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Association of sodium-glucose cotransporter-2 inhibitors with incident atrial fibrillation in older adults with type 2 diabetes

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Abstract

Importance—Sodium-glucose cotransporter-2 inhibitors (SGLT-2i) have demonstrated many cardiovascular and renal benefits for patients with type 2 diabetes (T2D). However, the results of

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Authors' Contributions: Data analysis: MZ and EP; study design, interpretation of the results: all authors. EP has full access to all the data in the study and takes responsibility for its integrity and the data analysis. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

TWEET

Compared to DPP-4i and GLP-1RA, the use of SGLT-2i was associated with a lower risk of atrial fibrillation in older adults with type 2 diabetes.

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Disclosures: ED and JP have nothing to disclose. MZ is a full-time employee of Visterra since May 2022. DW reports serving on Data Monitoring Committees for Novo Nordisk (oral and subcutaneous semaglutide), not directly related to the topic of the submitted work. BE reports consulting income from Eli Lilly & Company, Gilead Sciences, Inc., Johnson and Johnson, Provention Bio, and a research award from Novo Nordisk, not related to the topic of the submitted work. RJG reports grants from Amarin, Kowa, Novartis, and Pfizer outside the submitted work. SK has received research support to the Brigham and Women's Hospital from Pfizer, AbbVie, Roche and Bristol-Myers Squibb for unrelated studies. EP is co-investigator of a research grant to the Brigham and Women's Hospital from Boehringer-Ingelheim, outside the submitted work.

Access to data and data analysis: MZ and EP had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

SGLT-2i use on primary prevention of atrial fibrillation (AF) were inconsistent in clinical trials. Additionally, incident AF was not a pre-specified endpoint.

Objective—To examine the association of incident AF with initiation of an SGLT-2i compared to initiation of a dipeptidyl peptidase 4 inhibitor (DPP-4i) or a glucagon-like peptide 1 receptor agonist (GLP-1RA) amongst older adults (≥66 years of age) with T2D in routine practice.

Design, Setting and Participants—Population-based new-user cohort study including older adults with T2D who had no history of AF and were enrolled in Medicare fee-for-service from April 2013 to December 2018. Data analysis was performed in 2021.

Exposures—To control for potential confounding, new users of SGLT-2i were 1:1 propensity score (PS) matched to new users of DPP-4i or GLP-1RA, in two pairwise comparisons, based on 138 baseline covariates.

Main outcomes and measures—The primary outcome was incident AF, defined as an inpatient diagnosis code for AF. Hazard ratios (HRs) and rate differences (RDs) per 1000 person-years, with their 95% confidence intervals (CIs), were estimated in the PS-matched groups.

Results—A total of 74,868 and 80,475 new users of SGLT-2i were 1:1 PS-matched to new users of DPP-4i or GLP-1RA, respectively. Overall, the mean age of study participants was 72 years and nearly half of them were male. The risk of incident AF was lower in the SGLT-2i group than the matched DPP-4i group [HR, 0.82 (95% CI, 0.76–0.89); RD, −3.7 (95% CI, −5.2 to −2.2) per 1000 person-years] or the matched GLP-1RA group [HR, 0.90 (95% CI, 0.83–0.98); RD, −1.8 (95% CI, −3.2 to −0.3) per 1000 person-years]. Results were consistent across several sensitivity and subgroup analyses.

Conclusions and Relevance—In this cohort study of Medicare beneficiaries with T2D, we found that the initiation of an SGLT-2i was associated with a reduced risk of incident AF compared to a DPP-4i or GLP-1RA. Our results may be helpful when weighing the potential risks and benefits of various glucose-lowering agents in older adults with T2D.

INTRODUCTION

More than 30 million (10%) Americans have type 2 diabetes (T2D), with a higher prevalence—more than one in four—among adults aged 65 years or greater.[1] T2D is associated with a 35% to 60% relative increase in the risk of developing atrial fibrillation (AF) or atrial flutter (collectively referred to as AF).[2–4] Compared with T2D alone, the presence of comorbid T2D and new-onset AF carries a 3.8-fold increased risk for heart failure (HF) and a 2.7-fold increased risk for all-cause mortality.[5] Among patients older than 65 years, 27% of them develop AF in 10 years.[6] Due to the high risk of developing AF, preventing this condition in older patients is an important goal.

Large randomized controlled trials (RCTs) have proven the efficacy of sodium-glucose cotransporter-2 inhibitors (SGLT-2i) in reducing major cardiovascular events (MACE), hospitalization for heart failure (HHF), and kidney disease progression.[7–9] However, the role of SGLT-2i in incident AF remains controversial. In the DECLARE-TIMI 58 trial, compared with placebo, dapagliflozin reduced the incidence of AF by 19% in patients with T2D.[10] However, there was no consistent reduction in incident AF with SGLT-2i in

other RCTs.[7,9,11,12,13] Meta-analyses suggested either no effect or possible protective effects of SGLT-2i against AF.[13–18]However, incident AF was not a pre-specified endpoint and was typically reported as an adverse event in RCTs. This reporting generally depends on investigators identifying events and reporting them in a relatively unstructured way.[19] In addition, incident AF was not a common event in RCTs, further limiting the ability to assess this outcome robustly. Finally, head-to-head trials comparing SGLT-2i with other anti-diabetes drugs were lacking. Thus, we sought to quantify the association of SGLT-2i initiation with incident AF compared to two active comparators in a nationwide cohort of older adults with T2D.

METHODS

Study Design and Data Sources

We conducted a population-based cohort study using Medicare fee-for-service data. Medicare is a federally funded health insurer for eligible individuals primarily aged ≥65 years. We leveraged Medicare claims data from inpatient services (Part A), outpatient services (Part B), and prescription medications (Part D).

The initiators of SGLT-2i were compared to the initiators of dipeptidyl peptidase-4 inhibitors (DPP-4i) or glucagon-like peptide-1 receptor agonists (GLP-1RA) in two pair-wise comparisons. Any of these three anti-diabetes drug classes may have been selected as a second-line treatment for T2D, per clinical guidelines available during the study period.[20,21] This study was approved by the Mass General Brigham Institutional Review Board, and an appropriate data use agreement was in place. Informed consent was not obtained because the study used claims data with anonymous identifiers. Data analysis was performed in 2021. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for observational studies.

Study Population

We identified patients who newly filled a prescription for an SGLT-2i or a comparator between April 1, 2013 (date after the first SGLT-2i approval in the U.S.) and December 31, 2018 (end date for available data). For each pair-wise comparison, the cohort entry date was the date of the first prescription of an SGLT-2i or the specific comparator during the study period. Eligible patients had at least 365 days of continuous Medicare Part A, B, and D enrollment before cohort entry. We excluded patients with prior use of SGLT-2i or the specific comparator in the 365-day baseline period. We restricted the study population to patients with T2D aged ≥ 66 years. Patients with missing demographic information (age, gender, or race) were excluded, because these data may influence outcome. Race data in Medicare are derived from source data from the Social Security Administration and the results of an algorithm that applies to the source data. We also excluded those who had a diagnosis of any of the following during the baseline period: type 1 diabetes, secondary diabetes, malignancy, chronic kidney disease (CKD) stage 5 or dialysis, organ transplant, nursing home admission, prior AF or factors suggestive of AF[22]. Codes for inclusion and exclusion criteria are shown in eTable 1.

Follow-up and Outcomes

Follow-up began on the day after cohort entry and continued in an as-treated scheme until the first occurrence of any of the following: an outcome event, death, switching to a comparator class, discontinuation of index therapy, end of the study period, or end of healthcare or pharmacy enrollment. Medication use was evaluated by prescription refill date and supply. Treatment discontinuation was defined as not refilling a prescription within 60 days after the most recent filled prescription's days supply ran out.

The primary outcome was incident AF, defined as an inpatient diagnosis code for AF (henceforth called "AF hospitalization"), using a previously validated algorithm that has 95% sensitivity and 99% specificity.[23] Secondary outcomes included "AF diagnosis" (based on at least one inpatient or two outpatient diagnosis codes for AF),[24,25] any AF diagnosis code combined with dispensing of any AF medication within 30 days (henceforth "AF treated with medication"),[26] "hospitalization for AF" (defined as AF discharge diagnosis codes in the primary position). Other secondary outcomes included stroke or transient ischemic attack (stroke/TIA), HHF (HF discharge diagnosis codes in the primary position), AF hospitalization censored for HF, and hospitalization for AF and HF (AF and HF discharge diagnosis codes in any position). Codes for outcomes are available in eTable 2.

Statistical Analyses

To account for the non-random allocation of patients to the treatment groups, we used 1:1 propensity score (PS) matching. Propensity scores were calculated using a multivariable logistic regression that modeled the probability of initiating an SGLT-2i versus a comparator as a function of 138 predefined baseline covariates. Covariate selection was based on the best of our knowledge that these covariates were either confounders or risk factors for the outcome. These covariates were assessed during a 365-day period before the cohort entry date and included demographic (such as age, gender, or race), year of cohort entry, comorbid conditions (e.g., CKD, hypertension, or HF), drugs (e.g., anticoagulants or beta blockers), and health care utilization (e.g., electrocardiogram, hospitalization, or cardiologist visit). To further quantify the burden of comorbidities, we calculated a claims-based frailty index[27] and a combined comorbidity score[28]. For each of the two pair-wise comparisons, we created a 1:1 PS-matched cohort using a nearest-neighbor matching without replacement approach within a maximum caliper width of 0.01.[29] We assessed covariate balance among the matched cohorts by using standardized mean differences, with values less than 0.1 suggesting an adequate balance between matched groups.[30]

For all outcomes, in each PS-matched cohort we calculated the incidence rates (IRs) as well as hazard ratios (HRs) using Cox proportional hazards models and rate differences (RDs) using a weighted least-squares regression approach,[31] each with 95% CIs. For the primary outcome, we produced Kaplan-Meier plots of cumulative incidence and compared IRs between treatment groups with log-rank tests.

We performed several pre-specified sensitivity analyses. We changed the grace period and risk period from 60 days to 30 days and from 60 days to 90 days. In addition to the

primary as-treated analysis, we carried the index exposure forward to 365 days without considering treatment discontinuation or switching to mimic an intention-to-treat (ITT) approach. Finally, to assess the presence of potential unmeasured confounding, we evaluated the association of SGLT-2i with the risk for herpes zoster shown previously to be unrelated to this drug.[32]

We also quantified the association of SGLT-2i and AF in several relevant subgroups: (1) age ≤ 70 versus >70 years; (2) female versus male; (3) no history of HF versus a history of HF; (4) no history of atherosclerotic cardiovascular disease (ASCVD) versus a history of ASCVD.

All analyses were performed using Aetion Evidence Platform® (2020) version R4.34, software[33] for real-world data analysis.[34,35]

RESULTS

Study Cohort and Patient Characteristics

A total of 408,294 patients met study criteria for the SGLT-2i versus DPP-4i cohort (82,430 SGLT-2i users and 325,864 DPP-4i users) and 234,530 met criteria for the SGLT-2i versus GLP-1RA cohort (121,371 SGLT-2i users and 113,159 GLP-1RA users) (eFigures 1 and 2). Before PS-matching, patients initiating an SGLT-2i had lower frailty and combined comorbidity scores[28](eTables 3 and 4).

After 1:1 PS-matching (c-statistic of 0.5 for both models), we identified 149,736 patients (74,868 pairs) initiating either an SGLT-2i or DPP-4i and 160,950 patients (80,475 pairs) initiating either an SGLT-2i or GLP-1RA. The mean age was 72 years old and nearly half of them were male (selected list of variables in Table 1). In both matched cohorts, approximately 55% of SGLT-2i patients initiated canagliflozin, followed by empagliflozin (27%) and dapagliflozin (18%). After PS-matching, the median (interquartile range, IQR) duration of follow-up was 191 (90–401) days among SGLT-2i users and 214 (116–438) days among DPP-4i users in the SGLT-2i versus DPP-4i cohort, and 188 (90–395) days among SGLT-2i users and 173 (88–374) days among GLP-1RA users in the SGLT-2i versus GLP-1RA cohort.

Primary Outcome

Reasons for censoring in the matched cohorts are shown in eTable 5. After PS-matching, there were 1,082 AF hospitalization events amongst SGLT-2i users and 1,410 events amongst DPP-4i users in the SGLT-2i versus DPP-4i cohort (IR 16.8 vs 20.5 per 1000 person-years; HR, 0.82 [95% CI, 0.76–0.89]; RD, −3.7 [95% CI, −5.2 to −2.2] per 1000 person-years), and 1,175 events amongst SGLT-2i users and 1,235 events amongst GLP-1RA users in the SGLT-2i versus GLP-1RA cohort (17.0 vs 18.7 per 1000 person-years; HR, 0.90 [95% CI, 0.83–0.98]; RD, −1.8 [95% CI, −3.2 to −0.3] per 1000 person-years), as shown in Table 2.

Kaplan-Meier plots comparing the cumulative incidence of AF over time in the matched groups were shown in Figures 1 and 2.

Sensitivity and Subgroup Analyses

We performed several sensitivity analyses to assess the robustness of our primary study findings, which produced consistent results. The expected null association with SGLT-2i and the risk for herpes zoster was correctly estimated (eTable 6). There was no evidence of effect heterogeneity in the association between SGLT-2i and incident AF by age, gender, history of HF, or history of ASCVD (Figure 3).

Secondary Outcomes

Risks for AF diagnosis, AF treated with medication, and hospitalization for AF were also consistently lower for SGLT-2i users compared to matched DPP-4i users (HR, 0.85 [95% CI, 0.79–0.91]; HR, 0.88 [95% CI, 0.81–0.95]; HR, 0.91 [95% CI, 0.75–1.09], respectively) and GLP-1RA users (HR, 0.87 [95% CI, 0.81–0.94]; HR, 0.85 [95% CI, 0.78–0.92]; HR, 0.73 [95% CI, 0.61–0.87], respectively) (Table 2). SGLT-2i were associated with a lower risk of stroke/TIA (HR, 0.86 [95% CI, 0.77–0.96]), HHF (HR, 0.49 [95% CI, 0.43–0.56]), AF hospitalization censored for HF (HR, 0.86 [95% CI, 0.79–0.93]), and AF + HF (HR, 0.70 [95% CI, 0.62–0.80]) compared to DPP-4i. Compared to GLP-1RA, SGLT-2i were associated with a similar risk of stroke/TIA (HR, 1.01 [95% CI, 0.90–1.14]), a reduced risk of HHF (HR, 0.71 [95% CI, 0.62–0.81]), AF hospitalization censored for HF (HR, 0.92 [95% CI, 0.84–1.00]), and AF + HF (HR, 0.70 [95% CI, 0.62–0.80].

DISCUSSION

In this nationwide cohort study including more than 200,000 routine-care older patients with T2D, after PS-matching, we found that the initiation of SGLT-2i was associated with an 18% reduction in the risk of incident AF compared to DPP-4i and a 10% reduction compared to GLP-1RA. Study findings were robust to a range of predefined sensitivity analyses and did not appear to differ substantially across subgroups. SGLT-2i were associated with a lower risk of stroke/TIA compared to DPP-4i. Patients initiating SGLT-2i also experienced a decreased risk of HHF, AF hospitalization censored for HF, and AF + HF compared to DPP-4i or GLP-1RA initiation.

SGLT-2i have led to a paradigm shift in the management of T2D. However, the effects of SGLT-2i on incident AF in patients with T2D remained unclear from large RCTs,[7,8,11] and meta-analyses suggested either no effect or possible protective effects of SGLT-2i against AF.[13–18] Notably, patients with baseline AF were not excluded from RCTs and AF events were documented as serious adverse events, rather than being a pre-specified endpoint. In addition, patients older than 65 years with multiple co-morbidities, who are the patients at the greatest risk for AF, were not meaningfully represented in these RCTs. Similarly, the association between SGLT-2i use and the risk for AF in routine practice has been primarily evaluated among patients younger than 65 years. In an observational study including patients with T2D in Nordic countries, among 1:3 PS-matched new users (mean age 61 years) of dapagliflozin (n = 10,227) or DPP-4i, dapagliflozin was associated with a similar risk of AF as DPP-4i (HR, 0.92 [95% CI, 0.76–1.12]).[36] A cohort study from Taiwan found that patients with T2D who were prescribed an SGLT-2i (72% aged <60 years) had a similar risk of AF compared with 1:1 PS-matched patients not taking an SGLT-2i.[37] Another cohort

study showed that SGLT-2i (n = 15,606) were associated with a decreased risk of incident AF (HR, 0.61 [95% CI, 0.50–0.73]) compared with PS-weighted DPP-4i users (mean age 60 years).[38] Large population-based studies, which specifically focus on older adults with multiple co-morbidities, are lacking. In order to fill these knowledge gaps, we used a large nationwide sample drawn from 100% U.S. Medicare data, which include health care information on the vast majority of legal U.S. residents aged 65 years and older leading to high precision of the estimates and generalizability. The absolute rate reduction in incident AF we observed among SGLT-2i users in the SGLT-2i vs. DPP-4i cohort corresponds to a number needed to treat[39] for preventing an additional AF event of 435 at six months and 250 at 12 months after treatment initiation. In the SGLT-2i vs GLP-1RA group, the number needed to treat[39] for preventing an additional AF event at six months and 12 months after treatment initiation was 588 and 263, respectively.

Our study has important clinical implications. The latest clinical guidelines for the treatment of T2D recommend SGLT-2i, DPP-4i, and GLP-1RA as second-line therapies, and suggest the choice among these medications should be based on patient-specific characteristics, e.g., history of cardiovascular disease.[40] Notably, T2D affects 27% of U.S. adults aged 65 years or older.[1] T2D *per se* is a risk factor for AF,[3] as is older age, with each decade of advancing age increasing the risk of AF by more than two-fold.[3] All treatments for AF are associated with risk, and a number are also associated with high cost.[41] Therefore, a glucose-lowering medication preventing AF would be advantageous for older adults with T2D. To our knowledge, our study is the first real-world investigation to describe the risk of AF in older patients (mean age 72 years) with T2D who were started on an SGLT-2i. Our results are consistent with a previous study using the Food and Drug Administration adverse event reporting system (FAERS), which supports a protective role of SGLT-2i against the occurrence of AF.[42]

To date, the mechanisms through which SGLT-2i could reduce the risk of AF are still under investigation. In addition to potential AF protection through the reduction in risk of HF and atrial stretch, experimental and clinical data have suggested several explanations. It has been postulated that SGLT-2i reduce electrical and structural remodeling of the atrium,[43–45] as well as attenuate the late sodium current-induced calcium overload and arrhythmogenesis.[46] Furthermore, SGLT-2i improve mitochondrial function,[47] reverse diabetes-induced sodium/hydrogen exchanger hyperactivity and oxidative stress, stimulate adenosine monophosphate-activated protein kinase activation, and enhance myocardial energetics.[46,48,49] Lastly, SGLT-2i ameliorate many risk factors associated with AF development, such as obesity, hypertension, and hyperglycemia.[16] Further research is needed to better elucidate the mechanisms of protection against incident AF associated with SGLT-2i.

Our study has limitations. First, residual confounding by unmeasured factors cannot be ruled out. For example, socioeconomic status might affect the choice of diabetes treatments due to the Medicare reimbursement system,[50,51] and lower socioeconomic status is associated with higher risk of AF.[52] Despite extensive through propensity score adjustment for many measured confounders and confounder proxies, including previous use of generic and brand medications, it is possible that residual imbalances in socioeconomic status across treatment groups may still exist. Our Medicare dataset lacked laboratory results, which

limited our ability to match for baseline glucose control and renal function. However, a previous study has suggested PS-matching on claims-based data could achieve balance in unmeasured characteristics, such as hemoglobin A1c.[53] In addition, along with the changing guidelines, patients with HF were more likely to receive SGLT-2i in more recent years.[54,55] Although our PS model included the year of cohort entry, cardiac and renal comorbidities, we do not have data on ejection fraction or New York Heart Association (NYHA) functional class. Such potential residual imbalances in HF severity, however, would have disfavored SGLT-2i, resulting in conservative estimates. Second, we chose two commonly used second-line novel antidiabetic drug classes, DPP-4i and GLP-1RA, as active comparators. However, the association between DPP-4i or GLP-1RA and the risk of incident AF remains inconclusive.[18,56–59] Beyond anti-metabolic effects, GLP-1RA might prevent AF through anti-inflammatory effect, inhibition of vascular smooth muscle cell proliferation, and reducing cardiovascular events.[60–62] However, GLP-1RA may have a direct effect at the sinus node, increase heart rate, and raise the possibility of an increased risk of AF.[63] Third, our study had a median follow-up time of less than one year. The long-term effect of SGLT-2i use on AF remains undetermined. Nevertheless, the large size of our study population allowed us to generate results with high precision despite the relatively short follow-up duration compared to RCTs. Fourth, the magnitude of the observed absolute risk reduction in AF associated with SGLT-2i was not large. Health care professionals need to consider the absolute effect when making comparative therapeutic decisions. Finally, our findings may not be generalizable to younger adults with T2D.

CONCLUSION

In this large population-based cohort including more than 200,000 PS-matched older adults with T2D, initiating treatment with SGLT-2i, as compared with DPP-4i and GLP-1RA, was associated with an 18% and 10% reduction in the risk of incident AF, respectively. Our data suggest the initiation of SGLT-2i may be beneficial in older adults with T2D who are at risk of AF in clinical practice. Besides proven cardiovascular and renal benefits, the potential prevention of SGLT-2i in incident AF among older adults with T2D might be considered.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key points

- **Question:** Do sodium-glucose cotransporter-2 inhibitors (SGLT-2i) reduce the risk of atrial fibrillation (AF) in older patients with type 2 diabetes (T2D)?
- **Findings:** In this nationwide cohort study, we assessed the risk of AF among Medicare beneficiaries with T2D. After propensity score matching, the initiation of SGLT-2i was associated with an 18% and 10% decrease in the risk of AF compared with dipeptidyl peptidase 4 inhibitor (DPP-4i) or glucagon-like peptide 1 receptor agonist (GLP-1RA), respectively.
- **Meaning:** The use of SGLT-2i was associated with a reduced risk of AF in older adults with type 2 diabetes.

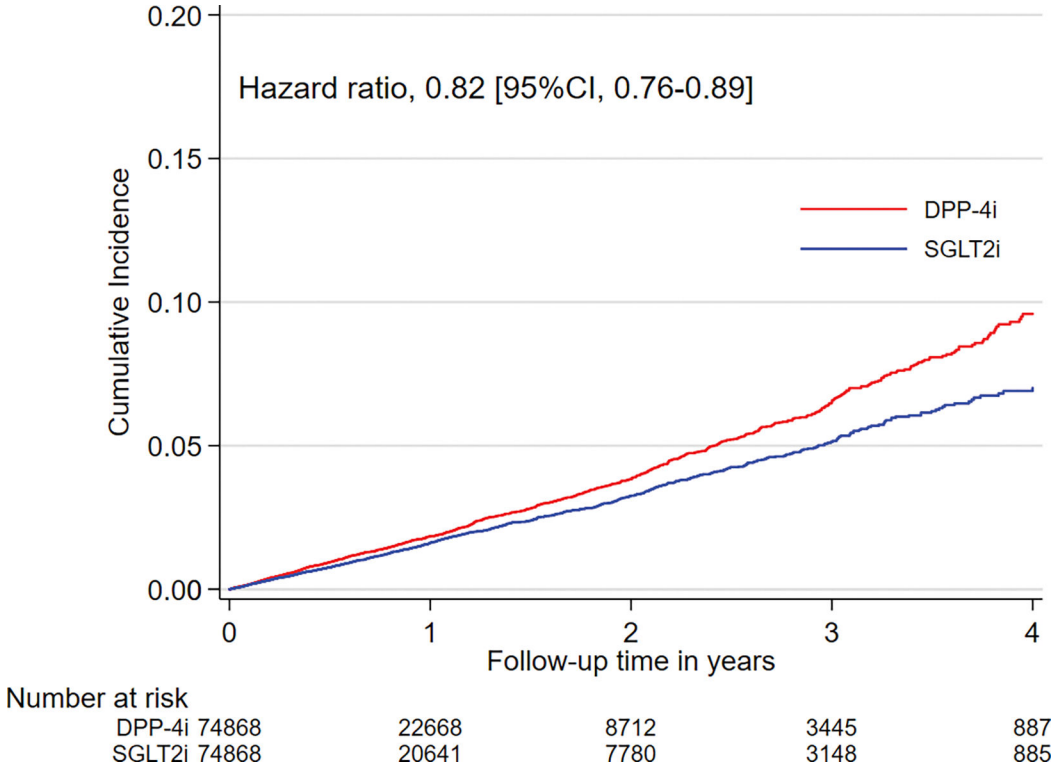

Figure 1. Kaplan-Meier plots for cumulative incidence of AF in propensity score matched SGLT-2i versus DPP-4i cohort.

Abbreviations: AF, atrial fibrillation; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; DPP-4i, dipeptidyl peptidase-4 inhibitors; CI, confidence interval. The graphs were truncated at four years of follow-up.

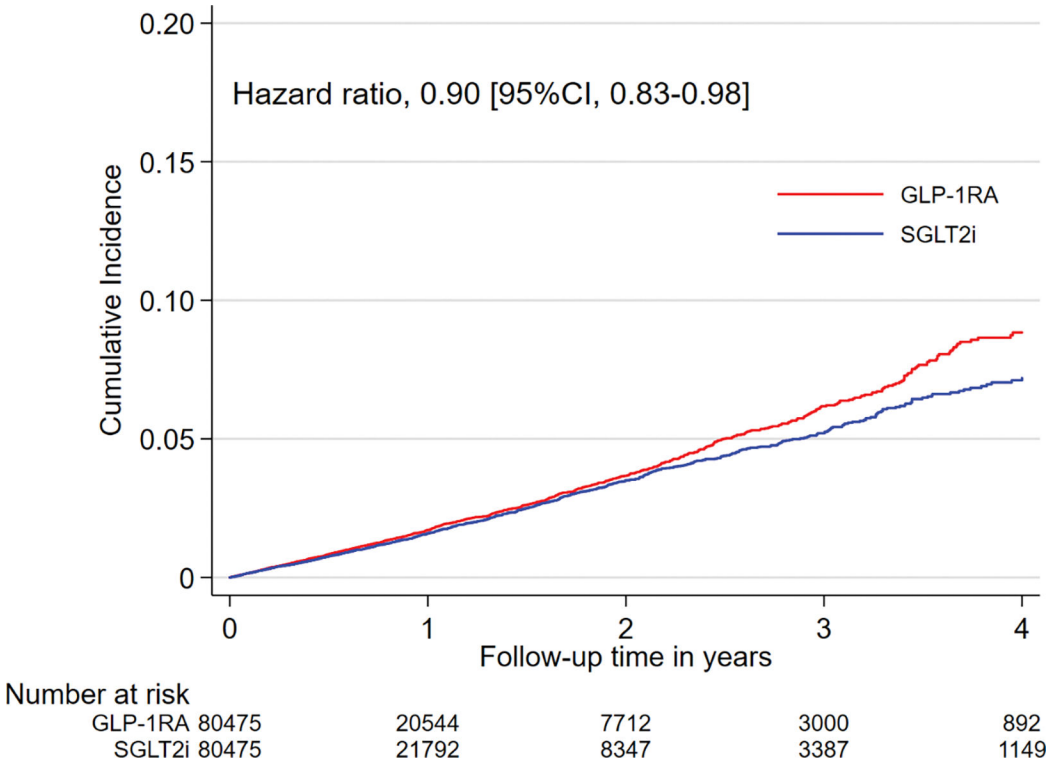

Figure 2. Kaplan-Meier plots for cumulative incidence of AF in propensity score matched SGLT-2i versus GLP-1RA cohort.

Abbreviations: AF, atrial fibrillation; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; GLP-1RA, glucagon-like peptide-1 receptor agonist; CI, confidence interval. The graphs were truncated at four years of follow-up.

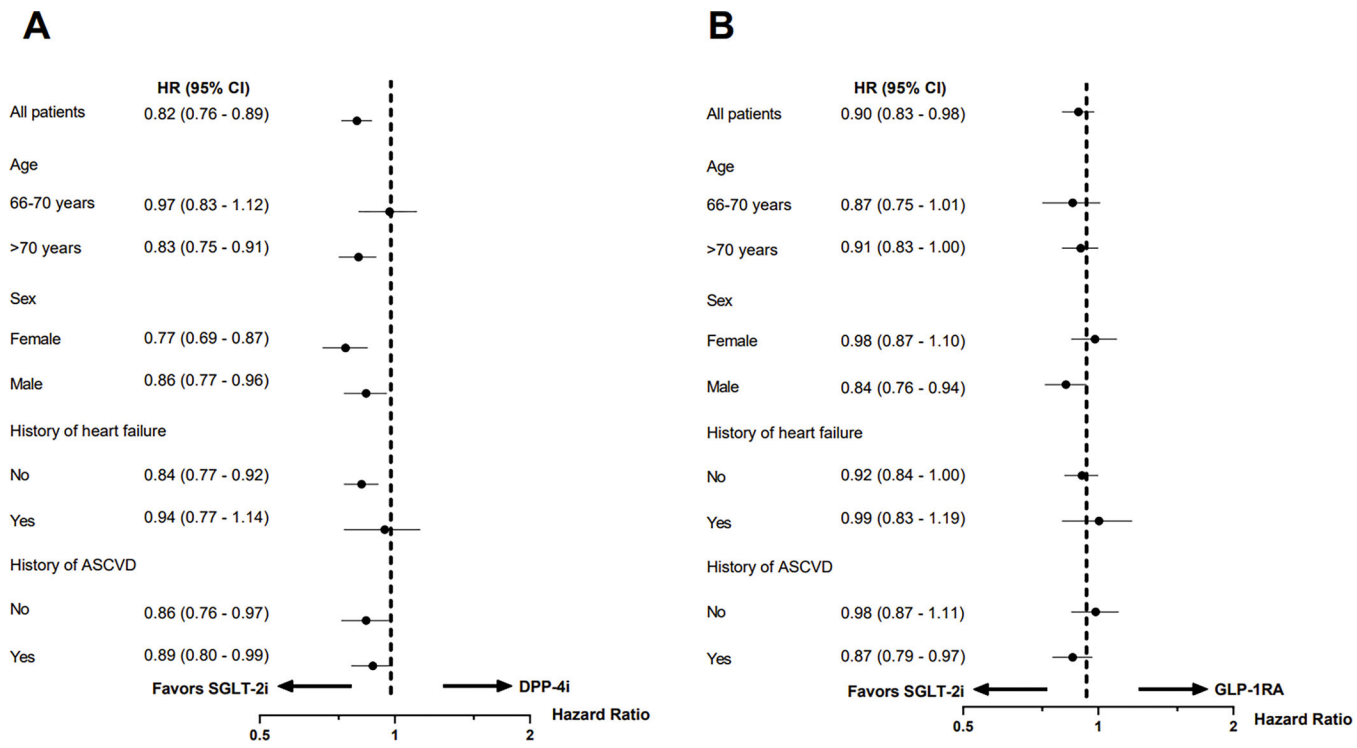

Figure 3. Subgroup analyses for incident AF in matched SGLT-2i versus DPP-4i cohort (A) and SGLT-2i versus GLP-1RA cohort (B).

Abbreviations: AF, atrial fibrillation; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; CI, confidence interval; ASCVD, atherosclerotic cardiovascular disease.

Table 1.

Selected baseline characteristics of SGLT-2i versus DPP-4i and SGLT-2i versus GLP-1RA cohorts after 1:1 propensity score matching.

Characteristics	SGLT-2i versus DPP-4i (n=74,868 pairs)			SGLT-2i versus GLP-1RA (n=80,475 pairs)		
	SGLT-2i Patients, No. (%)	DPP-4i Patients, No. (%)	St. D	SGLT-2i Patients, No. (%)	GLP-1RA Patients, No. (%)	St. D
Age, mean (SD), years	71.8 (5.0)	71.7 (5.1)	0.02	71.8 (5.1)	71.8 (5.1)	0.00
Male	36,302 (48.5)	36,398 (48.6)	0.00	35,977 (44.7)	36,025 (44.8)	0.00
Race						
Black	5,904 (7.9)	5,985 (8.0)	0.00	6,581 (8.2)	6,616 (8.2)	0.00
White	61,904 (82.7)	61,794 (82.5)	0.01	66,883 (83.1)	66,583 (82.7)	0.01
Other[a]	7,060 (9.4)	7,089 (9.5)	0.00	7,011 (8.7)	7,276 (9.0)	−0.01
Diabetes-related comorbidities						
Diabetic nephropathy	8,293 (11.1)	8,333 (11.1)	0.00	10,960 (13.6)	11,044 (13.7)	0.00
Diabetic neuropathy	18,495 (24.7)	18,420 (24.6)	0.00	21,951 (27.3)	21,972 (27.3)	0.00
Diabetic retinopathy	9,930 (13.3)	9,816 (13.1)	0.01	11,586 (14.4)	11,656 (14.5)	0.00
Hyperglycemia	25,879 (34.6)	26,023 (34.8)	−0.01	30,568 (38.0)	30,289 (37.6)	0.01
Hypoglycemia	6,251 (8.3)	6,126 (8.2)	0.00	7,230 (9.0)	7,212 (9.0)	0.00
Other comorbid conditions						
Hyperthyroidism	778 (1.0)	803 (1.1)	−0.01	905 (1.1)	916 (1.1)	0.00
Chronic kidney disease stages 3–4	5,896 (7.9)	5,763 (7.7)	0.01	8,636 (10.7)	8,780 (10.9)	−0.01
Hypertension	68,604 (91.6)	68,639 (91.7)	0.00	74,383 (92.4)	74,397 (92.4)	0.00
Coronary atherosclerosis	21,324 (28.5)	21,302 (28.5)	0.00	22,927 (28.5)	22,827 (28.4)	0.00
Cardiac conduction disorders[b]	3,157 (4.2)	3,173 (4.2)	0.00	3,494 (4.3)	3,537 (4.4)	0.00
Other cardiac dysrhythmia[c]	7,227 (9.7)	7,229 (9.7)	0.00	7,904 (9.8)	7,887 (9.8)	0.00
Cardiomyopathy	1,764 (2.4)	1,732 (2.3)	0.01	1,943 (2.4)	1,922 (2.4)	0.00
Congestive heart failure	5,907 (7.9)	5,865 (7.8)	0.00	6,883 (8.6)	6,864 (8.5)	0.00
Valve disorders	7,508 (10.0)	7,449 (9.9)	0.00	8,240 (10.2)	8,240 (10.2)	0.00
Other cardiovascular disease[d]	8,292 (11.1)	8,237 (11.0)	0.00	9,262 (11.5)	9,295 (11.6)	0.00
Transient ischemic attack	1,710 (2.3)	1,689 (2.3)	0.00	1,928 (2.4)	1,917 (2.4)	0.00

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Characteristics	SGLT-2i versus DPP-4i (n=74,868 pairs)			SGLT-2i versus GLP-1RA (n=80,475 pairs)		
	SGLT-2i Patients, No. (%)	DPP-4i Patients, No. (%)	St. D	SGLT-2i Patients, No. (%)	GLP-1RA Patients, No. (%)	St. D
Ischemic stroke	7,730 (10.3)	7,758 (10.4)	0.00	8,509 (10.6)	8,496 (10.6)	0.00
Peripheral artery disease	8,505 (11.4)	8,531 (11.4)	0.00	9,841 (12.2)	9,853 (12.2)	0.00
Alcohol abuse or dependence	860 (1.1)	854 (1.1)	0.00	832 (1.0)	815 (1.0)	0.00
Overweight	6,133 (8.2)	6,311 (8.4)	0.00	6,522 (8.1)	6,483 (8.1)	0.00
Obesity	24,452 (32.7)	24,383 (32.6)	0.00	29,408 (36.5)	29,319 (36.4)	0.00
Claims-based frailty index						
Non-frail	25,196 (33.7)	25,506 (34.1)	−0.01	23,802 (29.6)	23,779 (29.5)	0.00
Pre-frail	43,438 (58.0)	43,094 (57.6)	0.01	48,716 (60.5)	48,669 (60.5)	0.00
Frail	6,234 (8.3)	6,268 (8.4)	0.00	7,957 (9.9)	8,027 (10.0)	0.00
Combined comorbidity index (CCI), mean (SD)	1.0 (1.8)	1.0 (1.8)	0.00	1.2 (1.9)	1.2 (1.9)	0.00
Use of diabetes drugs						
Metformin	59,258 (79.1)	59,503 (79.5)	−0.01	61,810 (76.8)	61,816 (76.8)	0.00
Sulfonylureas	34,628 (46.3)	34,814 (46.5)	0.00	39,270 (48.8)	39,280 (48.8)	0.00
Insulin	20,174 (26.9)	20,112 (26.9)	0.00	25,194 (31.3)	25,180 (31.3)	0.00
GLP-1RA	8,686 (11.6)	8,114 (10.8)	0.03			
DPP-4i				29,216 (36.3)	29,545 (36.7)	−0.01
Number of antidiabetic medications at index date, mean (SD)	2.3 (0.9)	2.3 (0.8)	0.00	2.5 (1.0)	2.5 (1.0)	0.00
Other drugs						
Antiarrhythmics	91 (0.1)	96 (0.1)	0.00	97 (0.1)	106 (0.1)	0.00
Anticoagulants	796 (1.1)	802 (1.1)	0.00	879 (1.1)	875 (1.1)	0.00
Angiotensin converting enzyme inhibitors	34,519 (46.1)	34,580 (46.2)	0.00	37,156 (46.2)	37,080 (46.1)	0.00
Angiotensin II receptor blockers	26,959 (36.0)	26,801 (35.8)	0.00	30,279 (37.6)	30,455 (37.8)	0.00
Beta blockers	31,674 (42.3)	31,645 (42.3)	0.00	35,054 (43.6)	34,988 (43.5)	0.00
Calcium channel blockers	24,164 (32.3)	23,959 (32.0)	0.01	26,754 (33.2)	26,710 (33.2)	0.00
Antiplatelet agents	9,711 (13.0)	9,777 (13.1)	0.00	10,632 (13.2)	10,646 (13.2)	0.00
Statins	57,809 (77.2)	57,683 (77.0)	0.00	63,174 (78.5)	63,169 (78.5)	0.00
Number of total medications, mean (SD)	12.6 (5.7)	12.6 (5.8)	0.00	13.6 (6.1)	13.6 (5.8)	0.00
Health care utilization						

Characteristics	SGLT-2i versus DPP-4i (n=74,868 pairs)			SGLT-2i versus GLP-1RA (n=80,475 pairs)		
	SGLT-2i Patients, No. (%)	DPP-4i Patients, No. (%)	St. D	SGLT-2i Patients, No. (%)	GLP-1RA Patients, No. (%)	St. D
Electrocardiogram	33,390 (44.6)	33,344 (44.5)	0.00	36,342 (45.2)	36,337 (45.2)	0.00
Cardiac imaging	17,791 (23.8)	17,702 (23.6)	0.00	19,578 (24.3)	19,620 (24.4)	0.00
HbA1c test order	72,440 (96.8)	72,426 (96.7)	0.01	78,054 (97.0)	78,042 (97.0)	0.00
Metabolic panel test	71,881 (96.0)	71,923 (96.1)	−0.01	77,204 (95.9)	77,246 (96.0)	−0.01
Emergency department visit	18,739 (25.0)	18,740 (25.0)	0.00	21,157 (26.3)	21,214 (26.4)	0.00
Hospitalization	7,113 (9.5)	7,148 (9.5)	0.00	7,880 (9.8)	7,888 (9.8)	0.00
Internal medicine visit	66,533 (88.9)	66,620 (89.0)	0.00	71,508 (88.9)	71,537 (88.9)	0.00
Cardiologist visit	29,731 (39.7)	29,597 (39.5)	0.00	32,550 (40.4)	32,512 (40.4)	0.00
Endocrinologist visit	13,832 (18.5)	13,600 (18.2)	0.01	17,389 (21.6)	17,450 (21.7)	0.00
Nephrologist visit	2,927 (3.9)	2,958 (4.0)	−0.01	4,199 (5.2)	4,376 (5.4)	−0.01
Number of office visits, mean (SD)	10.3 (7.1)	10.3 (7.3)	0.00	11.0 (7.5)	11.0 (7.4)	0.00

Values are numbers (percentages) unless stated otherwise.

Abbreviations: SGLT-2i, sodium-glucose cotransporter-2 inhibitors; DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1RA, glucagon-like peptide-1 receptor agonist; St. D, standardized difference; SD, standard deviation; HbA1c, hemoglobin A1c

[a]Other: Asian, North American Native, Hispanic, and other (plus an unknown category).

[b]Cardiac conduction disorders: atrioventricular block, left bundle branch block, right bundle branch block, et al.

[c]Other cardiac arrhythmia: ventricular tachycardia, premature beats, et al.

[d]Other cardiovascular disease: rheumatic heart disease, pericarditis, myocarditis, et al.

Table 2.

Number of events, incidence rate, hazard ratios, and rate differences for primary and secondary outcomes in 1:1 propensity score matched initiators of SGLT-2i versus DPP-4i or GLP-1RA.

Outcomes	**SGLT-2i**	**DPP-4i**	**SGLT-2i vs DPP-4i (n=74,868 pairs)**		**SGLT-2i**	**GLP-1RA**	**SGLT-2i vs GLP-1RA (n=80,475 pairs)**	
Primary Outcome	**N events (IR)**	**N events (IR)**	**HR (95% CI)**	**RD (95% CI)**	**N events (IR)**	**N events (IR)**	**HR (95% CI)**	**RD (95% CI)**
AF hospitalization	1,082 (16.8)	1,410 (20.5)	0.82 (0.76, 0.89)	−3.7 (−5.2 to −2.2)	1,175 (17.0)	1,235 (18.7)	0.90 (0.83, 0.98)	−1.8 (−3.2 to −0.3)
Secondary Outcomes								
AF diagnosis	1,354 (21.1)	1,707 (24.9)	0.85 (0.79, 0.91)	−3.8 (−5.5 to −2.2)	1,438 (20.8)	1,562 (23.8)	0.87 (0.81, 0.94)	−3.0 (−4.6 to −1.4)
AF treated with medication	1,098 (17.1)	1,339 (19.5)	0.88 (0.81, 0.95)	−2.4 (−3.9 to −1.0)	1,143 (16.5)	1,281 (19.5)	0.85 (0.78, 0.92)	−3.0 (−4.4 to −1.5)
Hospitalization for AF	212 (3.3)	251 (3.6)	0.91 (0.75, 1.09)	−0.4 (−1.0 to 0.3)	211 (3.0)	275 (4.1)	0.73 (0.61, 0.87)	−1.3 (−1.9 to −0.8)
Stroke or transient ischemic attack (stroke/ TIA)	536 (8.3)	662 (9.5)	0.86 (0.77, 0.96)	−1.3 (−2.3 to −0.3)	587 (8.4)	552 (8.3)	1.01 (0.90, 1.14)	0.1 (0.9 to 1.1)
Hospitalization for heart failure (HHF)	312 (4.8)	684 (9.9)	0.49 (0.43, 0.56)	−5.1 (−6.0 to −4.1)	388 (5.6)	519 (7.8)	0.71 (0.62, 0.81)	−2.3 (−3.1 to −1.4)
AF hospitalization censored for HF hospitalization	988 (13.2)	1,215 (16.2)	0.86 (0.79, 0.93)	−2.6 (−4.0 to −1.2)	1,089 (13.5)	1,122 (13.9)	0.92 (0.84, 1.00)	−3.1 (−4.2 to −2.0)
Hospitalization for AF and heart failure (AF + HF)	376 (5.8)	574 (8.3)	0.70 (0.62, 0.80)	−2.5 (−3.4 to −1.6)	464 (6.7)	525 (7.9)	0.92 (0.83, 1.01)	−1.3 (−2.2 to −0.4)

Abbreviations: SGLT-2i, sodium-glucose cotransporter-2 inhibitors; DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1RA, glucagon-like peptide-1 receptor agonist; N events, number of events; IR, incidence rate in 1000 patient years; HR, hazard ratio; CI, confidence interval; RD, rate difference in 1000 patient years; AF, atrial fibrillation; HF, heart failure.