determine whether the association between SGLT2i and incident dementia or cardiovascular events could be modified by other protective medications. In the

multivariable model of the subgroup analyses, we adjusted for multiple confounders, including age, sex, underlying diseases (hypertension, hyperlipidaemia, hyperuricemia, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, thyroid disease, peripheral vascular disease, sleep apnoea, and rheumatic heart disease), AF ablation status, and medications (anti-arrhythmic drugs, warfarin, NOACs, anti-platelets, insulin, DPP4i, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists, calcium-channel blockers, beta-blockers, and statins).

To further assess the likelihood of residual confounding, falsification analysis was performed by calculating the PS-weighted rates of the study endpoints under a prior null hypothesis that the events of hip fracture[19-21] should be expected not to be associated with the effects of treatment (neutral association).[22] A $p$-value of less than 0.05 was considered statistically significant for all tests. All statistical analyses were conducted using SAS version 9.4 (SAS Institute).

## 3 | RESULTS

### 3.1 | Baseline characteristics

Figure 1 depicts the flow diagram of the study population. Initially, 98,771 diabetic patients with AF were identified from the registry. Table S2 shows the baseline characteristics of the original cohort. After 1:2 PS matching, the study population comprised 810 patients receiving SGLT2i and 1620 patients not receiving SGLT2i (Figure 1, Table 1). The scores of $CHA_2DS_2$-VASc and CCI were comparable between the non-SGLT2i and SGLT2i groups (Table 1). Patients within the group of SGLT2i were less likely to have chronic kidney disease but were more likely to receive AF ablation, NOACs, DPP4i, and other medications such as insulin, angiotensin-converting

**TABLE 1** Baseline characteristics after propensity score (PS) matching.

| Variables | Total cases (N = 2430) | Non-SGLT2i (N = 1620) | SGLT2i (N = 810) | p-value | Balance assessment: Standardized mean difference | |
| --- | --- | --- | --- | --- | --- | --- |
| | | | | | Before PS | After PS |
| Age at baseline (years) | 65.9 ± 6.72 | 65.9 ± 6.72 | 65.9 ± 6.72 | >0.99 | 0.52 | 0.00 |
| Men (n, %) | 1386 (57.0%) | 924 (57.0%) | 462 (57.0%) | >0.99 | 0.17 | 0.00 |
| CHA$_2$DS$_2$-VASc at baseline | 1.85 ± 1.04 | 1.83 ± 1.04 | 1.88 ± 1.04 | 0.34 | 0.06 | 0.04 |
| Charlson comorbidity index (CCI) at base line | 1.58 ± 1.35 | 1.57 ± 1.41 | 1.60 ± 1.22 | 0.58 | 0.04 | 0.02 |
| AF ablation (n, %) | 54 (2.22%) | 22 (1.36%) | 32 (3.95%) | <0.001 | 0.18 | 0.16 |
| Underlying diseases (n, %) | | | | | | |
| Hypertension | 1170 (48.2%) | 773 (47.7%) | 397 (49.0%) | 0.55 | 0.02 | 0.03 |
| Hyperlipidemia | 341 (14.0%) | 218 (13.5%) | 123 (15.2%) | 0.25 | 0.12 | 0.05 |
| Hyperuricemia | 42 (1.73%) | 28 (1.73%) | 14 (1.73%) | >0.99 | 0.00 | 0.00 |
| Chronic kidney disease | 79 (3.25%) | 68 (4.20%) | 11 (1.36%) | <0.001 | 0.21 | 0.17 |
| Chronic liver disease | 20 (0.82%) | 14 (0.86%) | 6 (0.74%) | 0.75 | 0.01 | 0.01 |
| Chronic obstructive pulmonary disease | 85 (3.50%) | 56 (3.46%) | 29 (3.58%) | 0.88 | 0.04 | 0.01 |
| Thyroid disease | 34 (1.40%) | 27 (1.67%) | 7 (0.86%) | 0.11 | 0.05 | 0.07 |
| Peripheral vascular disease | 28 (1.15%) | 22 (1.36%) | 6 (4.05%) | 0.18 | 0.06 | 0.06 |
| Sleep apnoea | 51 (2.10%) | 36 (2.22%) | 15 (1.85%) | 0.55 | 0.00 | 0.03 |
| Rheumatic heart disease | 91 (3.74%) | 65 (4.01%) | 26 (3.21%) | 0.33 | 0.02 | 0.04 |
| Medication uses (n, %) | | | | | | |
| Antiarrhythmic drugs | 849 (34.9%) | 561 (34.6%) | 288 (35.6%) | 0.65 | 0.06 | 0.02 |
| Warfarin | 664 (27.3%) | 430 (26.6%) | 234 (28.9%) | 0.22 | 0.05 | 0.05 |
| Non-vitamin K antagonist oral anticoagulants | 1240 (51.0%) | 723 (44.6%) | 517 (63.8%) | <0.001 | 0.42 | 0.39 |
| Anti-platelets | 1644 (67.7%) | 1089 (67.2%) | 555 (68.5%) | 0.52 | 0.06 | 0.03 |
| Dipeptidyl peptidase 4 inhibitors (DPP4i) | 1484 (61.1%) | 902 (55.7%) | 582 (71.9%) | <0.001 | 0.37 | 0.34 |
| Insulin | 457 (18.8%) | 282 (17.4%) | 175 (21.6%) | 0.013 | 0.03 | 0.11 |
| Angiotensin-converting enzyme inhibitors | 467 (19.2%) | 290 (17.9%) | 177 (21.9%) | 0.020 | 0.13 | 0.09 |
| Angiotensin receptor blockers | 1536 (63.2%) | 979 (60.4%) | 557 (68.8%) | <0.001 | 0.19 | 0.18 |
| Mineralocorticoid receptor antagonists | 549 (22.6%) | 332 (20.5%) | 217 (26.8%) | <0.001 | 0.10 | 0.15 |
| Calcium-channel blockers | 609 (25.1%) | 409 (25.3%) | 200 (24.7%) | 0.77 | 0.02 | 0.01 |
| Beta-blockers | 1454 (59.8%) | 941 (58.1%) | 513 (63.3%) | 0.013 | 0.18 | 0.11 |
| Statins | 1300 (53.5%) | 821 (50.7%) | 479 (59.1%) | <0.001 | 0.06 | 0.02 |

Abbreviations: AF, atrial fibrillation; N, number; PS, propensity score; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists, beta-blockers, or statins (Table 1).

## 3.2 | Incident dementia

For the primary outcome, Kaplan-Meier analyses revealed that the group of SGLT2i had a significantly lower rate of incident dementia compared with the non-SGLT2i group (log-rank test, P = 0.037) (Figure 2A). Patients receiving SGLT2i had a significantly lower risk of incident dementia (HR: 0.71, 95% CI: 0.51–0.98; Table 2) compared with those not receiving SGLT2i. Among the subtypes of incident dementia, patients in the group of SGLT2i had a significantly lower risk of vascular dementia than patients in the group of non-SGLT2i (P = 0.01 by CIF) (Figure 2B). In the Fine-Grey sub-distribution hazard model, patients receiving SGLT2i still had a significantly
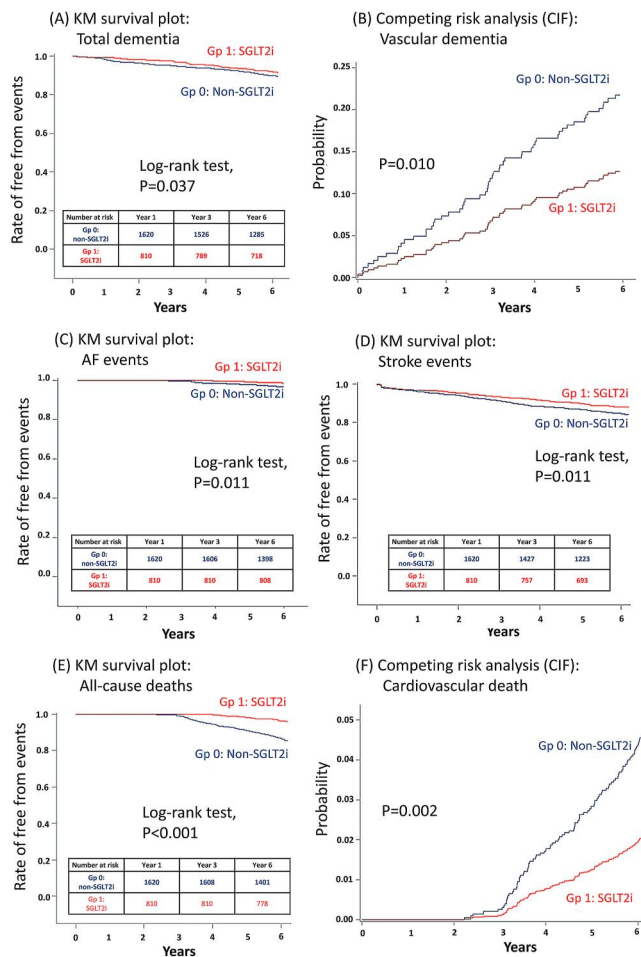
**FIGURE 2** Survival analyses for events of (A) incident dementia, (B) vascular dementia, (C) atrial fibrillation (AF)-related hospitalizations, (D) stroke, (E) all-cause death, and (F) cardiovascular death. CIF, cumulative incidence function.

lower risk for vascular dementia (HR: 0.44, 95% CI: 0.24–0.82) than those not receiving SGLT2i (Table 2). However, the risks for Alzheimer's disease and other/mixed dementia were not statistically different between the two groups, although the point estimates were suggestive of benefit, albeit with a wide 95% confidence interval (Table 2).

## 3.3 | Cardiovascular events

For the results of secondary outcomes, Kaplan-Meier analyses revealed that patients receiving SGLT2i had significantly lower cumulative incidences of AF-related hospitalizations (log-rank test, $P = 0.01$) and stroke (log-rank test, $P = 0.01$) compared with those not receiving SGLT2i (Figure 2C and D). Patients receiving SGLT2i had a significantly lower risk of all-cause death (log-rank test, $P < 0.001$) and cardiovascular death ($P = 0.002$ by CIF) as compared with those not receiving SGLT2i (Figure 2E and F). Patients receiving SGLT2i had a significantly lower risk for AF-related hospitalisation

(HR: 0.72, 95% CI: 0.56–0.93) and stroke (HR: 0.75, 95% CI: 0.60–0.94; Table 2) compared with the group of non-SGLT2i. The risks for all-cause death (HR: 0.33, 95% CI: 0.24–0.44) and cardiovascular death (HR: 0.42, 95% CI: 0.26–0.69) were also significantly lower in the group of SGLT2i than the group of non-SGLT2i. However, the study found no statistically significant differences in the risks of heart failure (HR: 1.07, 95% CI: 0.90–1.27) and myocardial infarction (HR: 0.92, 95% CI: 0.65–1.29) between the two groups (Table 2).

Additional analyses revealed a bidirectional association between stroke and dementia. We found that patients with incident stroke developed during the follow-up period had a significantly higher risk of subsequent development of dementia, as demonstrated in 40 out of 349 patients (5-year cumulative rate: 11.5%) (HR: 11.4, 95% CI: 8.44–15.4, $P < 0.001$, for the risk of incident total dementia; and HR: 3.62, 95% CI: 1.82–7.01, $P < 0.001$, for the risk of vascular dementia). In a reciprocal manner, the incident dementia developed during the follow-up period was also significantly associated with an increased risk of subsequent stroke, noted in 46 out of 118 patients (5-year cumulative rate: 39.0%) (HR: 10.2, 95% CI: 7.82–13.2, $P < 0.001$).

## 3.4 | Subgroup analyses

Table 3 displays the results of the subgroup analyses and interaction results between SGLT2i and warfarin, NOACs, or DPP4i. For incident dementia, we observed a similar benefit of SGLT2i among patients with and without NOACs ($P$ for interaction = 0.21) or DPP4i ($P$ for interaction = 0.12). That is, the protective effects of SGLT2i on incident dementia could be consistently found among diabetic patients with AF irrespective of the underlying use of NOACs/DPP4i or not. However, the benefit of SGLT2i could be primarily observed in patients not receiving warfarin ($P$ for interaction = 0.04). Similar results could also be found in cardiovascular events, such as AF-related hospitalizations and stroke. The protective effects of SGLT2i on all-cause death could be consistently found in the subgroups with or without the underlying use of warfarin, DOACs, or DPP4i (Table 3).

## 3.5 | Falsification analysis

Falsification analysis was conducted using the falsification endpoints of hip fracture in the primary analysis cohort and sub-cohorts of patients receiving warfarin, NOACs, or DPP4i. We compared the number of events, crude and weighted event rates for these outcomes and assessed whether any observed associations aligned with the prior null hypothesis of neutral associations. The use of SGLT2i was not associated with a higher incidence of hip fracture (Table 2). The results of the falsification analysis generally supported the null hypothesis, suggesting a lower likelihood of unaccounted confounding in the treatment-exposure relationship between SGLT2i and hip fracture (Table 2, Table 3, Table S3).

**TABLE 2** Risks of primary and secondary outcomes.

| Events | Total number | 5-year cumulative rate (%) | Incidence rate (per 1000 person-years, 95% CI) | Hazard ratio, 95% CI | p-value |
|---|---|---|---|---|---|
| **Primary outcome** | | | | | |
| Incident dementia[a] | | | | | |
| Non-SGLT2i | 1620 | 180 (11.1%) | 18.1 (15.4–20.7) | 1.0 | Ref. |
| SGLT2i | 810 | 77 (9.51%) | 14.6 (11.4–17.9) | 0.705 (0.506–0.984) | 0.040 |
| Subtypes | | | | | |
| Alzheimer's dementia [b] | | | | | |
| Non-SGLT2i | 1620 | 134 (8.27%) | 13.5 (11.2–15.7) | 1.0 | Ref. |
| SGLT2i | 810 | 60 (7.41%) | 11.4 (8.52–14.3) | 0.939 (0.721–1.222) | 0.64 |
| Vascular dementia [b] | | | | | |
| Non-SGLT2i | 1620 | 30 (1.85%) | 3.01 (1.93–4.09) | 1.0 | Ref. |
| SGLT2i | 810 | 12 (1.48%) | 2.28 (0.99–3.57) | 0.440 (0.235–0.824) | 0.010 |
| Other/mixed dementia [b] | | | | | |
| Non-SGLT2i | 1620 | 30 (1.85%) | 3.01 (1.93–4.09) | 1.0 | Ref. |
| SGLT2i | 810 | 10 (1.23%) | 1.90 (0.73–3.08) | 0.601 (0.296–1.220) | 0.16 |
| **Secondary outcomes** | | | | | |
| AF-related hospitalisation [a] | | | | | |
| Non-SGLT2i | 1620 | 209 (12.9%) | 20.0 (17.3–22.7) | 1.0 | Ref. |
| SGLT2i | 810 | 86 (10.6%) | 15.7 (12.4–19.1) | 0.722 (0.561–0.930) | 0.012 |
| Stroke [a] | | | | | |
| Non-SGLT2i | 1620 | 275 (17.0%) | 28.7 (25.3–32.1) | 1.0 | Ref. |
| SGLT2i | 810 | 109 (13.5%) | 21.4 (17.4–25.5) | 0.750 (0.601–0.937) | 0.011 |
| Heart failure [a] | | | | | |
| Non-SGLT2i | 1620 | 361 (22.3%) | 38.5 (34.5–42.4) | 1.0 | Ref. |
| SGLT2i | 810 | 196 (24.2%) | 41.1 (35.4–46.9) | 1.068 (0.898–1.271) | 0.46 |
| Myocardial infarction [a] | | | | | |
| Non-SGLT2i | 1620 | 95 (5.86%) | 9.07 (7.25–10.9) | 1.0 | Ref. |
| SGLT2i | 810 | 51 (6.30%) | 9.32 (6.77–11.9) | 0.915 (0.651–1.286) | 0.61 |
| All-cause death [a] | | | | | |
| Non-SGLT2i | 1620 | 267 (16.5%) | 25.5 (22.4–28.6) | 1.0 | Ref. |
| SGLT2i | 810 | 47 (5.80%) | 8.59 (6.14–11.0) | 0.326 (0.239–0.444) | <0.001 |
| Cardiovascular death [b] | | | | | |
| Non-SGLT2i | 1620 | 84 (5.19%) | 6.11 (4.61–7.61) | 1.0 | Ref. |
| SGLT2i | 810 | 19 (2.35%) | 2.56 (1.22–3.90) | 0.421 (0.256–0.693) | <0.001 |
| **Falsification endpoints** | | | | | |
| Hip fracture [a] | | | | | |
| Non-SGLT2i | 1620 | 30 (1.85%) | 2.87 (1.84–3.90) | 1.0 | Ref. |
| SGLT2i | 810 | 19 (2.35%) | 3.49 (1.92–5.06) | 1.155 (0.651–2.050) | 0.62 |

Abbreviations: AF, atrial fibrillation; CI, confidence interval; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

[a]Conditional Cox proportional hazard model.

[b]Fine-Grey sub-distribution hazard model.

**TABLE 3** Subgroup analyses by the use of warfarin, non-vitamin K antagonist oral anticoagulants (NOACs), and DPP4i or not.

| | Main analysis | | | | | | | | Falsification analyses | |
| | Incident dementia | | AF-related hospitalisation | | Stroke | | All-cause death | | Hip fracture | |
| Subgroup analyses | Hazard ratio[a], 95% CI | p-value | Hazard ratio[a], 95% CI | p-value | Hazard ratio[a], 95% CI | p-value | Hazard ratio[a], 95% CI | p-value | Hazard ratio[a], 95% CI | p-value |
|---|---|---|---|---|---|---|---|---|---|---|
| Warfarin = 0 | | Interaction: 0.038 | | Interaction: 0.06 | | Interaction: 0.029 | | Interaction: 0.64 | | Interaction: 0.49 |
| SGLT2i | 0.736 (0.524–0.993) | 0.043 | 0.590 (0.431–0.807) | 0.001 | 0.620 (0.471–0.815) | <0.001 | 0.308 (0.209–0.453) | <0.001 | 0.740 (0.380–1.442) | 0.38 |
| Warfarin = 1 | | Interaction: 0.21 | | Interaction: 0.09 | | Interaction: 0.53 | | Interaction: 0.18 | | Interaction: 0.09 |
| SGLT2i | 0.812 (0.479–1.378) | 0.44 | 0.767 (0.502–1.172) | 0.22 | 0.834 (0.560–1.242) | 0.37 | 0.370 (0.214–0.641) | <0.001 | 1.830 (0.604–5.538) | 0.29 |
| NOACs = 0 | | Interaction: 0.12 | | Interaction: 0.09 | | Interaction: 0.18 | | Interaction: 0.18 | | Interaction: 0.11 |
| SGLT2i | 0.727 (0.457–0.989) | 0.038 | 0.484 (0.282–0.832) | 0.009 | 0.591 (0.394–0.889) | 0.012 | 0.251 (0.152–0.413) | <0.001 | 0.294 (0.066–1.303) | 0.11 |
| NOACs = 1 | | Interaction: 0.046 | | Interaction: 0.13 | | Interaction: 0.029 | | Interaction: 0.008 | | Interaction: 0.13 |
| SGLT2i | 0.829 (0.580–0.999) | 0.046 | 0.754 (0.562–1.011) | 0.059 | 0.737 (0.560–0.969) | 0.029 | 0.402 (0.260–0.623) | <0.001 | 1.362 (0.694–2.673) | 0.37 |
| DPP4i = 0 | | Interaction: 0.12 | | Interaction: 0.13 | | Interaction: 0.18 | | Interaction: 0.008 | | Interaction: 0.13 |
| SGLT2i | 0.430 (0.227–0.815) | 0.010 | 0.446 (0.267–0.744) | 0.002 | 0.488 (0.309–0.771) | 0.002 | 0.113 (0.047–0.274) | <0.001 | 0.463 (0.106–2.028) | 0.31 |
| DPP4i = 1 | | Interaction: 0.043 | | Interaction: 0.046 | | Interaction: 0.030 | | Interaction: <0.001 | | Interaction: 0.72 |
| SGLT2i | 0.877 (0.634–0.994) | 0.043 | 0.734 (0.542–0.995) | 0.046 | 0.746 (0.573–0.972) | 0.030 | 0.435 (0.307–0.617) | <0.001 | 1.134 (0.568–2.264) | 0.72 |

Abbreviations: AF, atrial fibrillation; CI, confidence interval; DPP4i, dipeptidyl peptidase 4 inhibitors; NOACs, non-vitamin K antagonist oral anticoagulants; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

[a]SGLT2i group was compared with non-SGLT2i group, and models adjusted for age, sex, underlying diseases (hypertension, hyperlipidaemia, chronic kidney disease, chronic obstructive pulmonary disease, thyroid disease, peripheral vascular disease, sleep apnoea, and rheumatic heart disease), AF ablation status, and medications (anti-arrhythmic drugs, warfarin, non-vitamin K antagonist oral anticoagulants, anti-platelets, insulin, dipeptidyl peptidase 4 inhibitors, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists, calcium-channel blockers, beta-blockers, and statins).

# 4 | DISCUSSION

## 4.1 | Main findings

In this nationwide, population-based cohort study mainly focusing on patients with both diabetes and AF. Our key findings can be summarised as follows: firstly, the use of SGLT2i was associated with a lower risk of developing dementia, particularly vascular dementia, as well as lower risks for AF-related hospitalisation, stroke, cardiovascular death, and all-cause death; Secondly, the protective effects of SGL2i on incident dementia and cardiovascular events could be consistently observed irrespective of the underlying use of NOACs or DPP4i.

## 4.2 | Sodium-glucose co-transporter-2 inhibitor and reduced dementia risk in diabetic patients with atrial fibrillation

Compared with the previous population-based cohort study,[23] our research reported a higher incidence rate of dementia. By primarily enrolling patients with diabetes and AF, our result manifested the fact that diabetic patients with joint AF represented a higher-risk population that deserves further intervention.[1,24] Multifactorial mechanisms underlying the association between AF and cognitive dysfunction have been proposed, either by shared pathophysiology of AF and dementia or mediated through silent or overt cerebral cardioembolism.[2,25–28] As diabetic patients with AF conferred a 45% higher risk for incident dementia as compared with those without diabetes,[4] there was limited data on whether SGLT2i could still be beneficial among this high-risk subpopulation. In previous studies investigating the association between SGLT2i and incident dementia, only less than 10% of the study participants had AF.[8,9] By enrolling all the patients with AF, our study revealed that diabetic patients with AF receiving SGLT2i exhibited a 38.5% lower risk of incident dementia as compared with those not on SGLT2i. The benefit of SGLT2i was the most in reducing vascular dementia. Notably, although the effect sizes were not statistically significant in Alzheimer's disease and other/mixed dementia due to the limited event number, a protective trend of SGLT2i in reducing the risk of Alzheimer's disease and other/mixed dementia could still be observed in our study.

## 4.3 | Sodium-glucose co-transporter-2 inhibitors potential benefits for dementia prevention in diabetic patients with atrial fibrillation on anticoagulant

Among patients with AF, anticoagulation has become the cornerstone treatment for stroke prevention.[29] In a previous PS-matching retrospective cohort study in Sweden, anticoagulation was associated with a 29% lower risk of incident dementia compared to those without anticoagulant treatment in patients with AF.[5] A trend toward more benefits from treatment in patients with higher $CHA_2DS_2$-VASc scores could also be observed. It is plausible that oral anticoagulation may reduce subclinical microemboli and mitigate the risk of cognitive decline. However, inappropriate dosing of anticoagulants could confer a greater risk of dementia in patients with AF.[6] Therefore, whether SGLT2i provides incremental benefits in preventing dementia over anticoagulation among patients with AF becomes much more important. Our study discovered that among patients who already took NOACs, SGLT2i could further mitigate the risks of either stroke or total dementia compared with those not on SGLT2i. In addition, it was noteworthy that there was no statistically significant benefit in reducing stroke and total dementia in those receiving warfarin. However, a protective trend of SGLT2i could still be observed. Our study highlights the need for further investigation of SGLT2i as a potential therapy to prevent dementia in high-risk patients with AF,[30] further randomized controlled trials with pre-specified endpoints will be warranted to evaluate whether to prioritise the use of SGLT2i in this particularly high-risk group.

## 4.4 | Sodium-glucose co-transporter-2 inhibitors multi-faceted benefits: Beyond glycaemic control in dementia prevention

Our study results indicate an association between SGLT2i treatment and a lower incidence of both stroke and dementia. The potential for SGLT2i to mitigate the risks of stroke and dementia may be attributable to a combination of glycaemic and non-glycaemic effects, including improvements in cardiovascular and cerebrovascular function. By reducing the incidence of stroke, SGLT2i may indirectly lower the risk of secondary dementia as cerebrovascular insults are a known risk factor for cognitive decline. Conversely, by maintaining cerebrovascular integrity and possibly through direct neuroprotective mechanisms, SGLT2i may reduce the risk of stroke in patients with preexisting dementia. These findings underscore a complex interplay between cerebrovascular disease and cognitive dysfunction, suggesting a potential role for SGLT2i in disrupting this bidirectional relationship.[31]

Other antidiabetic medications such as metformin, DPP4i, and SGLT2i have been associated with a lower risk of dementia in patients with diabetes.[32–34] Previous literature mainly compared the efficacy between SGLT2i and DPP4i in reducing the risk of incident dementia.[7,8] The superiority of SGLT2i over other antidiabetic agents in reducing incident dementia indicated that the protective effects of SGLT2i could be beyond glycaemic control.[8,9,33,35] The insignificant interaction between SGLT2i and DPP4i shown in our study exhibited the consistent benefits of SGLT2i irrespective of the use of DPP4i or not. Pleomorphic effects of SGLT2i have been proposed in the preclinical studies that can be the plausible mechanisms for mitigating the risks of cognitive decline, including reducing oxidative stress, neuroinflammation, and improving brain mitochondrial function.[36–38] In addition to the protective metabolic pathways in the neurological system, initiation of SGLT2i was also found to be associated with a lower risk of incident or recurrent AF in diabetic patients.[39,40]

Compatible with previous studies, our study also showed that patients receiving SGLT2i were associated with reduced AF events, which can be the possible explanation of the lower risk of subsequent cerebral cardio-embolisation and cognitive impairment.

## 4.5 | Strengths and limitations

Our study benefits from the use of nationwide and population-based databases, allowing for a larger sample size and increased generalisability of key findings. Comprehensive clinical data enabled a thorough investigation of the research question, and rigorous analysis techniques, including competing risk models and falsification analysis, were applied to enhance result validity. However, several limitations should be acknowledged. Despite PS matching and adjustment for multiple confounders, the possibility of residual confounding remains. Unmeasured factors, such as the burden of AF, drug compliance, the severity of comorbidities, lifestyle factors, serum biomarkers, and socioeconomic status, were unavailable in the claimed database. To address this issue, we also performed the inverse probability of treatment-weighted analysis and the falsification analysis. The results showed that there was minimal residual confounding in the non-plausible outcomes.

## 5 | CONCLUSIONS

In conclusion, SGLT2i was associated with a lower risk of developing dementia, with a particular impact on vascular dementia, among AF patients with diabetes. SGLT2i was also associated with reduced risks for AF-related hospitalizations, stroke, cardiovascular death, and all-cause death. Notably, these protective effects on incident dementia remained consistent regardless of whether NOACs or DPP4i were used concurrently. Further prospective randomized controlled trials would be warranted to elucidate the efficacy of SGLT2i in lowering the risk of developing dementia, particularly among diabetic patients with AF.

## AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication: Concept construction: Yun-Yu Chen, Yenn-Jiang Lin; Statistical analysis: Yun-Yu Chen; Writing paper: Yun-Yu Chen, Hao-Chih Chang, Yenn-Jiang Lin, Gregory Y. H. Lip; Paper revision: Yenn-Jiang Lin, Gregory Y. H. Lip, Yu-Cheng Hsieh, Kuo-Liong Chien, Fa-Po Chung, Ching-Heng Lin, and Shih-Ann Chen.

## ETHICS STATEMENT

This study strictly adheres to international and institutional ethical standards in biomedical research. The research protocol was rigorously reviewed and received approval from the IRB of Taipei Veterans General Hospital (IRB number: 2021-09-014BC) in compliance with the Helsinki Declaration. As this study involved the analysis of de-identified data from Taiwan's National Health Insurance database, individual informed consent was deemed unnecessary by the IRB. The NHI database provides a comprehensive, anonymised dataset that ensures patient confidentiality and privacy. All analyses were performed in accordance with relevant guidelines and regulations. We have taken appropriate measures to ensure data security and integrity. This research did not involve direct interaction with human participants or animals, and as such, did not include any procedures that fall under the scope of informed consent or animal welfare regulations. Furthermore, the study adhered to all legal requirements and ethical standards set forth by Taiwanese law for the use of national health data.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

## ORCID

*Yu-Cheng Hsieh* 🄳 https://orcid.org/0000-0001-6218-7139

## PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1002/dmrr.3775.

## REFERENCES

1. de Bruijn RF, Heeringa J, Wolters FJ, et al. Association between atrial fibrillation and dementia in the general population. *JAMA Neurol*. 2015;72(11):1288-1294. https://doi.org/10.1001/jamaneurol.2015.2161

2. Islam MM, Poly TN, Walther BA, et al. Association between atrial fibrillation and dementia: a meta-analysis. *Front Aging Neurosci*. 2019;11:305. https://doi.org/10.3389/fnagi.2019.00305

3. Rivard L, Friberg L, Conen D, et al. Atrial fibrillation and dementia: a report from the AF-SCREEN international collaboration. *Circulation*. 2022;145(5):392-409. https://doi.org/10.1161/circulationaha.121.055018

4. Jiayaspathi A, Chen LY, Selvin E, et al. Relation of diabetes mellitus to incident dementia in patients with atrial fibrillation (from the atherosclerosis risk in communities study). *Am J Cardiol*. 2022;165:51-57. https://doi.org/10.1016/j.amjcard.2021.11.005

5. Friberg L, Rosenqvist M. Less dementia with oral anticoagulation in atrial fibrillation. *Eur Heart J*. 2018;39(6):453-460. https://doi.org/10.1093/eurheartj/ehx579

6. Jacobs V, Woller SC, Stevens S, et al. Time outside of therapeutic range in atrial fibrillation patients is associated with long-term risk of dementia. *Heart Rhythm*. 2014;11(12):2206-2213. https://doi.org/10.1016/j.hrthm.2014.08.013

7. Tang H, Shao H, Shaaban CE, et al. Newer glucose-lowering drugs and risk of dementia: a systematic review and meta-analysis of observational studies. *J Am Geriatr Soc*. 2023;71(7):2096-2106. https://doi.org/10.1111/jgs.18306

8. Mui JV, Zhou J, Lee S, et al. Sodium-glucose cotransporter 2 (SGLT2) inhibitors vs. Dipeptidyl peptidase-4 (DPP4) inhibitors for new-onset dementia: a propensity score-matched population-based study with competing risk analysis. *Front Cardiovasc Med*. 2021;8:747620. https://doi.org/10.3389/fcvm.2021.747620

9. Wu CY, Iskander C, Wang C, et al. Association of sodium-glucose cotransporter 2 inhibitors with time to dementia: a population-based cohort study. *Diabetes Care*. 2023;46:297-304. https://doi.org/10.2337/dc22-1705

10. Low S, Goh KS, Ng TP, et al. Association between use of sodium-glucose Co-Transporter-2 (SGLT2) inhibitors and cognitive function in a longitudinal study of patients with type 2 diabetes. *J Alzheimers Dis*. 2022;87:635-642. https://doi.org/10.3233/jad-215678

11. Hsieh CY, Su CC, Shao SC, et al. Taiwan's national health insurance research database: past and future. *Clin Epidemiol*. 2019;11:349-358. https://doi.org/10.2147/clep.s196293

12. Huang YT, Wei T, Huang YL, Wu YP, Chan KA. Validation of diagnosis codes in healthcare databases in Taiwan, a literature review. *Pharmacoepidemiol Drug Saf*. 2023;32(7):795-811. https://doi.org/10.1002/pds.5608

13. Pan CT, Liao CW, Tsai CH, et al. Influence of different treatment strategies on new-onset atrial fibrillation among patients with primary aldosteronism: a nationwide longitudinal cohort-based study. *J Am Heart Assoc*. 2020;9(5):e013699. https://doi.org/10.1161/jaha.119.013699

14. Yang YH, Chiang HJ, Yip HK, et al. Risk of new-onset atrial fibrillation among Asian chronic hepatitis C virus carriers: a nationwide population-based cohort study. *J Am Heart Assoc*. 2019;8(22):e012914. https://doi.org/10.1161/jaha.119.012914

15. Olesen JB, Torp-Pedersen C, Hansen ML, Lip GY. The value of the CHA2DS2-VASc score for refining stroke risk stratification in patients with atrial fibrillation with a CHADS2 score 0-1: a nationwide cohort study. *Thromb Haemost*. 2012;107(06):1172-1179. https://doi.org/10.1160/th12-03-0175

16. Sundararajan V, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA. New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. *J Clin Epidemiol*. 2004;57(12):1288-1294. https://doi.org/10.1016/j.jclinepi.2004.03.012

17. Austin PC, Lee DS, D'Agostino RB, Fine JP. Developing points-based risk-scoring systems in the presence of competing risks. *Stat Med*. 2016;35(22):4056-4072. https://doi.org/10.1002/sim.6994

18. Noordzij M, Leffondré K, van Stralen KJ, Zoccali C, Dekker FW, Jager KJ. When do we need competing risks methods for survival analysis in nephrology? *Nephrol Dial Transpl*. 2013;28(11):2670-2677. https://doi.org/10.1093/ndt/gft355

19. Hidayat K, Du X, Shi BM. Risk of fracture with dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, or sodium-glucose cotransporter-2 inhibitors in real-world use: systematic review and meta-analysis of observational studies. *Osteoporos Int*. 2019;30(10):1923-1940. https://doi.org/10.1007/s00198-019-04968-x

20. Zhuo M, Hawley CE, Paik JM, et al. Association of sodium-glucose cotransporter-2 inhibitors with fracture risk in older adults with type 2 diabetes. *JAMA Netw Open*. 2021;4(10):e2130762. https://doi.org/10.1001/jamanetworkopen.2021.30762

21. Patil T, Cook M, Hobson J, Kaur A, Lee A. Evaluating the safety of sodium-glucose cotransporter-2 inhibitors in a nationwide veterans health administration observational cohort study. *Am J Cardiol*. 2023;201:281-293. https://doi.org/10.1016/j.amjcard.2023.06.016

22. Lipsitch M, Tchetgen Tchetgen E, Cohen T. Negative controls: a tool for detecting confounding and bias in observational studies. *Epidemiology*. 2010;21(3):383-388. https://doi.org/10.1097/ede.0b013e3181d61eeb

23. Ganguli M, Lee CW, Snitz BE, Hughes TF, McDade E, Chang CC. Rates and risk factors for progression to incident dementia vary by age in a population cohort. *Neurology*. 2015;84(1):72-80. https://doi.org/10.1212/wnl.0000000000001113

24. Alsharif AA, Wei L, Ma T, et al. Prevalence and incidence of dementia in people with diabetes mellitus. *J Alzheimers Dis*. 2020;75(2):607-615. https://doi.org/10.3233/jad-191115

25. Bunch TJ, Weiss JP, Crandall BG, et al. Atrial fibrillation is independently associated with senile, vascular, and Alzheimer's dementia. *Heart Rhythm*. 2010;7(4):433-437. https://doi.org/10.1016/j.hrthm.2009.12.004

26. Dietzel J, Haeusler KG, Endres M. Does atrial fibrillation cause cognitive decline and dementia? *Europace*. 2018;20(3):408-419. https://doi.org/10.1093/europace/eux031

27. Banerjee G, Chan E, Ambler G, et al. Effect of small-vessel disease on cognitive trajectory after atrial fibrillation-related ischaemic stroke or TIA. *J Neurol*. 2019;266(5):1250-1259. https://doi.org/10.1007/s00415-019-09256-6

28. Iadecola C, Duering M, Hachinski V, et al. Vascular cognitive impairment and dementia: JACC scientific expert panel. *J Am Coll Cardiol*. 2019;73(25):3326-3344. https://doi.org/10.1016/j.jacc.2019.04.034

29. Katsanos AH, Kamel H, Healey JS, Hart RG. Stroke prevention in atrial fibrillation: looking forward. *Circulation*. 2020;142(24):2371-2388. https://doi.org/10.1161/circulationaha.120.049768

30. Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycemia in type 2 diabetes, 2022. A consensus report by the American diabetes association (ADA) and the European association for the study of diabetes (EASD). *Diabetes Care*. 2022;45(11):2753-2786. https://doi.org/10.2337/dci22-0034

31. Pawlos A, Broncel M, Woźniak E, Gorzelak-Pabiś P. Neuroprotective effect of SGLT2 inhibitors. *Molecules*. 2021;26(23):7213. https://doi.org/10.3390/molecules26237213

32. Wium-Andersen IK, Osler M, Jørgensen MB, Rungby J, Wium-Andersen MK. Antidiabetic medication and risk of dementia in patients with type 2 diabetes: a nested case-control study. *Eur J Endocrinol*. 2019;181(5):499-507. https://doi.org/10.1530/eje-19-0259

33. Siao WZ, Lin TK, Huang JY, Tsai CF, Jong GP. The association between sodium-glucose cotransporter 2 inhibitors and incident dementia: a nationwide population-based longitudinal cohort study. *Diab Vasc Dis Res*. 2022;19(3):14791641221098168. https://doi.org/10.1177/14791641221098168

34. Orkaby AR, Cho K, Cormack J, Gagnon DR, Driver JA. Metformin vs sulfonylurea use and risk of dementia in US veterans aged ≥65 years

with diabetes. *Neurology*. 2017;89(18):1877-1885. https://doi.org/10.1212/wnl.0000000000004586

35. Rizzo MR, Di Meo I, Polito R, et al. Cognitive impairment and type 2 diabetes mellitus: focus of SGLT2 inhibitors treatment. *Pharmacol Res*. 2022;176:106062. https://doi.org/10.1016/j.phrs.2022.106062

36. Lin B, Koibuchi N, Hasegawa Y, et al. Glycemic control with empagliflozin, a novel selective SGLT2 inhibitor, ameliorates cardiovascular injury and cognitive dysfunction in obese and type 2 diabetic mice. *Cardiovasc Diabetol*. 2014;13(1):148. https://doi.org/10.1186/s12933-014-0148-1

37. Sa-Nguanmoo P, Tanajak P, Kerdphoo S, et al. SGLT2-inhibitor and DPP-4 inhibitor improve brain function via attenuating mitochondrial dysfunction, insulin resistance, inflammation, and apoptosis in HFD-induced obese rats. *Toxicol Appl Pharmacol*. 2017;333:43-50. https://doi.org/10.1016/j.taap.2017.08.005

38. Arab HH, Safar MM, Shahin NN. Targeting ROS-dependent AKT/GSK-3β/NF-κB and DJ-1/Nrf2 pathways by Dapagliflozin attenuates neuronal injury and motor dysfunction in rotenone-induced Parkinson's disease rat model. *ACS Chem Neurosci*. 2021;12(4):689-703. https://doi.org/10.1021/acschemneuro.0c00722

39. Zhuo M, D'Andrea E, Paik JM, et al. Association of sodium-glucose cotransporter-2 inhibitors with incident atrial fibrillation in older adults with type 2 diabetes. *JAMA Netw Open*. 2022;5(10):e2235995. https://doi.org/10.1001/jamanetworkopen.2022.35995

40. Usman MS, Siddiqi TJ, Memon MM, et al. Sodium-glucose co-transporter 2 inhibitors and cardiovascular outcomes: a systematic review and meta-analysis. *Eur J Prev Cardiol*. 2018;25(5):495-502. https://doi.org/10.1177/2047487318755531

## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Chen Y-Y, Chang H-C, Lin Y-J, et al. The impact of sodium-glucose co-transporter-2 inhibitors on dementia and cardiovascular events in diabetic patients with atrial fibrillation. *Diabetes Metab Res Rev*. 2024;e3775. https://doi.org/10.1002/dmrr.3775