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ORIGINAL RESEARCH

Differing Efficacy of Dapagliflozin Versus Empagliflozin on the Risk of Incident Atrial Fibrillation in Patients With Type 2 Diabetes: A Real-World Observation Using a Nationwide, Population-Based Cohort

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BACKGROUND: Meta-analyses of large clinical trials investigating SGLT2 (sodium-glucose cotransporter-2) inhibitors have suggested their protective effects against atrial fibrillation in patients with type 2 diabetes. However, the results were predominantly driven from trials involving dapagliflozin.

METHODS AND RESULTS: We used a nationwide, population-based cohort of patients with type 2 diabetes who initiated either dapagliflozin or empagliflozin between May 2016 and December 2018. An active-comparator, new-user design was used, and the 2 groups of patients were matched using propensity scores. The primary outcome was incident nonvalvular atrial fibrillation, which was analyzed using both the main intention-to-treat and sensitivity analysis that censored patients who skipped their medications for ≥30 days. Men ≥55 years of age and women ≥60 years of age with ≥1 traditional risk factor or those with established cardiovascular disease were categorized as high cardiovascular risk group. Patients not included in the high-risk group were categorized as low risk. After 1:1 propensity-score matching, a total of 137 928 patients (mean age, 55 years; 58% men) were included and followed up for 2.2±0.6 years. The risk of incident atrial fibrillation was significantly lower in the dapagliflozin group in both the main (hazard ratio [HR], 0.885 [95% CI, 0.789–0.992]) and sensitivity analyses (HR, 0.835 [95% CI, 0.719–0.970]). Notably, this was consistent in both the low and high cardiovascular risk groups. There was no effect modification by age, sex, body mass index, duration of diabetes, or renal function.

CONCLUSIONS: This real-world, population-based study demonstrates that patients with type 2 diabetes using dapagliflozin may have a lower risk of developing nonvalvular atrial fibrillation than those using empagliflozin.

Key Words: atrial fibrillation ■ dapagliflozin ■ empagliflozin ■ sodium-glucose cotransporter-2 inhibitor ■ type 2 diabetes

Atrial fibrillation (AF) is the most common cardiac arrhythmia that has become a growing concern in aging societies. The prevalence of AF is on the rise due to increased life expectancy, better detection, and improved survival rates of patients with AF or comorbidities that promote the risk of AF.[1] Type 2

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CLINICAL PERSPECTIVE

What Is New?

- This study serves as the first real-world, population-based cohort study, highlighting the differential risks of atrial fibrillation between dapagliflozin and empagliflozin in patients with type 2 diabetes across a range of cardiovascular risks.
- New users of dapagliflozin were associated with a lower risk of atrial fibrillation compared with those initiating empagliflozin.

What Are the Clinical Implications?

- The exclusive advantage of dapagliflozin against atrial fibrillation among sodium-glucose cotransporter-2 inhibitors, as demonstrated in previous meta-analyses of randomized clinical trials, appears to be mirrored in our real-world observational data.
- Our research potentially expands the relevance of previous meta-analyses, which were largely confined to individuals at high cardiovascular risk, by extending its applicability to a more diverse range of patients with type 2 diabetes.

Nonstandard Abbreviations and Acronyms

ASD	absolute standardized difference
DECLARE-TIMI 58	Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58
DPP4	dipeptidyl peptidase-4
NHIS	National Health Insurance Service
PS	propensity score
SGLT	sodium-glucose cotransporter
T2D	type 2 diabetes

diabetes (T2D) is 1 of these comorbidities and was found to be an independent risk factor for the development of AF.[2,3] The underlying mechanisms that mediate this association include atrial structural remodeling, proarrhythmic electrical remodeling, unregulated sympathetic activity induced by cardiac autonomic neuropathy, oxidative stress, inflammation, and glycemic fluctuations.[4–7] Given the increasing global prevalence of T2D, interventions that can reduce or slow these mechanisms are required for aging societies.

SGLT2 (sodium-glucose cotransporter-2) inhibitors are a relatively new class of oral hypoglycemic agents that have demonstrated cardiovascular benefits over placebos in multiple randomized controlled trials.[8–14] These benefits are believed to be due to a reduction of sympathetic activity, oxidative stress, and glycemic fluctuations,[15–18] which are also suggested mechanisms linking T2D and AF. Correspondingly, recent meta-analyses with pooled data from randomized controlled trials investigating SGLT2 inhibitors have suggested that they may confer an additional benefit of lowering the risk of AF incidence.[19–22] However, upon a closer look into these meta-analyses, the reduced incidence of AF was mainly driven by trials that used dapagliflozin. In addition, these randomized controlled trials were confined to patients with high cardiovascular risk.

Oral hypoglycemic agents within the same drug class may exhibit varying antiarrhythmic effects. For example, among thiazolidinediones, pioglitazone, but not rosiglitazone, has been linked to a lower risk of incident AF.[23] Whether the protective effect against incident AF is more exclusive to dapagliflozin or is a class effect of SGLT2 inhibitors needs further clarification. Furthermore, it remains to be clarified whether patients with low cardiovascular risk can also benefit from these effects. For this purpose, we compared the risk of incident nonvalvular AF between the 2 most-widely used SGLT2 inhibitors, dapagliflozin and empagliflozin, using real-world data from a nationwide, population-based cohort in Korea.

METHODS

The data used in this study are available to authorized researchers from designated terminals (https://nhiss.nhis.or.kr/), subject to approval by the Korean National Health Insurance Service (NHIS).

Study Cohort

The study population was selected from the database of the NHIS, which is a single insurer covering almost the entire Korean population. The database characteristics and its validity have been previously described in detail.[24] Briefly, the NHIS database contains sociodemographic information and data on health care service use including outpatient visits and hospitalizations for the Korean population.[24] In the NHIS database, individual medical records are maintained based on the *International Classification of Diseases, Tenth Revision* (*ICD-10*) codes. The NHIS–Health Screening Program database, which can be interlocked with the NHIS database, includes the results of annual or biennial health check-ups, which are recommended and provided without charge for all insured Koreans. The health check-ups include physical examinations, measures of

blood pressure or body mass index, blood tests, and self-questionnaires on lifestyle behavior such as smoking, alcohol consumption, and physical activity.

The institutional review board of Seoul National University Hospital approved the study protocol (institutional review board number: E-2310-107-1478), and the requirement for informed consent was waived, because the NHIS provides an anonymized data set. We followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines.

Study Design, Confounder Control, and Propensity-Score Matching

We used an active comparator, new-user design, and followed an intention-to-treat approach to define drug exposure for the main analysis. We identified patients with T2D using *ICD-10* codes E11–E14 and included those who started SGLT2 inhibitors between May 2016 and December 2018 (Figure 1). Of note, dapagliflozin and empagliflozin gained approval for insurance coverage in Korea in January 2016 and May 2016, respectively, and thus, the study cohort was constructed to include patients who initiated the SGLT2 inhibitors after both drugs were approved. The date of the first prescription of either SGLT2 inhibitor was considered the index date, and patients who underwent national health screening within 2 years of the index date were included (Figure S1). If the patient underwent multiple health screenings within 2 years of the index date, the data closest to the index date were used. Data on the medical history of the study population were available from the NHIS database starting from 2002, and these data were used to assess baseline comorbidities, medication, and duration of diabetes. Comorbidities were assessed using *ICD-10* codes, medications used, and procedure codes recorded within 3 years before the index date (Table S1). We excluded any patients who were <20 years of age, were exposed to both drugs during the study period, were diagnosed with AF or end-stage renal disease before the index date, and who used SGLT2 inhibitors other than dapagliflozin or empagliflozin. We also excluded patients who developed AF within 30 days of the initiation of dapagliflozin or empagliflozin, because this was considered too short a duration for the drug to have a discernible impact on the development of AF. Finally, we excluded patients with missing variables.

The propensity score (PS) of each group was calculated using a logistic regression model based on 49 covariates presented in Data S1. These covariates included variables related to diabetes control, such as fasting blood glucose, duration of diabetes, and prior and concomitant oral hypoglycemic agents used, as well as demographic variables, anthropometric variables, laboratory results, lifestyle habits, and various comorbidities. In this study, we stratified the study population by cardiovascular risk, using a definition previously defined by the DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58) investigators.[10] Specifically, the high cardiovascular risk group comprised men ≥55 years of age and women ≥60 years of age with ≥1 traditional risk factor of hypertension, dyslipidemia, or current tobacco use, as well as patients with a history of ischemic heart disease, ischemic stroke, or peripheral artery disease. Patients not included in the high-risk group were categorized as low risk. Each dapagliflozin user was matched with 1 empagliflozin user using a 1:1 nearest-neighbor matching algorithm without replacement.

Study Outcomes

The primary outcome of the study was incident nonvalvular AF, which was defined as ≥1 hospitalization or ≥2 outpatient visits, with a primary diagnosis of AF. The *ICD-10* codes I48.0–I48.4 and I48.9 were used to identify patients who developed nonvalvular AF; this operational definition in the Korean NHIS database was previously validated with a positive predictive value of 94.1%.[25] We also assessed hospitalization for heart failure as an exploratory outcome, given its robust benefits in patients with T2D regardless of prior heart failure or atherosclerotic cardiovascular disease status, and its potential role in precipitating AF.[8–14,26] The risk of hypoglycemia, which might potentially trigger AF, was also assessed as a safety outcome; although SGLT2 inhibitors have a low risk of hypoglycemia due to their insulin-independent mechanism of action, they can increase the risk of hypoglycemia in a real-world setting where they are used in combination with other hypoglycemic agents.[27] Definitions for these conditions are detailed in Table S1.

Statistical Analysis

Patients were followed from drug initiation to the outcome event, death, or the end of the study period, whichever came first. Patients whose health care coverage ended (ie, emigration) were censored. Baseline characteristics were presented as numbers (percentages) for categorical variables and mean±SD or median (interquartile range [IQR]) for continuous variables. Absolute standardized differences (ASDs) were calculated to assess the comparability between the 2 groups before and after PS matching. An ASD value <0.10, which is equivalent to a φ coefficient of 0.05, was considered to indicate a negligible difference between the groups.[28] The incidence rate was calculated as the number of outcomes divided by the total follow-up duration per 1000 person-years. The incidence probability was plotted using Kaplan-Meier curves, with statistical comparisons using the log-rank test. Cox proportional hazard regression was used to estimate hazard ratios

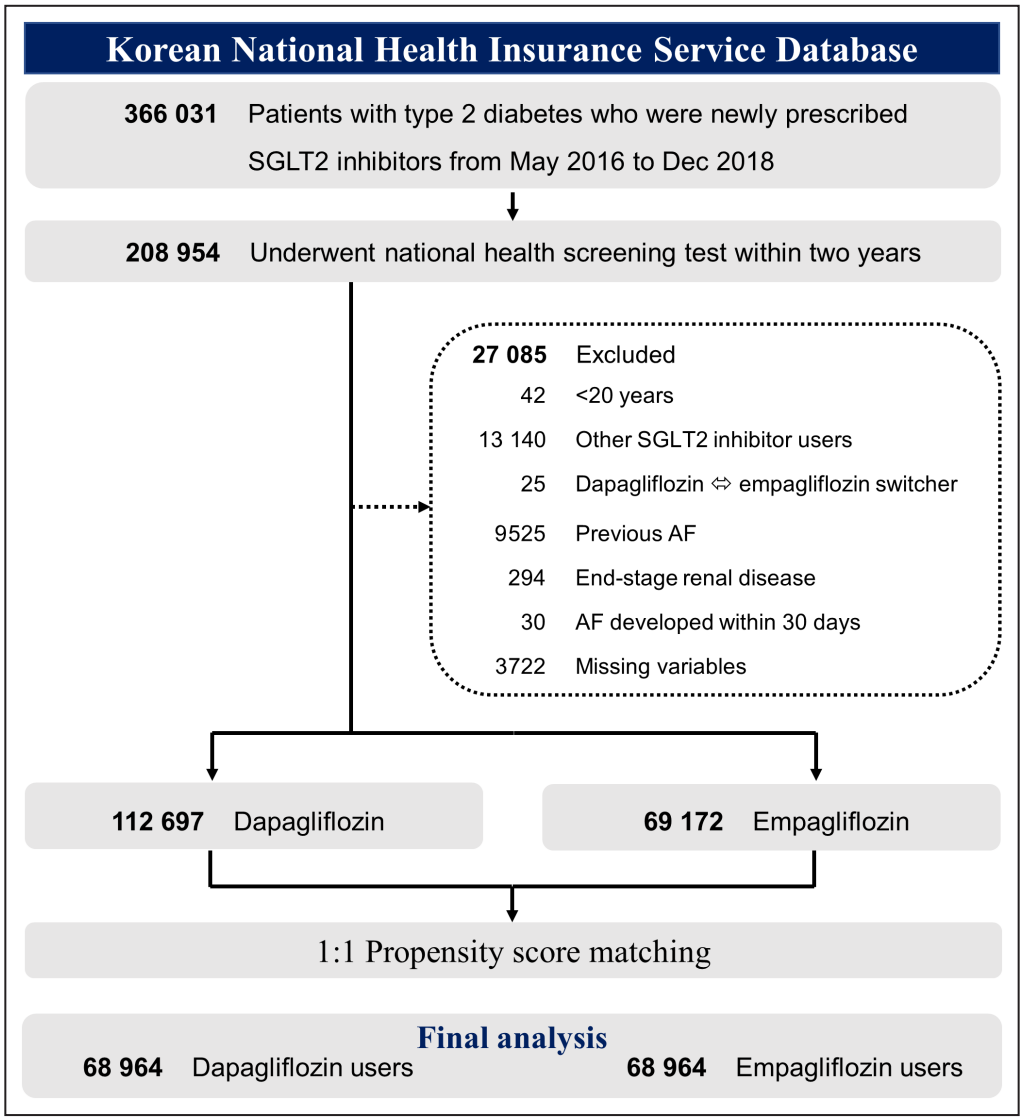

Figure 1. Flowchart of patient inclusion in the study cohort of new users of dapagliflozin and empagliflozin in Korea.
AF indicates atrial fibrillation; and SGLT2, sodium-glucose cotransporter 2.

(HRs), and a robust variance estimator was used in the computation of the standard error for the effect estimates. The proportional hazards assumption was assessed visually and confirmed for each variable using both the Schoenfeld residuals plot and the log-log survival plot. The results were considered significant if the 95% CI did not overlap or cross 1.0.

Subgroup analyses according to age (<65 and ≥65 years), sex, body mass index (<25 kg/m^2 and ≥25 kg/m^2), duration of diabetes (<5 and ≥5 years), cardiovascular risk group, and a prior history of chronic kidney disease or heart failure were conducted to evaluate possible interactions. Two-sided *P* values for the interaction of <0.05 were considered significant.

We also conducted a sensitivity analysis, which additionally censored patients who discontinued the study drug, defined as a gap of ≥30 days between successive prescriptions. In addition, the medication possession ratio, which is the total days' supply of a medication divided by the follow-up period, was calculated for each group to compare prescription adherence between treatment groups. SAS software (version 9.4; SAS Institute, Cary, NC) was used for all statistical analyses.

RESULTS

Baseline Characteristics

We initially identified 366 031 patients who initiated SGLT2 inhibitor therapy between May 2016 and December 2018. Among these patients, 208 954

underwent health screening within 2 years before the index date, allowing us to use clinical data including vital signs and laboratory test results. After applying exclusion criteria, we identified 112 697 new dapagliflozin users and 69 172 new empagliflozin users. The 2 groups did not significantly differ in baseline characteristics, even before PS matching (ASD <0.10), except for number of hospital visits during follow-ups (Table S2). After PS matching at a 1:1 ratio, 68 964 dapagliflozin users and 68 964 empagliflozin users were included in the final analyses. Of note, there were no clinically meaningful differences observed between patients who underwent health screenings and those who did not, or between those who were matched and not matched using PSs. In addition, the dapagliflozin group and the empagliflozin group were well matched, with ASDs <0.05 for all variables, including number of hospital visits during follow-ups (Table 1). The mean age was 55±11 years, and ≈58% of the study population were men. The median durations of diabetes were 6.9 (IQR, 5.5) years and 7.0 (IQR, 5.5) years for the dapagliflozin and empagliflozin groups, respectively. Notably, patients with low cardiovascular risk constituted 38.9% (26 849/68 964) and 37.3% (25 715/68 964) of each group, respectively.

Study Outcomes

During the mean follow-up period of 2.2 years, nonvalvular AF had newly developed in 1183 patients, with 553 and 630 events occurring in the dapagliflozin and empagliflozin groups, respectively. The cumulative incidence of AF was significantly lower in dapagliflozin users compared with empagliflozin users (Figure 2). On Cox regression analysis, dapagliflozin was associated with a significantly lower risk of incident AF (HR, 0.885 [95% CI, 0.789–0.992]; Table 2). Of note, the medication possession ratio levels between the 2 treatment groups were not statistically different (mean 0.62±0.40 and 0.60±0.40 for empagliflozin and dapagliflozin users, respectively) (Table S3). The sensitivity analysis, which censored patients who discontinued treatment for ≥30 days, also showed consistent results (HR, 0.835 [95% CI, 0.719–0.970]; Table 2; Figure S2).

Subgroup analyses demonstrated that dapagliflozin users were associated with a consistently lower risk of AF incidence, regardless of age, sex, body mass index, duration of diabetes, and prior history of chronic kidney disease. Importantly, this trend was consistent in both the low and high cardiovascular risk groups. There were no significant interaction effects on the multiplicative scale with respect to the aforementioned subgroups (Table 3). The exploratory outcome of heart failure hospitalization and the safety outcome of hypoglycemic events were not significantly different between the 2 groups (HR for heart failure hospitalization,

Table 1. Baseline Characteristics

Variables	Empagliflozin (n=68 964)	Dapagliflozin (n=68 964)	ASD
Age, y	55.8±11.0	55.4±10.9	0.0312
Men	39 991 (58.0)	40 236 (58.3)	0.0071
Body mass index, kg/m^2	26.9±4.0	26.9±4.0	0.0109
Systolic blood pressure, mm Hg	128.4±14.8	128.4±14.9	0.0002
Diastolic blood pressure, mm Hg	78.7±10.0	78.8±10.0	0.0091
Duration of diabetes, y	7.0±5.5	6.9±5.5	0.0283
<5	4796 (7.0)	4346 (6.3)	0.0261
<10	30 346 (44.0)	30 346 (44.0)	0
≥10	33 822 (49.0)	34 272 (49.7)	0.0132
Income, low 20%	13 969 (20.3)	13 862 (20.1)	0.0040
Urban residence	29 592 (42.9)	29 678 (43.0)	0.0024
Smoking habit			
Nonsmoker	36 911 (53.52)	36 793 (53.35)	0.0034
Ex-smoker	15 103 (21.9)	15 109 (21.91)	0.0002
Current smoker	16 950 (24.58)	17 062 (24.74)	0.0037
Alcohol consumption habit			
Nondrinker	40 078 (58.11)	39 716 (57.59)	0.0105
Mild drinker	23 052 (33.43)	23 321 (33.82)	0.0083
Heavy drinker	5834 (8.46)	5927 (8.59)	0.0047
Regular exerciser	14 377 (20.85)	14 250 (20.66)	0.0047
Comorbidities			
Hypertension	39 575 (57.39)	39 156 (56.78)	0.0123
Dyslipidemia	50 250 (72.86)	49 860 (72.3)	0.0126
Congestive heart failure	258 (0.37)	226 (0.33)	0.0068
Myocardial infarction	868 (1.26)	796 (1.15)	0.0101
Peripheral artery disease	21 101 (30.6)	20 773 (30.12)	0.0104
Ischemic stroke	541 (0.78)	545 (0.79)	0.0011
COPD	11 990 (17.39)	11 911 (17.27)	0.0032
Liver cirrhosis	803 (1.16)	827 (1.2)	0.0037
Hyperthyroidism	3409 (4.94)	3384 (4.91)	0.0014
Medication			
ACE inhibitor	2012 (2.92)	1880 (2.73)	0.0115
ARB	34 570 (50.13)	34 311 (49.75)	0.0076
β-Blocker	6799 (9.86)	6455 (9.36)	0.0170
Calcium channel blocker	22 066 (32)	21 828 (31.65)	0.0075
Diuretics	9532 (13.82)	9440 (13.69)	0.0038
Antidiabetic agents used before the index date			
≥3 antidiabetic agents users	32 673 (47.38)	32 250 (46.76)	0.0124
Metformin	64 666 (93.77)	64 706 (93.83)	0.0025
Sulfonylurea	37 347 (54.15)	36 839 (53.42)	0.0146
Meglitinides	324 (0.47)	315 (0.46)	0.0015
Thiazolidinedione	10 378 (15.05)	10 246 (14.86)	0.0053
Dipeptidyl peptidase-4 inhibitor	43 297 (62.78)	42 946 (62.27)	0.0105

(*Continued*)

Table 1. Continued

Variables	Empagliflozin (n=68 964)	Dapagliflozin (n=68 964)	ASD
α-Glucosidase inhibitor	1455 (2.11)	1395 (2.02)	0.0063
Insulin	9793 (14.2)	9921 (14.39)	0.0054
Glucagon-like peptide-1 agonist	603 (0.87)	591 (0.86)	0.0011
Antidiabetic agents used with SGLT2 inhibitors			
≥3 antidiabetic agents users	28 847 (41.83)	28 434 (41.23)	0.0122
Metformin	58 521 (84.86)	58 732 (85.16)	0.0084
Sulfonylurea	27 032 (39.2)	26 689 (38.7)	0.0103
Meglitinides	28 (0.04)	21 (0.03)	0.0053
Thiazolidinedione	1187 (1.72)	1103 (1.6)	0.0094
Dipeptidyl peptidase-4 inhibitor	5009 (7.26)	5164 (7.49)	0.0088
α-Glucosidase inhibitor	110 (0.16)	100 (0.15)	0.0025
Insulin	5192 (7.53)	5433 (7.88)	0.0131
Glucagon-like peptide-1 agonist	47 (0.07)	60 (0.09)	0.0071
Laboratory results			
Hemoglobin, g/dL	14.4±1.6	14.4±1.6	0.0201
Fasting blood glucose, mg/dL	157.6±55.4	158.1±56.0	0.0105
Total cholesterol, mg/dL	182.7±46.1	183.7±46.2	0.0222
Estimated glomerular filtration rate	92.9±47.6	93.2±46.3	0.0058
<60 mL/min per 1.73 m^2	29 152 (42.27)	29 952 (43.43)	0.0234
60–90 mL/min per 1.73 m^2	16 233 (23.54)	16 058 (23.28)	0.0061
≥90 mL/min per 1.73 m^2	23 579 (34.19)	22 954 (33.28)	0.0192
Urine protein dipstick test			
Negative	59 136 (85.75)	59 124 (85.73)	0.0006
Trace	3473 (5.04)	3622 (5.25)	0.0095
Positive	6355 (9.21)	6218 (9.02)	0.0066
Follow-up duration, y	2.19±0.64	2.17±0.65	0.0252
Health care use during follow-up			
Total hospital visits	62.8±60.3	63±62.6	0.0029
Outpatient visits	61.8±59.6	61.9±61.8	0.0016
Inpatient visits	1.1±2.9	1.1±3.2	0.0270

ACE indicates angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; ASD, absolute standardized difference; COPD, chronic obstructive pulmonary disease; and SGLT2, sodium-glucose cotransporter-2.

0.923 [95% CI, 0.752–1.134]; HR for hypoglycemia, 1.065 [95% CI, 0.937–1.211]; Table S4).

DISCUSSION

This large, population-based cohort involving ≈140 000 Korean patients with T2D suggests that the risk of incident AF is lower in new users of dapagliflozin than in new users of empagliflozin. This study provides credible evidence through consistent findings from both the main and sensitivity analyses; dapagliflozin users exhibited an 11.5% lower risk of AF in the main intention-to-treat analysis, and a 16.5% lower risk of AF in the sensitivity analysis. The results were consistent across all subgroups of age, sex, body mass index, duration of diabetes, and a prior history of chronic kidney disease or heart failure. Notably, consistent results were also observed in patients with low cardiovascular risk, a group of patients who were unexplored in previous clinical trials or meta-analyses.[19–22,29,30]

The strength of our study lies in its large sample size, as well as the well-balanced distribution of the 2 groups. Specifically, the 2 groups were well-matched, with the largest ASD for age (0.0312) showing only a 0.4-year difference, which is clinically negligible. The similarities between the 2 groups before PS matching are attributed to the fact that in Korea, dapagliflozin and empagliflozin received regulatory approval for the same medical indications, and their prices are comparable, with both drugs covered by insurance. For example, as of 2017 (which is in the middle of the study period), the actual costs paid by patients with T2D for 10 mg of empagliflozin and dapagliflozin were $70.9 per year and $80.0 per year, respectively. Thus, the decision on which drug to prescribe was at the discretion of the physician. Matching with socioeconomic status may have further reduced biases associated with differences in drug cost. The diabetic status of both groups was also well balanced; there were negligible differences between covariates such as fasting plasma glucose levels, duration of diabetes, and prior or concomitant oral hypoglycemic agents used. It is also important to note that the amount of health care use during follow-up, which could significantly influence the detection of AF, did not differ between the 2 groups. Given the negligible ASD values in 49 covariates before PS matching, as well as further reduction of potential bias through PS matching, we believe that the patients in each arm are unlikely to have had clinically meaningful differences in baseline characteristics. Additionally, this study is distinguished by the inclusion and analysis of a significant number of patients with low cardiovascular risk, who were excluded from previous studies that exclusively focused on patients with high cardiovascular risk or established cardiovascular diseases.[19–22,29–32] In the present study, patients with low cardiovascular risks comprised almost two-fifths of the study population. It is noteworthy that the study results were consistent in this group of patients, which may extend the generalizability of the previous results on high-risk groups to a wider range of patients with T2D.

Interpretation and Comparison With Previous Studies

Several mechanisms have been proposed to explain the protective effect of SGLT2 inhibitors against incident AF in patients with T2D. These potential causes

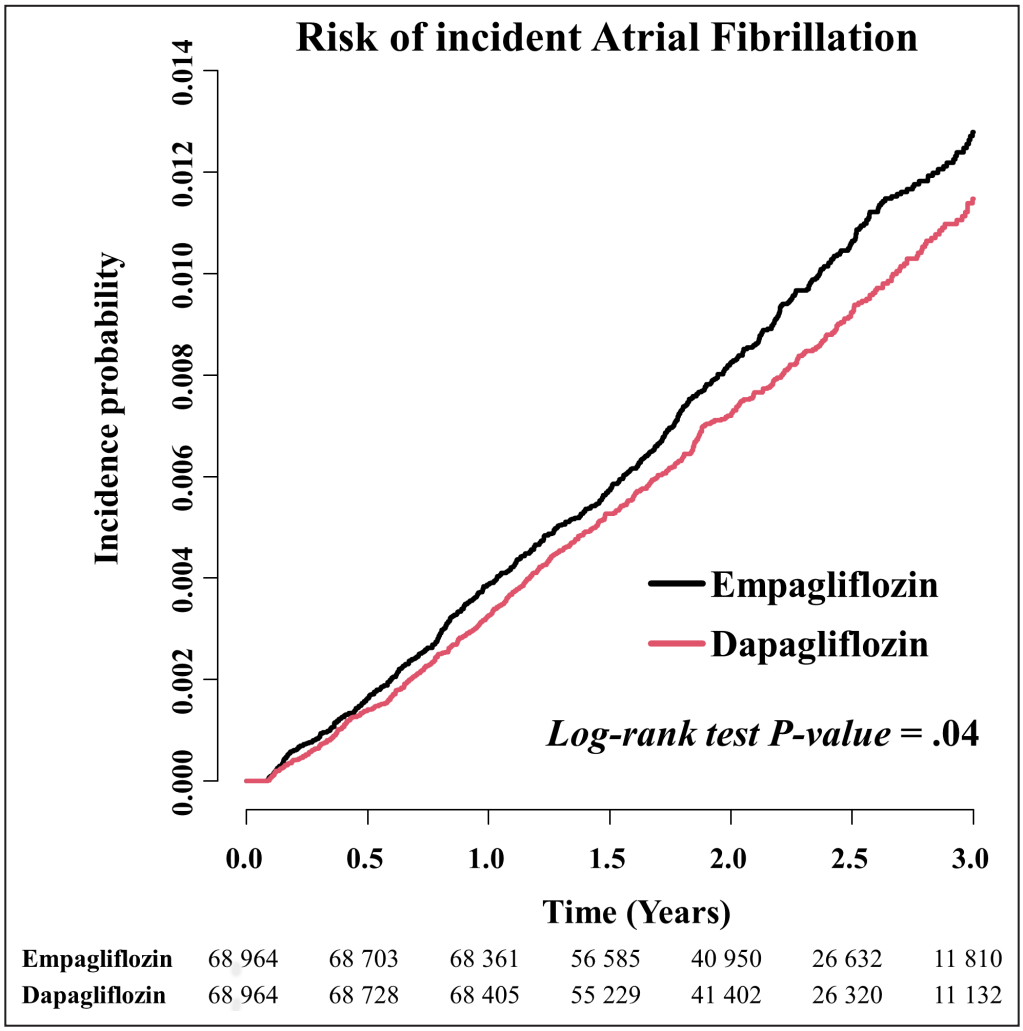

Figure 2. Incidence probabilities of atrial fibrillation.
Different incidence probabilities of atrial fibrillation were compared between new dapagliflozin and empagliflozin users. The outcome was analyzed using the intention-to-treat approach.

include reductions in electrical and structural remodeling of the atrium, oxidative stress, as well as arrhythmogenic epicardial fat.[15–18] However, the exact mechanism explaining the distinct and superior benefit of dapagliflozin has not been established. If the anti-AF mechanisms mentioned above are a class effect shared by all SGLT2 inhibitors, the higher SGLT2 and SGLT1 affinity of dapagliflozin compared with that of empagliflozin may explain our findings.[31] However, some studies support that the observed findings in our study might be drug specific, rather than a class effect. A prospective cohort study of patients with T2D and congestive heart failure in Japan reported that empagliflozin was distinctively associated with increased

Table 2. Main and Sensitivity Analyses

Variable	N	No. of incident AF	Follow-up duration (person-years)	Incidence rate (per 1000 person-years)	Hazard ratio (95% CI)
Intention-to-treat analysis					
Empagliflozin	68964	630	150864	4.176	1 (reference)
Dapagliflozin	68964	553	149743	3.693	0.885 (0.789–0.992)
Sensitivity analysis					
Empagliflozin	68964	384	101328	3.790	1 (reference)
Dapagliflozin	68964	312	98706	3.161	0.835 (0.719–0.970)

AF indicates atrial fibrillation.

Table 3. Subgroup Analysis

Variable	SGLT2 inhibitor	N	No. of incident AF	Incidence rate (per 1000 person-years)	Adjusted HR (95% CI)	*P* for interaction
Age						
<65 y	Empagliflozin	54 950	342	2.843	1 (reference)	0.7626
	Dapagliflozin	55 750	303	2.514	0.882 (0.755–1.029)	
≥65 y	Empagliflozin	14 014	288	9.427	1 (reference)	
	Dapagliflozin	13 214	250	8.557	0.914 (0.771–1.083)	
Sex						
Men	Empagliflozin	39 991	400	4.621	1 (reference)	0.1828
	Dapagliflozin	40 236	330	3.845	0.843 (0.728–0.975)	
Women	Empagliflozin	28 973	230	3.577	1 (reference)	
	Dapagliflozin	28 728	223	3.489	0.989 (0.822–1.189)	
Body mass index						
<25 kg/m^2	Empagliflozin	22 720	213	4.267	1 (reference)	0.1485
	Dapagliflozin	22 083	202	4.195	1.004 (0.828–1.217)	
≥25 kg/m^2	Empagliflozin	46 244	417	4.131	1 (reference)	
	Dapagliflozin	46 881	351	3.455	0.841 (0.730–0.970)	
Duration of diabetes						
<5 y	Empagliflozin	29 152	209	3.315	1 (reference)	0.2469
	Dapagliflozin	29 952	169	2.666	0.812 (0.663–0.994)	
≥5 y	Empagliflozin	39 812	421	4.794	1 (reference)	
	Dapagliflozin	39 012	384	4.447	0.938 (0.817–1.078)	
Chronic kidney disease						
No	Empagliflozin	64 168	530	3.776	1 (reference)	0.9831
	Dapagliflozin	64 618	474	3.384	0.899 (0.794–1.017)	
Yes	Empagliflozin	4796	100	9.536	1 (reference)	
	Dapagliflozin	4346	79	8.159	0.895 (0.666–1.204)	
Congestive heart failure						
No	Empagliflozin	68 706	618	4.110	1 (reference)	0.612
	Dapagliflozin	68 738	540	3.618	0.892 (0.795–1.002)	
Yes	Empagliflozin	258	12	23.789	1 (reference)	
	Dapagliflozin	226	13	26.596	1.096 (0.498–2.412)	
Cardiovascular risk group*						
Low risk	Empagliflozin	25 715	98	1.737	1 (reference)	0.396
	Dapagliflozin	26 849	82	1.430	0.829 (0.618–1.111)	
High risk	Empagliflozin	43 239	532	5.632	1 (reference)	
	Dapagliflozin	42 115	471	5.097	0.911 (0.805–1.032)	

AF indicates atrial fibrillation; HR, hazard ratio; and SGLT2, sodium-glucose cotransporter-2.

*The high cardiovascular risk group comprised (1) men ≥55 years of age and women ≥60 years of age with ≥1 traditional risk factor of hypertension, dyslipidemia, or current tobacco use; and (2) patients with a history of ischemic heart disease, ischemic stroke, or peripheral artery disease. Those not included in the high cardiovascular risk group were classified into the low cardiovascular risk group.

plasma aldosterone and noradrenaline levels, whereas there was no evidence of neurohormonal activation with dapagliflozin.[32] These findings partially explain a potentially greater protective effect against incident AF that is specific to dapagliflozin.

Previous cohort studies and meta-analyses that involve recent, large-scale randomized controlled trials are in line with the results of our study.[19–22,33–36] A retrospective cohort study by Chan et al compared the risk of AF in patients with T2D treated with SGLT2 inhibitors, glucagon-like peptide-1 receptor agonists, and DPP4 (dipeptidyl peptidase-4) inhibitors.[36] Although this study was not directly aimed at comparing the efficacies of SGLT2 inhibitors, subgroup analysis showed that only dapagliflozin was exclusively associated with a lower risk of new-onset AF when compared with DPP4 inhibitors. Moreover, several meta-analyses have suggested that the reports of reduced AF in patients using SGLT2 inhibitors compared with that in patients receiving placebos in the comprehensive pooled analyses were

mainly driven by dapagliflozin trials.[19,20,22,29,30] Thus, these previous studies indicated that dapagliflozin was the agent associated with a significantly reduced risk of AF in their subgroup analyses. In particular, a post hoc analysis of the DECLARE-TIMI 58 trial, which carried the most weight in the meta-analyses, showed that participants assigned to the dapagliflozin arm had a 19% lower risk of developing AF than those in the control arm.[29] In contrast, empagliflozin showed neutral or rather increased risks of AF or atrial flutter, despite the decreased risk of heart failure.[19,20,22] It is important to note that the subgroup analyses in these studies may have a higher likelihood of type II errors due to the lower statistical power when compared with the comprehensive pooled analyses including all SGLT2 inhibitors and trials.[37] Furthermore, several limitations might be present because the analyses were performed with study-level data, and the data obtained from adverse event documentation were not specifically designed for the systematic identification of AF in the clinical trials. Therefore, our study provides additional support for previous findings based on a larger sample of real-world, well-matched patients with T2D.

Limitations

Some limitations need to be acknowledged. First, although it seems that patients were allocated to either dapagliflozin or empagliflozin almost randomly at the discretion of the physician, as evidenced by negligible ASDs in the baseline characteristics even before PS matching, there may still be residual confounding due to the observational study design. Second, despite the large sample size, the study was limited to a single ethnic group with a relatively short follow-up duration. Third, the claims database did not provide information on the type or burden of AF, such as whether it was paroxysmal, persistent, or permanent, and this information therefore could not be evaluated in this study. The ongoing trials for empagliflozin (Empagliflozin and Atrial Fibrillation Treatment; NCT04583813), dapagliflozin (Use of Dapagliflozin to Reduce Burden of Atrial Fibrillation in Patients Undergoing Catheter Ablation of Symptomatic Atrial Fibrillation; NCT04792190), and for both medications (The Effect of SGLT-2 Inhibitor in Patient With Atrial Fibrillation and Diabetes Mellitus; NCT05029115) will provide additional data. In addition, although health care use between the 2 groups did not differ, the study could not investigate whether there existed any disparity in the use of medical resources such as mobile cardiac telemetry between them. Fourth, although SGLT2 inhibitors have been approved for use in patients with T2D and those with heart failure, this study only focused on the former. The number of patients who had both T2D and heart failure was too small to be analyzed, and the differential roles of dapagliflozin versus empagliflozin in patients with heart failure remain to be investigated. Finally, our study did not investigate underlying mechanisms for the differential efficacy of these 2 drugs (ie, dapagliflozin and empagliflozin) in relation to incident AF. Future research on different pharmacokinetics and pharmacodynamics of these 2 drugs is warranted.

CONCLUSIONS

This real-world, population-based study suggests that users of dapagliflozin have a lower risk of incident AF compared with users of empagliflozin among patients with T2D. This association was consistent in patients with diabetes at low as well as high risk for cardiovascular disease, which may further confirm and extend previous findings of the exclusive benefit of dapagliflozin against AF among SGLT2 inhibitors.

ARTICLE INFORMATION

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J.L. conducted overall research; contributed to the discussion; and wrote, reviewed, and edited the article. S.K., Y.-J.C., T.-M.R., and C.S.P. participated in analyzing the data and contributed to the discussion. B.K. and K.-D.H. analyzed the data. H.L. and J.-B.P. contributed to the discussion and reviewed the article. Y.-J.K. reviewed and edited the article. H.-J.L. and H.-K.K. reviewed, edited the article, and contributed to the discussion. All authors approved the final version of the article. J.L. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Disclosures

None.

Supplemental Material

Data S1
Tables S1–S4
Figures S1–S2

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