Korean Circ J. 2024 May;54(5):256-267
https://doi.org/10.4070/kcj.2023.0234
pISSN 1738-5520·eISSN 1738-5555

kcj
Korean Circulation Journal

Original Research

Check for updates

Lower Atrial Fibrillation Risk With Sodium-Glucose Cotransporter 2 Inhibitors Than With Dipeptidyl Peptidase-4 Inhibitors in Individuals With Type 2 Diabetes: A Nationwide Cohort Study

Min Kim, MD[1,*], Kyoung Hwa Ha, PhD[2,*], Junyoung Lee, MD[1], Sangshin Park, MD[1], Kyeong Seok Oh, MD[1], Dae-Hwan Bae, MD[1], Ju Hee Lee, MD, PhD[1], Sang Min Kim, MD, PhD[1], Woong Gil Choi, MD, PhD[1], Kyung-Kuk Hwang, MD, PhD[1,3], Dong-Woon Kim, MD, PhD[1,3], Myeong-Chan Cho, MD, PhD[1,3], Dae Jung Kim, MD, MS[2], and Jang-Whan Bae, MD, PhD[1,3]

[1]Department of Cardiology, Chungbuk National University Hospital, Cheongju, Korea
[2]Department of Endocrinology and Metabolism, Ajou University School of Medicine, Suwon, Korea
[3]Department of Cardiology, Chungbuk National University College of Medicine, Cheongju, Korea

OPEN ACCESS

Received: Aug 21, 2023
Revised: Jan 22, 2024
Accepted: Feb 13, 2024
Published online: Mar 13, 2024

Correspondence to
Dae Jung Kim, MD, MS
Department of Endocrinology and Metabolism, Ajou University School of Medicine, 164, World Cup-ro, Yeongtong-gu, Suwon 16499, Korea.
Email: djkim@ajou.ac.kr

Jang-Whan Bae, MD, PhD
Department of Cardiology, Chungbuk National University College of Medicine, 1, Chungdae-ro, Seowon-gu, Cheongju 28644, Korea.
Email: drcorazon@hanmail.net

*Min Kim and Kyoung Hwa Ha equally contributed to this work.

ORCID iDs
Min Kim
https://orcid.org/0000-0002-8132-9873
Kyoung Hwa Ha
https://orcid.org/0000-0002-3408-7568
Junyoung Lee
https://orcid.org/0009-0003-9428-3362
Sangshin Park
https://orcid.org/0000-0002-0990-3682

AUTHOR'S SUMMARY

Limited data are available on whether sodium-glucose cotransporter 2 inhibitors reduce the risk of atrial fibrillation (AF) in individuals with type 2 diabetes. In this study, individuals treated with sodium-glucose cotransporter 2 inhibitors had a lower likelihood of developing AF compared to those treated with dipeptidyl peptidase-4 inhibitors, across various subgroups. These results provide important clues for prevention of this common arrhythmia in individuals with type 2 diabetes.

ABSTRACT

Background and Objectives: Accumulating evidence shows that sodium-glucose cotransporter 2 inhibitors (SGLT2is) reduce adverse cardiovascular outcomes. However, whether SGLT2i, compared with other antidiabetic drugs, reduce the new development of atrial fibrillation (AF) is unclear. In this study, we compared SGLT2i with dipeptidyl peptidase-4 inhibitors (DPP-4is) in terms of reduction in the risk of AF in individuals with type 2 diabetes.
Methods: We included 42,786 propensity score-matched pairs of SGLT2i and DPP-4i users without previous AF diagnosis using the Korean National Health Insurance Service database between May 1, 2016, and December 31, 2018.
Results: During a median follow-up of 1.3 years, SGLT2i users had a lower incidence of AF than DPP-4i users (1.95 vs. 2.65 per 1,000 person-years; hazard ratio [HR], 0.73; 95% confidence interval [CI], 0.55–0.97; p=0.028]). In individuals without heart failure, SGLT2i users was associated with a decreased risk of AF incidence (HR, 0.70; 95% CI, 0.52–0.94;

kcj
Korean Circulation Journal

Kyeong Seok Oh
https://orcid.org/0000-0002-1638-4470
Dae-Hwan Bae
https://orcid.org/0000-0002-4464-8613
Ju Hee Lee
https://orcid.org/0000-0002-0858-0973
Sang Min Kim
https://orcid.org/0000-0002-1300-6079
Woong Gil Choi
https://orcid.org/0000-0002-2235-8041
Kyung-Kuk Hwang
https://orcid.org/0000-0003-3464-3023
Dong-Woon Kim
https://orcid.org/0000-0002-1988-2002
Myeong-Chan Cho
https://orcid.org/0000-0002-0047-0227
Dae Jung Kim
https://orcid.org/0000-0003-1025-2044
Jang-Whan Bae
https://orcid.org/0000-0003-1362-9804

Funding
This work was supported by a 2022 research grant from Chungbuk National University Hospital.

Conflict of Interest
The authors have no financial conflicts of interest.

Data Sharing Statement
All data created and/or used during this study are not publicly available according to the NHIS policy. Researchers can submit an application form through the NHIS website (https://nhiss.nhis.or.kr) to access and analyze the database.

Author Contributions
Conceptualization: Kim M, Ha KH, Kim DJ, Bae JW; Data curation: Kim M, Ha KH, Kim DJ, Bae JW; Formal analysis: Kim M, Ha KH, Bae JW; Funding acquisition: Kim M, Bae JW; Investigation: Kim M, Ha KH, Lee J, Park S, Oh KS, Bae DH, Lee JH, Cho MC, Kim DJ, Bae JW; Methodology: Kim M, Ha KH, Bae DH, Lee JH, Kim SM, Choi WG, Hwang KK, Kim DW, Cho MC, Kim DJ, Bae JW; Project administration: Kim M, Ha KH, Kim DJ, Bae JW; Resources: Kim M, Ha KH, Kim DJ; Software: Ha KH, Kim DJ; Supervision: Kim SM, Choi WG, Hwang KK, Kim DW, Cho MC, Kim DJ, Bae JW; Validation: Kim M, Ha KH, Kim DJ, Bae JW; Visualization: Kim M, Ha KH, Lee J, Park S, Oh KS, Kim DJ, Bae JW; Writing - original draft: Kim M, Ha KH, Kim DJ, Bae JW; Writing - review & editing: Kim M, Ha KH, Kim DJ, Bae JW.

p=0.019) compared to DPP-4i users. However, individuals with heart failure, SGLT2i users was not significantly associated with a change in risk (HR, 1.04; 95% CI, 0.44–2.44; p=0.936). **Conclusions:** In this nationwide cohort study of individuals with type 2 diabetes, treatment with SGLT2i was associated with a lower risk of AF compared with treatment with DPP-4i.

Keywords: Atrial fibrillation; Diabetes mellitus; Sodium-glucose transporter 2 inhibitors; Dipeptidyl-peptidase IV inhibitors

INTRODUCTION

Atrial fibrillation (AF), the most common cardiac rhythm disturbance, increases the risk of ischemic stroke and mortality and impairs the quality of life of affected individuals.[1] Type 2 diabetes is a metabolic disorder, and the prevalence of AF is at least two times higher in individuals with diabetes than in those without.[2] Moreover, the risk of AF development increases with increasing severity of complications from diabetes, which is a well-known risk factor for AF.[3]

The mechanism underlying the higher risk of AF development in individuals with diabetes is unclear. Impaired atrial electromechanical function, fibrosis, inflammation, oxidative stress, and altered autonomic function may contribute to this increased susceptibility to atrial rhythm disturbance.[4] In addition, type 2 diabetes and AF are likely to share interconnected mechanisms that increase the risk of blood clot formation and collectively enhance the risk of stroke. Therefore, the prevention of AF in individuals with type 2 diabetes contributes to a reduced risk of stroke.

There is emerging interest in the role of glucose-lowering drugs in moderating changes to atrial arrhythmias.[4] Sodium-glucose cotransporter 2 inhibitors (SGLT2is) have been shown to reduce the risk of major adverse cardiac events[5]; however, studies investigating their impact in reducing the risk of AF have reported inconsistent results.[6][7] SGLT2i have pleiotropic effects that are not related to glycemic control: they mitigate the abnormal sodium concentration in cardiomyocytes that may lead to changes in cardiac contraction and arrhythmias.[8] Therefore, in this study, we aimed to compare the effectiveness of SGLT2i with that of dipeptidyl peptidase-4 inhibitors (DPP-4is) in reducing the incidence of AF in individuals with type 2 diabetes in the real-world setting.

METHODS

Ethical statement

This study confirmed to the 2013 revision of the Declaration of Helsinki and the Institutional Review Board approved the study protocol (Chungbuk National University Hospital, approval number: 2022-04-027). The need for informed consent was waived by the same ethics committee (Institutional Review Board of Chungbuk National University Hospital) as anonymized data were used.

Data source

Data were collected from the Korean National Health Insurance Service (NHIS) database. The NHIS is the single provider of universal healthcare coverage in South Korea. The NHIS

https://doi.org/10.4070/kcj.2023.0234

kcj
Korean Circulation Journal

database includes information on sociodemographic characteristics, reimbursement claims, and deaths (linked to the National Death Registry via unique resident registration numbers). Reimbursement claims include information on disease diagnoses based on International Classification of Diseases 10th revision (ICD-10) codes, prescriptions of drugs based on Anatomical Therapeutic Chemical (ATC) codes, and clinical procedures.[9]

Study population

We identified individuals with type 2 diabetes who were new users of an SGLT2i or a DPP-4i between May 1, 2016, and December 31, 2018. New users were defined as individuals who were newly initiated on an SGLT2i or a DPP-4i and had no SGLT2i or DPP-4i use in the previous 12 months. The date of the new initiation of either study drug was defined as the index date. Individuals who initiated both SGLT2i and DPP-4i on the index date were excluded. Individuals were excluded based on the following criteria: i) age <20 years at the index date, ii) end-stage kidney disease or a history of kidney transplantation, iii) type 1 diabetes, iv) gestational diabetes, v) previous diagnosis of AF, and vi) prescription of antiarrhythmic drugs or anticoagulants during the 12 months before the index date.

Exposure and outcome

Drug use was assumed to have started on the date of prescription, which was recorded based on the ATC codes (**Supplementary Table 1**). The duration of drug exposure was calculated based on the days' supply variable for each prescription, with a grace period of 100% of the calculated duration of drug exposure. The initial occurrence of AF was set as the outcome. AF was defined as more than two outpatient visits or one hospitalization with ICD-10 code I48; this definition has been previously validated in the NHIS database, with a positive predictive value of 94.1%.[10]

Covariates

We considered approximately 103 potential confounders, including sex, age, household income, calendar date of cohort entry, diabetes complications, comorbidities, and previous or concomitant use of glucose-lowering drugs within the last 12 months including the index date. Detailed descriptions of the covariates are provided in **Supplementary Table 1**.

Statistical analysis

Continuous variables are reported as means with standard deviations (SDs), and categorical variables are expressed as numbers with percentages. To mitigate potential biases due to any imbalance in baseline characteristics between SGLT2i and DPP-4i users, a propensity score-matched analysis was performed in which multivariable logistic regression was employed to model the probability of SGLT2i use versus DPP-4i use. This matching used the nearest-neighbor algorithm with a caliper of 0.2 SD on the probability scale. We performed an on-treatment analysis, followed participants from the index date until the earliest of the following events: discontinuation of treatment, switching to a comparator drug, new onset of AF, the date of death, or the end of the study period on December 31, 2018. For supplementary analyses, we conducted an intention-to-treat (ITT) analyses, participants were followed from the index date until the earliest of the following events: new onset of AF, the date of death, or the end of the study period on December 31, 2018.

The incidence of AF was estimated by dividing the number of incident AF cases by the total number of person-years of follow-up. Cumulative incidence curves were compared using the log-rank test. A Cox proportional hazards model using hazard ratios (HRs) and

https://doi.org/10.4070/kcj.2023.0234

kcj
Korean Circulation Journal

95% confidence intervals (CIs) was applied to evaluate the association between treatment with the study drugs and the risk of incident AF. The proportional hazards assumption in the Cox models was assessed using Schoenfeld residuals test, and no violation were detected (p>0.05). Additionally, subgroup analyses were performed to examine whether the association between SGLT2i or DPP-4i use and incident AF differed based on the participants' demographic characteristics, comorbidities, or thromboembolic risk (determined using the CHA_2DS_2-VAS score).[11] All statistical analyses were performed using SAS Enterprise Guide 7.1 (SAS Institute, Cary, NC, USA).

RESULTS

Baseline characteristics of sodium-glucose cotransporter 2 inhibitors and dipeptidyl peptidase-4 inhibitors users

After the application of the exclusion criteria, 42,806 (8.7%) new users of an SGLT2i and 448,715 (91.3%) new users of a DPP-4i remained for analysis (**Figure 1**). After the matching procedure, 85,572 participants (42,786 in each group) remained; the baseline characteristics were well balanced, with no standardized difference >10%, between the two groups. The study included patients with an average age of 54.7 years, 42.4% women, a median follow-up of 1.3 years, and 38.1% had cardiovascular disease. **Table 1** presents the results for the 46 key variables, while **Supplementary Table 2** provides outcomes for a total of 103 variables.

Among SGLT2i users, dapagliflozin, empagliflozin, and ipragliflozin were prescribed in 54.6%, 38.9%, and 6.6%, respectively. Among DPP-4i users, the following drugs were

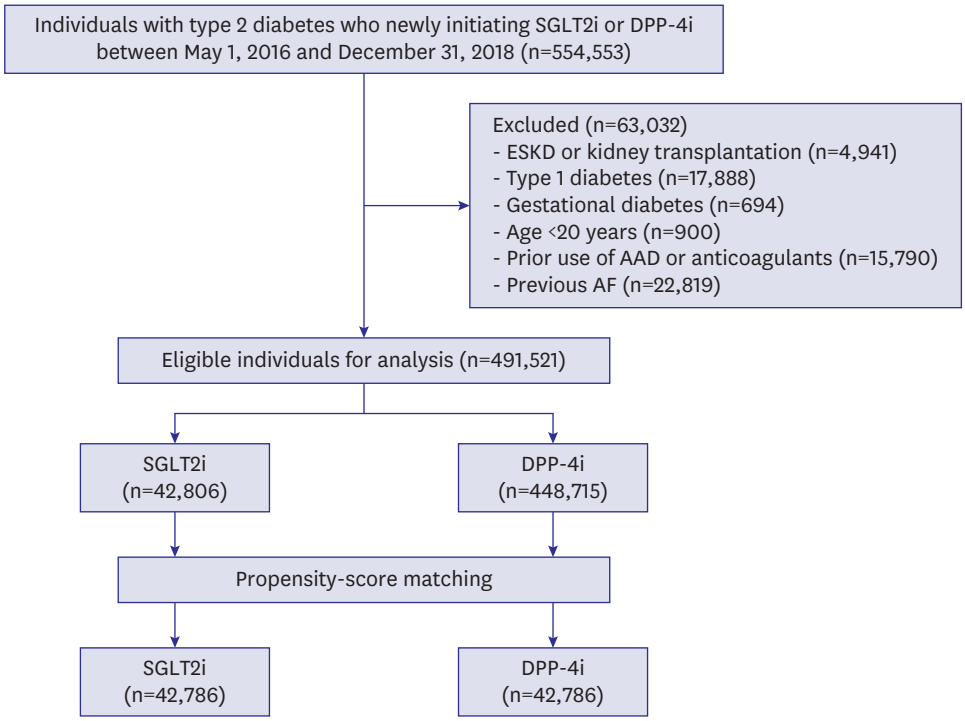

Figure 1. Flowchart of participant inclusion.
AAD = antiarrhythmic drug; AF = atrial fibrillation; DPP-4i = dipeptidyl peptidase-4 inhibitor; ESKD = end-stage kidney disease; SGLT2i = sodium-glucose cotransporter 2 inhibitor.

https://doi.org/10.4070/kcj.2023.0234

prescribed: sitagliptin (22.1%), gemigliptin (20.6%), linagliptin (20.5%), teneligliptin (10.3%), alogliptin (7.7%), vildagliptin (6.0%), saxagliptin (4.7%), evogliptin (4.3%), and anagliptin (3.8%) (**Supplementary Table 3**).

Comparison of the risk of atrial fibrillation occurrence between sodium-glucose cotransporter 2 inhibitors and dipeptidyl peptidase-4 inhibitors users

After matching, the incidence of AF was significantly lower in SGLT2i users (1.95 per 1,000 person-years) than in DPP-4i users (2.65 per 1,000 person-years), with an absolute difference of −0.7 (95% CI, −1.3 to −0.1) per 1,000 person-years (p=0.034). SGLT2i use was associated with a lower incidence of AF compared with DPP-4i use (HR, 0.73; 95% CI, 0.55–0.97; p=0.028) (**Table 2**). The cumulative incidence of AF in the propensity score-matched cohort over time, along with the corresponding p values for the log-rank test, is shown in **Figure 2**.

Subgroup analyses according to age, sex, comorbidities, and CHA_2DS_2-VAS scores

The risk of AF was consistently lower in SGLT2i users than in DPP-4i users, regardless of age, sex, comorbid diseases, and estimated stroke risk (**Figure 3**) in the main analysis.

Table 1. Baseline characteristics before and after propensity score matching

Variables	Before matching			After matching		
	SGLT2i (n=42,806)	DPP-4i (n=448,715)	ASD (%)	SGLT2i (n=42,786)	DPP-4i (n=42,786)	ASD (%)
Age (years)	54.6±12.1	62.0±12.6	59.8	54.7±12.1	54.7±12.2	0.1
Women	18,178 (42.5)	192,658 (42.9)	0.9	18,167 (42.5)	18,139 (42.4)	0.1
Index year						
2016	9,325 (21.8)	131,997 (29.4)	17.6	9,325 (21.8)	9,185 (21.5)	0.8
2017	18,402 (43.0)	189,874 (42.3)	1.4	18,395 (43.0)	18,259 (42.7)	0.6
2018	15,079 (35.2)	126,844 (28.3)	15.0	15,066 (35.2)	15,342 (35.8)	1.3
Household income						
Low	9,908 (23.1)	105,046 (23.4)	0.6	9,901 (23.1)	9,885 (23.1)	0.1
Intermediate	14,960 (34.9)	147,605 (32.9)	4.3	14,954 (35.0)	14,982 (35.0)	0.1
High	16,179 (37.8)	170,707 (38.0)	0.5	16,172 (37.8)	16,153 (37.8)	0.1
Missing	1,759 (4.1)	25,357 (5.7)	7.2	1,759 (4.1)	1,766 (4.1)	0.1
Diabetic complications						
Neuropathy	6,362 (14.9)	77,886 (17.4)	6.8	6,359 (14.9)	6,431 (15.0)	0.5
Retinopathy	6,593 (15.4)	73,665 (16.4)	2.8	6,587 (15.4)	6,651 (15.5)	0.4
Nephropathy	4,399 (10.3)	41,935 (9.3)	3.1	4,393 (10.3)	4,402 (10.3)	0.1
Comorbidities						
Heart failure	2,027 (4.7)	20,925 (4.7)	0.3	2,026 (4.7)	2,030 (4.7)	0.0
Hypertension	24,871 (58.1)	265,842 (59.2)	2.3	24,857 (58.1)	24,744 (57.8)	0.5
Dyslipidemia	36,546 (85.4)	361,998 (80.7)	12.5	36,527 (85.4)	36,492 (85.3)	0.2
Ischemic stroke	1,703 (4.0)	30,626 (6.8)	12.6	1,703 (4.0)	1,768 (4.1)	0.8
Transient ischemic attack	734 (1.7)	10,566 (2.4)	4.5	734 (1.7)	740 (1.7)	0.1
Hemorrhagic stroke	233 (0.5)	3,317 (0.7)	2.4	233 (0.5)	219 (0.5)	0.5
Acute coronary syndrome	1,410 (3.3)	12,538 (2.8)	2.9	1,409 (3.3)	1,385 (3.2)	0.3
Chronic coronary syndrome	1,654 (3.9)	16,778 (3.7)	0.7	1,654 (3.9)	1,606 (3.8)	0.6
Peripheral artery disease	8,607 (20.1)	102,401 (22.8)	6.6	8,605 (20.1)	8,621 (20.1)	0.1
Chronic kidney disease	535 (1.2)	11,708 (2.6)	9.9	535 (1.3)	533 (1.2)	0.0
End-stage kidney disease	109 (0.3)	3,604 (0.8)	7.6	109 (0.3)	103 (0.2)	0.3
COPD	5,914 (13.8)	73,864 (16.5)	7.4	5,911 (13.8)	5,854 (13.7)	0.4
Osteoporosis	4,620 (10.8)	75,730 (16.9)	17.7	4,620 (10.8)	4,636 (10.8)	0.1
Hyperthyroidism	1,450 (3.4)	14,000 (3.1)	1.5	1,449 (3.4)	1,548 (3.6)	1.3
Hypothyroidism	4,084 (9.5)	37,415 (8.3)	4.2	4,081 (9.5)	3,856 (9.0)	1.8
Obstructive sleep apnea	288 (0.7)	1,270 (0.3)	5.7	287 (0.7)	247 (0.6)	1.2
Liver disease	24,945 (58.3)	242,620 (54.1)	8.5	24,928 (58.3)	24,946 (58.3)	0.1
Dementia	788 (1.8)	23,577 (5.3)	18.5	788 (1.8)	769 (1.8)	0.3
Alcoholism	244 (0.6)	2,827 (0.6)	0.8	244 (0.6)	223 (0.5)	0.7

(continued to the next page)

https://doi.org/10.4070/kcj.2023.0234

Table 1. (Continued) Baseline characteristics before and after propensity score matching

Variables	Before matching			After matching		
	SGLT2i (n=42,806)	DPP-4i (n=448,715)	ASD (%)	SGLT2i (n=42,786)	DPP-4i (n=42,786)	ASD (%)
Other antidiabetic drugs						
Metformin	30,040 (70.2)	234,057 (52.2)	37.6	30,020 (70.2)	30,104 (70.4)	0.4
Sulfonylurea, second generation	11,500 (26.9)	144,455 (32.2)	11.7	11,498 (26.9)	11,732 (27.4)	1.2
GLP-1 receptor agonist	12 (<0.1)	41 (<0.1)	1.4	12 (0.0)	11 (0.0)	0.1
Thiazolidinedione	1,849 (4.3)	23,096 (5.1)	3.9	1,849 (4.3)	1,923 (4.5)	0.8
Meglitinide	117 (0.3)	1,832 (0.4)	2.3	117 (0.3)	97 (0.2)	0.9
Alpha-glucosidase inhibitor	606 (1.4)	10,543 (2.3)	6.9	606 (1.4)	559 (1.3)	0.9
Insulin	3,174 (7.4)	36,112 (8.0)	2.4	3,168 (7.4)	3,132 (7.3)	0.3
Other drugs						
Antiplatelet agent	13,560 (31.7)	156,886 (35.0)	7.0	13,556 (31.7)	13,650 (31.9)	0.5
ACE inhibitor	756 (1.8)	7,779 (1.7)	0.2	755 (1.8)	742 (1.7)	0.2
ARB	18,210 (42.5)	185,229 (41.3)	2.6	18,205 (42.5)	18,086 (42.3)	0.6
Beta-blocker	5,205 (12.2)	52,700 (11.7)	1.3	5,199 (12.2)	5,208 (12.2)	0.1
CCB	6,323 (14.8)	82,452 (18.4)	9.7	6,319 (14.8)	6,326 (14.8)	0.0
Loop diuretic	1,617 (3.8)	27,127 (6.0)	10.5	1,617 (3.8)	1,628 (3.8)	0.1
Thiazide	3,279 (7.7)	37,179 (8.3)	2.3	3,278 (7.7)	3,338 (7.8)	0.5
Other diuretic	814 (1.9)	9,733 (2.2)	1.9	814 (1.9)	802 (1.9)	0.2
Statin	28,568 (66.7)	268,038 (59.7)	14.6	28,552 (66.7)	28,605 (66.9)	0.3
Nitrate	1,641 (3.8)	16,162 (3.6)	1.2	1,640 (3.8)	1,609 (3.8)	0.4
COPD medication	10,166 (23.7)	109,623 (24.4)	1.6	10,160 (23.7)	10,099 (23.6)	0.3
Oral corticosteroid	14,856 (34.7)	153,759 (34.3)	0.9	14,850 (34.7)	14,641 (34.2)	1.0
Bisphosphonate	1,142 (2.7)	25,213 (5.6)	14.8	1,142 (2.7)	1,112 (2.6)	0.4

Among the variables used in the propensity score matching, only the primary variables were included.
Data are presented as number (%) or mean ± standard deviation.
ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; ASD = absolute standardized difference; CCB = calcium channel blocker; COPD = chronic obstructive pulmonary disease; DPP-4i = dipeptidyl peptidase-4 inhibitor; GLP = glucagon-like peptide; SGLT2i = sodium-glucose cotransporter 2 inhibitor.

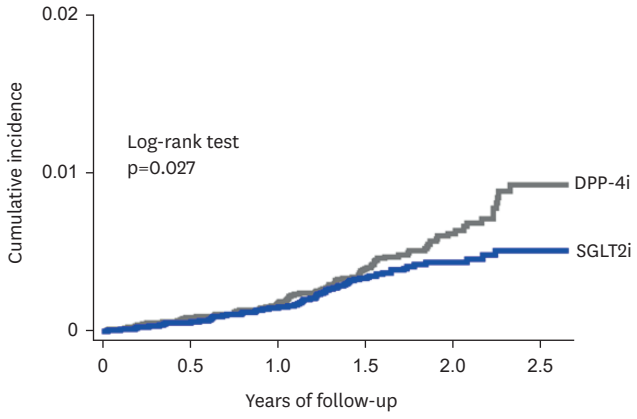

Figure 2. Cumulative incidence curves of atrial fibrillation in the propensity score-matched cohort.
DPP-4i = dipeptidyl peptidase-4 inhibitor; SGLT2i = sodium-glucose cotransporter 2 inhibitor.

Table 2. Hazard ratios of atrial fibrillation events associated with SGLT2i use versus DPP-4i use in the propensity score-matched cohort

Type of treatment	Total follow-up years	No. of events	Event rate	Absolute event rate difference	HR (95% CI)	p value
SGLT2i (n=42,786)	44,013	86	1.95	−0.7 (−1.3 to −0.1)	0.73 (0.55–0.97)	0.028
DPP-4i (n=42,786)	40,744	108	2.65	Reference		

Event rates were estimated per 1,000 person-years.
CI = confidence interval; DPP-4i = dipeptidyl peptidase-4 inhibitor; HR = hazard ratio; SGLT2i = sodium-glucose cotransporter 2 inhibitor.

https://doi.org/10.4070/kcj.2023.0234

kcj
Korean Circulation Journal

	No. of participants	Total follow-up years	No. of Events	Event rate SGLT2i	Event rate DPP–4i	HR (95% CI)	p value	p for interaction
Age, years								0.318
20-74	81,094	80,478	163	1.67	2.41	0.68 (0.50–0.93)	0.017	
≥75	4,478	4,279	31	7.32	7.17	1.02 (0.50–2.06)	0.963	
Sex								0.460
Men	49,266	47,814	121	2.10	3.04	0.67 (0.45–0.96)	0.029	
Women	36,306	36,943	73	1.82	2.15	0.84 (0.53–1.32)	0.444	
Hypertension								0.663
Yes	49,601	52,121	154	2.48	3.47	0.71 (0.51–0.97)	0.032	
No	35,971	32,636	40	1.12	1.34	0.82 (0.44–1.53)	0.539	
Heart failure								0.393
Yes	4,056	3,844	21	5.58	5.34	1.04 (0.44–2.44)	0.936	
No	81,516	80,913	173	1.78	2.52	0.70 (0.52–0.94)	0.019	
CVD								0.352
Yes	32,581	32,368	121	3.37	4.14	0.81 (0.56–1.15)	0.235	
No	52,991	52,389	73	1.07	1.74	0.60 (0.38–0.97)	0.355	
CHA_2DS_2–VAS score								0.923
≥3	36,924	36,711	126	2.90	3.98	0.72 (0.51–1.01)	0.060	
<3	48,648	48,046	68	1.17	1.56	0.74 (0.45–1.21)	0.230	

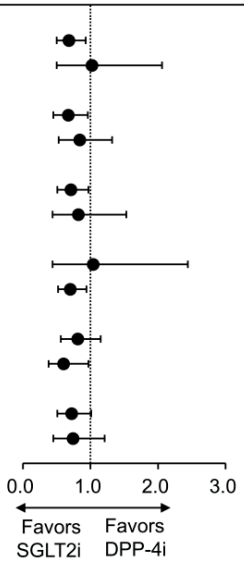

Figure 3. Subgroup analyses of the risk of atrial fibrillation according to age, sex, comorbidities, and estimated thromboembolic risk. CVD is defined as heart failure, ischemic stroke, transient ischemic attack, hemorrhagic stroke, acute coronary syndrome, chronic coronary syndrome, and peripheral disease (listed in **Table 1**). CI = confidence interval; CVD = cardiovascular disease; DPP-4i = dipeptidyl peptidase-4 inhibitor; HR = hazard ratio; SGLT2i = sodium-glucose cotransporter 2 inhibitor.

Supplementary analyses (ITT analyses) also revealed similar trends, but the lower risk of AF was more pronounced in SGLT2i users without a history of heart failure (HF) (p for interaction=0.036, as shown in **Supplementary Figure 1**). **Supplementary Table 4** shows the distribution of the CHA_2DS_2-VAS scores. Among the participants, 19.1%, 37.8%, and 43.1% had a CHA_2DS_2-VAS score of 1 point, 2 points, and ≥3 points, respectively, and the scores were well-balanced between the SGLT2i and DPP-4i groups. The cumulative incidence curves showed a higher risk of AF with higher CHA_2DS_2-VAS scores (**Supplementary Figure 2**).

DISCUSSION

In this real-world comparison of the effects of glucose-lowering drugs among individuals with type 2 diabetes, we observed a significant difference in the incidence of AF between SGLT2i users and DPP-4i users. The incidence of AF was lower in patients treated with SGLT2i (1.95 per 1,000 person-years) as compared to those treated with DPP-4i (2.65 per 1,000 person-years), with a 27% risk reduction. In our subgroup analysis, we identified no significant interactions with respect to age, sex, comorbid diseases, and estimated stroke risk. This suggests a potentially significant role of SGLT2i in AF prevention.

The incidence of AF is higher in individuals with type 2 diabetes than in the general population and has been rapidly increasing. Type 2 diabetes has deteriorative effects on atrial function and structure, thereby contributing to the development, progression, and maintenance of AF; it is also associated with complications such as autonomic dysfunction, which has the potential to increase the risk of AF.[3] These shared risk factors facilitate the occurrence of stroke; moreover, a longer duration of diabetes, which increases the risk of AF, is associated with a higher risk of thromboembolism.[12] Therefore, current guidelines recommend both antithrombotic therapy for stroke prevention and optimal glycemic

https://doi.org/10.4070/kcj.2023.0234

kcj
Korean Circulation Journal

control in individuals with diabetes and AF.[1] Furthermore, a recent multi-ethnic genome-wide association study demonstrated that AF is a causal risk factor for kidney function impairment, which is known to be accelerated by the presence of diabetes.[13]

Conflicting results have been reported on whether intensive glycemic control or treatment with antidiabetic drugs lower the risk of AF. In a randomized trial, no association was found between intensive (glycated hemoglobin [HbA1c] level <6.0%) or standard (HbA1c level 7.0–7.9%) glycemic control and AF incidence.[14] However, Huxley et al.[15] reported that HbA1c levels were associated with the incidence of AF in individuals with or without diabetes. A recent cohort study conducted in Sweden found that patients with diabetes with poor glycemic control had an increased risk of AF.[16]

The results of studies regarding the risk of AF according to the type of antidiabetic drugs are also conflicting.[17] Metformin and pioglitazone may be associated with a lower long-term risk of AF in individuals with diabetes through the attenuation of tachypacing-induced myofibril degradation and activation of peroxisome proliferator-activated receptor gamma, which has anti-inflammatory and antioxidant effects. However, rosiglitazone was not associated with the incidence of AF in a meta-analysis. Regarding the potential of DPP-4i to reduce the incidence of AF, clear evidence is still lacking.

SGLT2i are a novel class of glucose-lowering agents that demonstrate beneficial effects on the heart and kidneys in a range of conditions, including type 2 diabetes, chronic kidney disease, and HF.[18] Furthermore, a randomized trial showed that dapagliflozin reduces AF or atrial flutter events in patients with high-risk type 2 diabetes, and other studies revealed that SGLT2i users were less likely to develop AF than those receiving other antidiabetic treatments.[6][19] Shao et al.[20] recently reported that intensified antidiabetic treatment with SGLT2i had more favorable pleiotropic effects on the metabolic profile than treatment with DPP-4i, and they inferred that this could lead to a cardioprotective effect under similar glycemic control. Although the precise mechanism is unclear, SGLT2i are believed to maintain Na^+ and Ca^{2+} homeostasis and rescue mitochondrial function. Similarly, Ling et al.[21] reported that the risk of AF was decreased up to 39% by SGLT2i, rather than DPP-4i, in real-world patients with type 2 diabetes in Taiwan. In our study, consistent with these studies in Asian populations, we observed a preventive effect of SGLT2i on the development of AF. However, Caucasian-based studies predominantly did not show a protective effect of SGLT2i against AF.[7][22] The biological mechanisms responsible for ethnic disparities in AF outcomes and the varied effects of newer glucose-lowering drugs are still not fully understood. Although definitions of race or ethnicity varied across cardiovascular outcome trials,[23] further research is warranted in this area.

In the current study, SGLT2i use was associated with a reduced incidence of AF. It is worth noting that this correlation remained consistent across all subgroups, without exception. The CHA_2DS_2-VAS score was used to discriminate the risk groups for predicting the AF incidence.[11] The appropriate cut-off points of the CHA_2DS_2-VASc score for predicting AF occurrence in diabetic patients are not clear. However, based on recent research, 3 points were chosen as the cut-off value in our study.[24] Although other risk models (CHARGE-AF, C_2HEST score) for predicting AF incidence have been proposed, they require many instrumental and laboratory variables that might be difficult to access in clinical practice, thereby limiting their application for risk assessment in real-world settings.[25][26]

https://doi.org/10.4070/kcj.2023.0234

kcj
Korean Circulation Journal

The present study had several limitations. First, the accuracy of diagnoses in the claims database is questionable, and a possibility of misclassification exists. However, to minimize this possibility, we used a disease definition that has been validated in previous studies. Second, a previous study has suggested the existence of a drug class effect[21]; however, whether the lowering of AF risk by SGLT2i is a drug class effect or not is unclear in this study. Third, retrospective studies cannot demonstrate causal relationships, and residual confounding may persist even after propensity score matching or weighting. To address potential confounding, we performed propensity score matching using comorbidities as covariates. However, there is still a possibility of residual confounding due to our inability to measure laboratory test results, such as HbA1c and estimated glomerular filtration rate. Additionally, we did not account for variables pertaining to the duration of diabetes. Instead, we employed the presence of diabetes-related complications and the use of insulin as proxies in our propensity score matching process. Furthermore, although SGLT2i address several risk factors related to the onset of AF, including obesity, hypertension, and hyperglycemia, aside from cardiac reverse remodeling, our study did not incorporate data on weight or blood pressure changes. Consequently, additional research is warranted to elucidate the specific impacts of SGLT2i on AF development. Fourth, the DECLARE-TIMI 58 trial[19] elucidated that dapagliflozin significantly diminished the incidence of AF episodes, with the divergence in outcomes becoming evident around the 1 year and intensifying beyond the 2 year of follow-up. Previous studies have indicated that cardiac reverse remodeling following SGLT2i treatment might require a time longer than 6 months.[27] Our study's findings are consistent with these prior observations. Nevertheless, the median follow-up duration of our study was 1.3 years, which is insufficient to observe long-term outcomes. Therefore, further studies are needed to evaluate the long-term effects. Fifth, in real-world clinical settings, changes in drug treatment are often more significant than those in randomized trials, and OT analysis is a potentially more accurate representation of the effects of treatment. However, estimates of cumulative AF incidence may be affected by bias from drug treatment changes, such as discontinuation of treatment, switch to a comparator drug, or concurrent use of different drugs. Sixth, among the DPP-4i agents, saxagliptin is noted to elevate the risk of heart failure, as highlighted by the SAVOR-TIMI 53 trial.[28] This could potentially impact our findings, yet it's worth noting that proportion of saxagliptin in our study was relatively minimal, accounting for just 4.7% and a recent systematic meta-analysis confirmed the neutral effects of DPP-4i on cardiovascular outcomes.[29] Seventh, the potential cardiac detrimental effect of DPP-4i, due to its ability to increase vascular permeability,[30] could have skewed the results. However, a nationwide cohort study has shown that DPP-4i reduced the incidence of AF, suggesting that using DPP-4i as a comparator group may be reasonably appropriate.[31] Eighth, the incidence of AF in our study appears to be low. However, according to a recent study conducted in Korea,[32] the incidence over a 10-year period is reported to be 1.8 per 1,000 person-years. Moreover, the incidence decreases to 1.7 per 1,000 person-years for those aged 50–59 and further drops to 0.71 per 1,000 person-years for the 40–49 age group. Given that the average age of our study's participants is in the early 50s, we believe the incidence of AF is not negligible. Ninth, we did not incorporate data on the use of angiotensin receptor-neprilysin inhibitors (ARNIs) in our analysis. A recent meta-analysis of randomized controlled trials[33] indicated that ARNIs showed similar efficacy to angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers in the incidence of AF among patients with HF. Given that the prevalence of HF in our study was a modest 4.7%, we surmised that ARNI utilization would be minimal, which influenced our decision to exclude it from our assessment. Tenth, further studies are needed to determine whether SGLT2i reduce the risk of AF, beyond reducing adverse cardiovascular outcomes, in individuals without diabetes but

https://doi.org/10.4070/kcj.2023.0234

with recently developed HF with preserved ejection fraction. Finally, we did not account for competing risks. When the proportion of participants experiencing a competing risk is equal to or greater than the proportion of participants experiencing the primary outcome, or when the follow-up period exceeds 5 years, a failure to consider competing risks can lead to biased results. However, it's worth noting that in this study, the follow-up period was relatively short, with a median follow-up of 1.3 years, and the all-cause mortality rate was lower than the incidence rate of AF (1.9 vs. 2.3 per 1,000 person-years). Moreover, the SGLT2i showed a lower all-cause mortality rate compared to DPP-4i (1.8 vs. 2.0 per 1,000 person-years).

In conclusion, initiating an SGLT2i for the treatment of type 2 diabetes had a greater benefit in terms of AF prevention than initiating a DPP-4i in South Korea.

ACKNOWLEDGMENTS

This study used data from the National Health Information Database (NHIS-2023-1-071) provided by the National Health Insurance Service (NHIS). The authors have no conflicts of interest with the NHIS.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Definitions and codes used for defining comorbidities, drug treatments, and procedures using propensity score-matching

Supplementary Table 2
Baseline characteristics before and after propensity score matching

Supplementary Table 3
Proportion of study drugs

Supplementary Table 4
The distributions of CHA_2DS_2-VAS score

Supplementary Figure 1
Total and subgroup analyses of the risk of atrial fibrillation according to age, sex, comorbidities, and CHA_2DS_2-VAS score (≥3 or <3 points) in intention-to-treat analyses. CVD is defined as heart failure, ischemic stroke, transient ischemic attack, hemorrhagic stroke, acute coronary syndrome, chronic coronary syndrome, and peripheral disease (listed in **Table 1**).

Supplementary Figure 2
Cumulative incidence curves of atrial fibrillation by CHA_2DS_2-VAS score in propensity-matched cohort. CHA_2DS_2-VAS score calculated as follows; heart failure, hypertension, age ≥75 years (doubled), diabetes, stroke/transient ischemic attack/thromboembolism (doubled), vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque), age 65–75 years, sex category (female).

REFERENCES

1. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021;42:373-498. PUBMED | CROSSREF
2. Movahed MR, Hashemzadeh M, Jamal MM. Diabetes mellitus is a strong, independent risk for atrial fibrillation and flutter in addition to other cardiovascular disease. *Int J Cardiol* 2005;105:315-8. PUBMED | CROSSREF
3. Bohne LJ, Johnson D, Rose RA, Wilton SB, Gillis AM. The association between diabetes mellitus and atrial fibrillation: clinical and mechanistic insights. *Front Physiol* 2019;10:135. PUBMED | CROSSREF
4. Wang A, Green JB, Halperin JL, Piccini JP Sr. Atrial fibrillation and diabetes mellitus: JACC review topic of the week. *J Am Coll Cardiol* 2019;74:1107-15. PUBMED | CROSSREF
5. Newman JD, Vani AK, Aleman JO, Weintraub HS, Berger JS, Schwartzbard AZ. The changing landscape of diabetes therapy for cardiovascular risk reduction: JACC state-of-the-art review. *J Am Coll Cardiol* 2018;72:1856-69. PUBMED | CROSSREF
6. Li HL, Lip GY, Feng Q, et al. Sodium-glucose cotransporter 2 inhibitors (SGLT2i) and cardiac arrhythmias: a systematic review and meta-analysis. *Cardiovasc Diabetol* 2021;20:100. PUBMED | CROSSREF
7. 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;25:495-502. PUBMED | CROSSREF
8. Braunwald E. Gliflozins in the management of cardiovascular disease. *N Engl J Med* 2022;386:2024-34. PUBMED | CROSSREF
9. Cheol Seong S, Kim YY, Khang YH, et al. Data resource profile: the national health information database of the National Health Insurance Service in South Korea. *Int J Epidemiol* 2017;46:799-800. PUBMED
10. Kim D, Yang PS, Jang E, et al. Increasing trends in hospital care burden of atrial fibrillation in Korea, 2006 through 2015. *Heart* 2018;104:2010-7. PUBMED | CROSSREF
11. Saliba W, Gronich N, Barnett-Griness O, Rennert G. Usefulness of CHADS2 and CHA2DS2-VASc Scores in the prediction of new-onset atrial fibrillation: a population-based study. *Am J Med* 2016;129:843-9. PUBMED | CROSSREF
12. Overvad TF, Skjøth F, Lip GY, et al. Duration of diabetes mellitus and risk of thromboembolism and bleeding in atrial fibrillation: nationwide cohort study. *Stroke* 2015;46:2168-74. PUBMED | CROSSREF
13. Park S, Lee S, Kim Y, et al. Atrial fibrillation and kidney function: a bidirectional Mendelian randomization study. *Eur Heart J* 2021;42:2816-23. PUBMED | CROSSREF
14. Fatemi O, Yuriditsky E, Tsioufis C, et al. Impact of intensive glycemic control on the incidence of atrial fibrillation and associated cardiovascular outcomes in patients with type 2 diabetes mellitus (from the Action to Control Cardiovascular Risk in Diabetes Study). *Am J Cardiol* 2014;114:1217-22. PUBMED | CROSSREF
15. Huxley RR, Alonso A, Lopez FL, et al. Type 2 diabetes, glucose homeostasis and incident atrial fibrillation: the Atherosclerosis Risk in Communities study. *Heart* 2012;98:133-8. PUBMED | CROSSREF
16. Seyed Ahmadi S, Svensson AM, Pivodic A, Rosengren A, Lind M. Risk of atrial fibrillation in persons with type 2 diabetes and the excess risk in relation to glycaemic control and renal function: a Swedish cohort study. *Cardiovasc Diabetol* 2020;19:9. PUBMED | CROSSREF
17. Bell DS, Goncalves E. Atrial fibrillation and type 2 diabetes: Prevalence, etiology, pathophysiology and effect of anti-diabetic therapies. *Diabetes Obes Metab* 2019;21:210-7. PUBMED | CROSSREF
18. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet* 2019;393:31-9. PUBMED | CROSSREF
19. Zelniker TA, Bonaca MP, Furtado RH, et al. Effect of dapagliflozin on atrial fibrillation in patients with type 2 diabetes mellitus: insights from the DECLARE-TIMI 58 trial. *Circulation* 2020;141:1227-34. PUBMED | CROSSREF
20. Shao SC, Chang KC, Lin SJ, et al. Favorable pleiotropic effects of sodium glucose cotransporter 2 inhibitors: head-to-head comparisons with dipeptidyl peptidase-4 inhibitors in type 2 diabetes patients. *Cardiovasc Diabetol* 2020;19:17. PUBMED | CROSSREF
21. Ling AW, Chan CC, Chen SW, et al. The risk of new-onset atrial fibrillation in patients with type 2 diabetes mellitus treated with sodium glucose cotransporter 2 inhibitors versus dipeptidyl peptidase-4 inhibitors. *Cardiovasc Diabetol* 2020;19:188. PUBMED | CROSSREF

22. Birkeland KI, Jørgensen ME, Carstensen B, et al. Cardiovascular mortality and morbidity in patients with type 2 diabetes following initiation of sodium-glucose co-transporter-2 inhibitors versus other glucose-lowering drugs (CVD-REAL Nordic): a multinational observational analysis. *Lancet Diabetes Endocrinol* 2017;5:709-17. PUBMED | CROSSREF

23. Lee MM, Ghouri N, McGuire DK, Rutter MK, Sattar N. Meta-analyses of results from randomized outcome trials comparing cardiovascular effects of SGLT2is and GLP-1RAs in Asian versus white patients with and without type 2 diabetes. *Diabetes Care* 2021;44:1236-41. PUBMED | CROSSREF

24. Hu WS, Lin CL. Role of CHA_2DS_2-VASc score in predicting new-onset atrial fibrillation in patients with type 2 diabetes mellitus with and without hyperosmolar hyperglycaemic state: real-world data from a nationwide cohort. *BMJ Open* 2018;8:e020065. PUBMED | CROSSREF

25. Alonso A, Krijthe BP, Aspelund T, et al. Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF consortium. *J Am Heart Assoc* 2013;2:e000102. PUBMED | CROSSREF

26. Li YG, Bisson A, Bodin A, et al. C_2 HEST score and prediction of incident atrial fibrillation in poststroke patients: a French nationwide study. *J Am Heart Assoc* 2019;8:e012546. PUBMED | CROSSREF

27. Verma S, Mazer CD, Yan AT, et al. Effect of empagliflozin on left ventricular mass in patients with type 2 diabetes mellitus and coronary artery disease: the EMPA-HEART CardioLink-6 randomized clinical trial. *Circulation* 2019;140:1693-702. PUBMED | CROSSREF

28. Scirica BM, Braunwald E, Raz I, et al. Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. *Circulation* 2014;130:1579-88. PUBMED | CROSSREF

29. Sinha B, Ghosal S. Meta-analyses of the effects of DPP-4 inhibitors, SGLT2 inhibitors and GLP1 receptor analogues on cardiovascular death, myocardial infarction, stroke and hospitalization for heart failure. *Diabetes Res Clin Pract* 2019;150:8-16. PUBMED | CROSSREF

30. Lee CS, Kim YG, Cho HJ, et al. Dipeptidyl peptidase-4 inhibitor increases vascular leakage in retina through VE-cadherin phosphorylation. *Sci Rep* 2016;6:29393. PUBMED | CROSSREF

31. Chang CY, Yeh YH, Chan YH, et al. Dipeptidyl peptidase-4 inhibitor decreases the risk of atrial fibrillation in patients with type 2 diabetes: a nationwide cohort study in Taiwan. *Cardiovasc Diabetol* 2017;16:159. PUBMED | CROSSREF

32. Kim D, Yang PS, Jang E, et al. 10-year nationwide trends of the incidence, prevalence, and adverse outcomes of non-valvular atrial fibrillation nationwide health insurance data covering the entire Korean population. *Am Heart J* 2018;202:20-6. PUBMED | CROSSREF

33. Liu X, Liu H, Wang L, Zhang L, Xu Q. Role of sacubitril-valsartan in the prevention of atrial fibrillation occurrence in patients with heart failure: a systematic review and meta-analysis of randomized controlled trials. *PLoS One* 2022;17:e0263131. PUBMED | CROSSREF