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Comparative effects of second-line oral antidiabetic medications on atrial fibrillation risk in patients with type 2 diabetes: a nationwide retrospective cohort study

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Abstract

Backgrounds Despite numerous studies investigating the effects of antidiabetic medications on cardiovascular outcomes, the optimal second-line oral antidiabetic medication for atrial fibrillation (AF) prevention remains unclear. This study aims to compare the effects of second-line oral antidiabetic medications including sodium-glucose cotransporter 2 (SGLT2) inhibitors, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, or sulfonylureas, on the risk of incident AF in patients with type 2 diabetes.

Methods This retrospective study analyzed data from the National Health Insurance Service data on adults with type 2 diabetes who simultaneously initiated metformin and second-line oral antidiabetic medication (SGLT2 inhibitors, thiazolidinediones, DPP-4 inhibitors, or sulfonylureas) between September 2014 and December 2017. Exact matching by sex and age categories was conducted in a 1:1:5:5 ratio corresponding to SGLT2 inhibitor, thiazolidinedione, DPP-4 inhibitor, and sulfonylurea users, with inverse probability of treatment weighting used to balance the baseline characteristics. The primary outcome was incident AF, which was analyzed using a Fine–Gray model treating all-cause mortality as a competing risk.

Results During a mean follow-up of 6.2 years, 774 cases of AF occurred among the 36,744 participants (mean age 55.3 years; 33.6% female). Compared with SGLT2 inhibitors, the risk of AF was significantly higher in patients using thiazolidinediones (subdistribution hazard ratio [SHR], 1.22; 95% confidence interval [CI], 1.09–1.36), DPP-4 inhibitor (SHR, 1.14; 95% CI, 1.02–1.28), and sulfonylureas (SHR, 1.20; 95% CI, 1.07–1.34). However, pairwise comparisons among

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thiazolidinediones, DPP-4 inhibitors, and sulfonylureas revealed no significant differences in AF risk. Subgroup analyses revealed significant effect modifications according to age, hypertension status, and renal function.

Conclusions This study showed that SGLT2 inhibitor use was associated with a significantly lower risk of AF than use of thiazolidinediones, DPP-4 inhibitors, and sulfonylureas.

Keywords Antidiabetic drug, type 2 diabetes, Atrial fibrillation

What is currently known about this topic?

Atrial fibrillation (AF) is a common cardiovascular complication in type 2 diabetes. However, the comparative effect of second-line oral antidiabetic medications on AF risk remains unclear.

What is the key research question?

Does the use of different second-line antidiabetic medications confer differential risks of incident AF among patients with type 2 diabetes?

What is new?

Treatment with SGLT2 inhibitors was associated with a significantly lower risk of AF compared with thiazolidinediones, DPP-4 inhibitors, and sulfonylureas. In contrast, pairwise comparisons among thiazolidinediones, DPP-4 inhibitors, and sulfonylureas showed no significant differences in AF risk.

How might this study influence clinical practice?

These findings suggest that SGLT2 inhibitors may be a preferred second-line option for AF prevention in patients with type 2 diabetes.

Introduction

Atrial fibrillation (AF) is the most commonly sustained cardiac arrhythmia [1], and significantly increases the risk of stroke, heart failure, and mortality [2]. The global prevalence of AF has risen substantially with an aging population and growing cardiovascular risk factors [1]. Among these risk factors, type 2 diabetes mellitus has emerged as an important contributor to the development of AF [3]. Diabetes-related risk factors such as hyperglycemia, obesity, and insulin resistance have been shown to contribute to incident AF [4, 5]. Additionally, the pathophysiological mechanisms of type 2 diabetes, including oxidative stress, inflammation, and impaired glycemic control, are strongly associated with AF [6, 7]. Given the significant effect of type 2 diabetes on AF, effective treatment strategies are essential to prevent diabetes-related AF.

Recently, the potential cardioprotective effects of antidiabetic medications have gained attention, suggesting that certain drugs may influence cardiovascular outcomes beyond glycemic control. However, the effect of second-line antidiabetic medications on AF remains inconclusive, with conflicting findings. In line with previous evidence that sodium-glucose cotransporter-2 (SGLT2) inhibitors exhibit cardioprotective effects [8–10], several retrospective studies have shown that SGLT2 inhibitors are associated with a lower risk of AF compared with dipeptidyl peptidase-4 (DPP-4) inhibitors [11–13]. Nevertheless, meta-analyses and large clinical trials have reported no significant difference in the incidence of AF among patients treated with SGLT2 inhibitors versus placebo or insulin therapy [14, 15]. Similarly, although a cohort study suggested that DPP-4 inhibitors were associated with a lower risk of AF [16], larger cohort studies and cardiovascular outcome trials have found no significant association [17, 18]. Conversely, sulfonylureas, which are commonly associated with hypoglycemia [19], have been linked to an increased risk of AF compared to metformin [20, 21]. Despite these studies examining the effects of antidiabetic medications on AF development, the optimal treatment for AF prevention remains unclear due to the limited number of direct comparative studies among second-line oral antidiabetic medications. Therefore, this study aims to compare the effects of second-line oral antidiabetic medications including SGLT2 inhibitors, thiazolidinediones, DPP-4 inhibitors, and sulfonylureas, on the risk of incident AF in patients with type 2 diabetes.

Methods

Data source

This study utilized data from the National Health Insurance Service (NHIS), which is a public, single-payer system covering 98% population in South Korea. Data were obtained from the NHIS database. The NHIS is a public, single-payer system that covers 98% of South Korea [22]. The remaining 2% of lower-income individuals are covered by a government Medical Aid program. The NHIS database includes data on health screening, healthcare utilization, sociodemographic variables, and mortality. The NHIS provides regular health screening programs annually for non-office workers and biennially for office workers, non-workers, and dependent subscribers aged over 40 years. All diagnoses were based on the International Classification of Diseases, 10th revision (ICD-10).

This study adhered to the Declaration of Helsinki, and the protocol was approved by the Institutional Review Board of the Yonsei University Health System (4–2024-0231). Informed consent was not required because all the data provided by the NHIS (2024–08-1–030) were anonymized.

Study population

This study constructed an incident type 2 diabetes cohort based on the following criteria: patients aged ≥ 19 years who were diagnosed with type 2 diabetes, identified by ICD-10 codes E11–E14, initiated metformin between September 2014 and December 2017, and underwent a health screening within 1 year before or during the prescription year. Patients diagnosed with type 1 diabetes mellitus (ICD-10 code E10) or those who had prior use of other antidiabetic medications were excluded.

Among this cohort, this study included patients who simultaneously initiated combination therapy with metformin and one of the second-line antidiabetic medications (i.e., SGLT2 inhibitors, thiazolidinediones, DPP-4 inhibitors, or sulfonylureas) for the first time between September 2014 and December 2017. Patients were considered to have started combination therapy if metformin and second-line agents were prescribed for ≥ 80% of the days within 90 days after metformin initiation [23]. The index date was defined as 90 days after the initiation of second-line antidiabetic medications. Patients were excluded if they had (1) a diagnosis of AF, (2) a history of valvular disease, (3) a history of pacemaker or implantable cardioverter-defibrillator insertion, or (4) prior use of antiarrhythmic drugs or anticoagulation therapy before the index date.

After applying the exclusion criteria, patients were exact-matched by sex and age categories (20–39, 40–64, and ≥ 65 years) across treatment groups. This matching was implemented to address substantial baseline imbalances in age and sex distribution among drug classes, which could compromise the stability of subsequent weighting procedures. To improve statistical efficiency while retaining comparability, the exact-matching process was performed using a 1:5:5 ratio for thiazolidinedione, DPP-4 inhibitor, and sulfonylurea users relative to SGLT2 inhibitor users, a ratio selected to balance precision gains with preservation of the available sample [24]. After exact matching on age and sex, inverse probability of treatment weighting (IPTW) was applied as a second-stage adjustment to address residual imbalances and to achieve covariate balance across the remaining baseline characteristics [25]. A total of 36,744 patients were included in the final analysis (Fig. 1).

Data collection

The health screening programs collected demographic data, anthropometric measurements, and health-related behaviors and included laboratory tests such as fasting glucose, serum creatinine, and total cholesterol. The estimated glomerular filtration rate (eGFR) was calculated using the 2021 Chronic Kidney Disease Epidemiology Collaboration equation [26]. Economic status was determined based on the type of healthcare insurance coverage. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Smoking status and alcohol consumption data were obtained using standardized self-reported questionnaires. The participants reported exercise frequency and physical activity intensity categorized into three levels: vigorous exercise (running, aerobics, fast cycling, fieldwork, and carrying heavy objects upstairs), moderate exercise (brisk walking, tennis, cycling at normal speed, carrying light objects, and cleaning), and walking. Regular exercise was defined, based on self-reported questionnaire, as engaging in moderate-intensity exercise for at least five days per week or vigorous-intensity exercise for at least three days per week. Comorbidities and outcome diagnoses were identified using the ICD-10 codes based on the NHIS claims database (Supplement Table 1). Medication use, including antihypertensive and antiplatelet agents, was assessed based on prescription claim records for drugs prescribed for at least 90 days within the one year preceding the index date (Supplement Table 2).

Primary outcome

The primary outcome was AF development. Incident AF was defined as either a discharge diagnosis or being confirmed twice in the outpatient data based on the ICD-10 codes (I48.0–I48.4 and I48.9). The positive predictive value of this definition was 94.1% in previous studies [27, 28]. Patients were followed up from the index date until AF development, death, or the end of the study period (December 31, 2022).

Statistical analysis

Baseline characteristics were described according to second-line antidiabetic medication. To balance baseline characteristics across second-line antidiabetic medications, we applied the covariate balancing propensity score (CBPS) to estimate generalized propensity scores for a multi-category treatment and derived stabilized inverse-probability weights targeting the average treatment effect (ATE) to reduce the variability of the weights and control for the inflation of the effective sample size. The following baseline variables were included in the CBPS model: age, sex, BMI, economic status, alcohol consumption, smoking status, regular exercise, comorbidities (hypertension, dyslipidemia, congestive heart failure [HF], myocardial infarction, cerebrovascular diseases, chronic obstructive pulmonary disease, and thyroid diseases), laboratory tests (fasting glucose and eGFR), and medication use (antiplatelets, renin–angiotensin system blockers, beta-blockers, and other antihypertensive drugs). Age, BMI, fasting glucose level, and eGFR were treated as continuous variables, whereas sex, alcohol intake status, smoking status, regular exercise, comorbidities, and medication use were treated as categorical variables. The

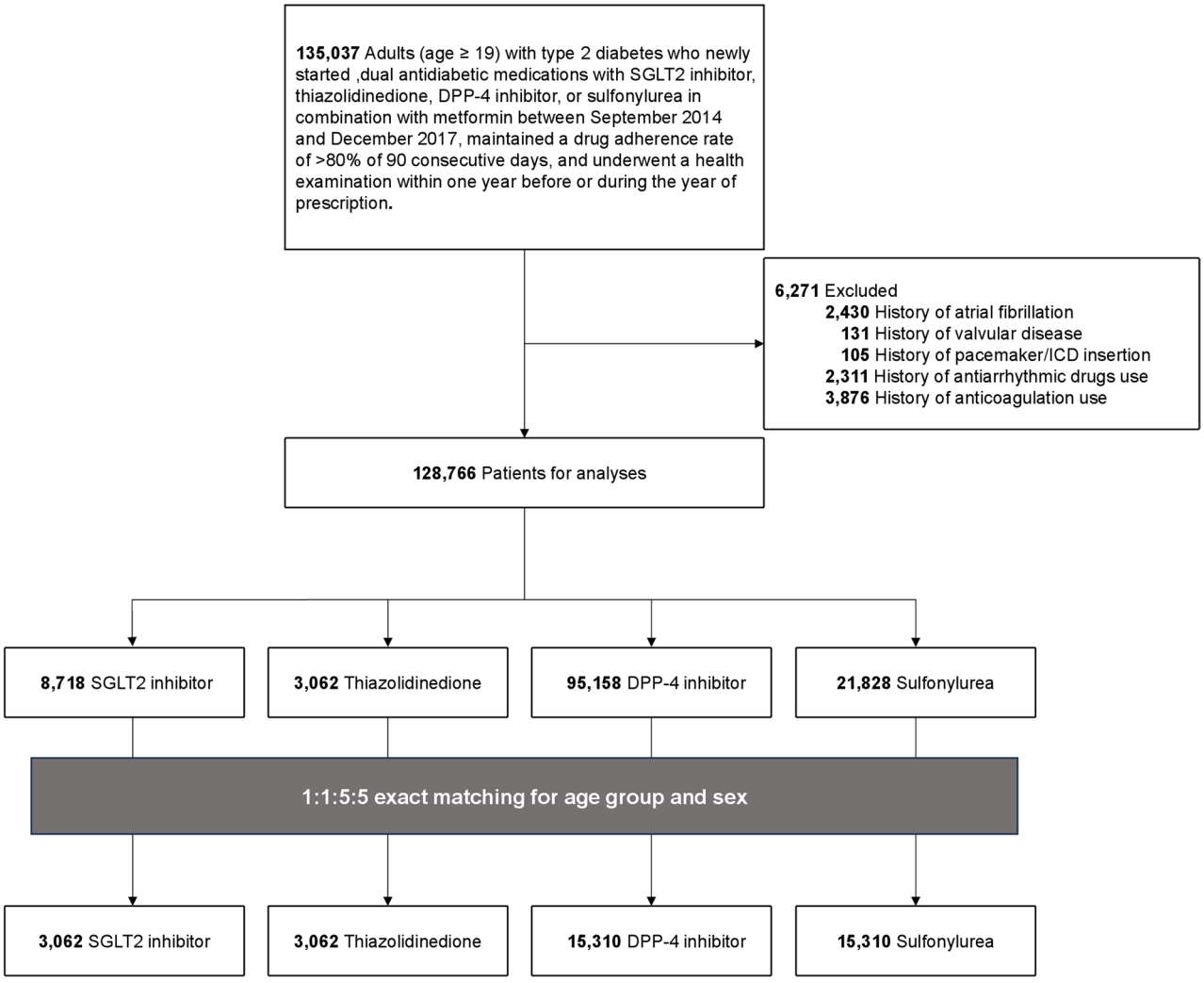

Fig. 1 Study flow. Abbreviations: SGLT2 inhibitor, sodium-glucose cotransporter-2 inhibitor; DPP-4 inhibitor, dipeptidyl peptidase-4 inhibitor; ICD, implantable cardioverter defibrillator.

weights were truncated to the 99.5th percentile to reduce the high variability and address non-positivity issues from extreme weights. A maximum absolute standardized difference of < 0.1 was maintained in the baseline covariates between the groups [29, 30]. After weighting, the weighted incidence rates of AF and all-cause mortality were calculated by dividing each weighted event number by the total follow-up duration and presented per 1000 person-years. A Fine–Gray subdistribution hazard model was used to treat all-cause mortality that occurred before incident AF as a competing risk [31]. Results are reported as subdistribution hazard ratios (SHRs) with 95% confidence intervals (CIs). All statistical analyses were performed using R (version 4.0.3; www.r-project.org; R Foundation for Statistical Computing, Vienna, Austria) and SAS Enterprise Guide 7.1 supports SAS 9.4 (SAS Institute, Cary, NC, USA).

Subgroup and sensitivity analyses

Subgroup analyses were performed based on age (< 65 vs. ≥ 65 years), sex, BMI (< 25 vs. ≥ 25 kg/m^2), eGFR (< 90 vs. ≥ 90 mL/min/1.73 m^2), hypertension status, and smoking status. The *P*-value for the interaction was calculated to assess whether the results were consistent across subgroups. We performed several sensitivity analyses to examine the robustness of our results. First, the association between antidiabetic medication use and risk of incident AF was examined after excluding patients who had taken beta-blockers before the index date. Second, the analysis was repeated after excluding patients who were prescribed antiplatelet agents before the index date. Third, a 1 year landmark analysis was performed by excluding patients who developed AF within the first year after the index date, thereby reducing potential reverse causation and ensuring temporal alignment between drug exposure and AF onset. Fourth, to capture

longer-term treatment maintenance, sensitivity analyses were conducted by redefining treatment duration from 90 days to 180 and 365 days. Finally, to examine whether the results were sensitive to potential bias introduced by the matching ratio, we repeated the analyses using alternative exact-matching ratios (1:1:1:1 and 1:1:3:3).

Results

Baseline characteristics

Table 1 presents the baseline characteristics of the study population after exact matching by sex and age categories across treatment groups. The 36,744 participants had a mean age of 55.3 ± 11.2 years, and 12,360 (33.6%) were women.

Before IPTW adjustment, significant baseline differences existed across the treatment groups. SGLT2 inhibitor users had higher BMI (27.7 kg/m^2) and better renal function (eGFR 95.1 mL/min/1.73 m^2) than the other groups, and the highest prevalence of dyslipidemia (70.0%) and myocardial infarction (1.2%). Thiazolidinedione users had the highest prevalence of hypertension (59.1%) and cerebrovascular disease (7.3%), whereas

Table 1 Baseline characteristics of participants according to different second-line antidiabetic medications

Variables	Total (N=36744)	Second-line antidiabetic medications				Maximum pairwise standardized difference	
		SGLT2 inhibitor (N=3062)	Thiazolidinedione (N=3062)	DPP-4 inhibitor (N=15310)	Sulfonylurea (N=15310)	Before IPTW	After IPTW
Demographic data							
Age, years	55.3 ± 11.2	53.8 ± 10.6	55.4 ± 11.1	55.3 ± 11.2	55.5 ± 11.3	0.151	0.015
20-39 years	2808 (7.6)	234 (7.6)	234 (7.6)	1170 (7.6)	1170 (7.6)	< 0.001	0.085
40-64 years	21036 (57.3)	1753 (57.3)	1753 (57.3)	8765 (57.3)	8765 (57.3)		
≥ 65 years	12900 (35.1)	1075 (35.1)	1075 (35.1)	5375 (35.1)	5375 (35.1)		
Women	12360 (33.6)	1030 (33.6)	1030 (33.6)	5150 (33.6)	5150 (33.6)	< 0.001	0.013
BMI, kg/m^2	26.4 ± 3.8	27.7 ± 4.0	26.6 ± 4.0	26.2 ± 3.6	26.3 ± 3.8	0.404	0.054
Medical beneficiaries	693 (1.9)	46 (1.5)	44 (1.4)	255 (1.7)	348 (2.3)	0.062	0.010
Alcohol intake							
None	18895 (51.4)	1545 (50.5)	1577 (51.5)	7861 (51.3)	7912 (51.7)	0.092	0.005
1–2 days/week	11181 (30.4)	1016 (33.2)	932 (30.4)	4675 (30.5)	4558 (29.8)		
3–4 days/week	4539 (12.4)	361 (11.8)	365 (11.9)	1895 (12.4)	1918 (12.5)		
>5 days/week	2129 (5.8)	140 (4.6)	188 (6.1)	879 (5.7)	922 (6.0)		
Smoking status							
Never	17285 (47.0)	1492 (48.7)	1442 (47.1)	7201 (47.0)	7150 (46.7)	0.075	0.011
Former	8780 (23.9)	738 (24.1)	733 (23.9)	3824 (25.0)	3485 (22.8)		
Current	10,679 (29.1)	832 (27.2)	887 (29.0)	4285 (28.0)	4675 (30.5)		
Regular exercise*	6372 (17.3)	544 (17.8)	517 (16.9)	2754 (18.0)	2557 (16.7)	0.034	0.009
Comorbidity							
Hypertension	20587 (56.0)	1756 (57.3)	1809 (59.1)	8355 (54.6)	8667 (56.6)	0.091	0.011
Dyslipidemia	23028 (62.7)	2142 (70.0)	2077 (67.8)	9933 (64.9)	8876 (58.0)	0.251	0.026
Congestive heart failure	1055 (2.9)	100 (3.3)	100 (3.3)	461 (3.0)	394 (2.6)	0.041	0.006
Myocardial infarction	289 (0.8)	36 (1.2)	22 (0.7)	142 (0.9)	89 (0.6)	0.064	0.004
Cerebrovascular disease	2269 (6.2)	181 (5.9)	225 (7.3)	981 (6.4)	882 (5.8)	0.064	0.006
Chronic pulmonary disease	8845 (24.1)	767 (25.0)	786 (25.7)	3817 (24.9)	3475 (22.7)	0.064	0.018
Thyroid diseases	2521 (6.9)	207 (6.8)	235 (7.7)	1042 (6.8)	1037 (6.8)	0.035	0.017
Medication use							
Antiplatelet	5379 (14.6)	464 (15.2)	507 (16.6)	2242 (14.6)	2166 (14.1)	0.067	0.014
RAS blocker	13485 (36.7)	1281 (41.8)	1256 (41.0)	5562 (36.3)	5386 (35.2)	0.137	0.005
Beta-blocker	1973 (5.4)	161 (5.3)	161 (5.3)	735 (4.8)	916 (6.0)	0.052	0.005
Other hypertensive drugs	13742 (37.4)	1198 (39.1)	1208 (39.5)	5420 (35.4)	5916 (38.6)	0.084	0.013
Laboratory findings							
Fasting glucose, mg/dL	167.4 ± 67.1	156.2 ± 56.7	157.6 ± 61.3	165.4 ± 63.1	173.6 ± 73.1	0.267	0.059
eGFR, mL/min/1.73 m^2	94.1 ± 16.8	95.1 ± 16.3	93.9 ± 17.2	94.0 ± 16.7	94.0 ± 16.9	0.073	0.008

The values for categorical variables are given as the number (percentage); values for continuous variables are given as the mean ± standard deviation.

*Regular exercise was defined as moderate-intensity exercise for at least 5 days per week or vigorous-intensity exercise for at least 3 days per week.

SGLT2 inhibitor, sodium-glucose cotransporter-2 inhibitor; DPP-4 inhibitor, dipeptidyl peptidase-4 inhibitor; IPTW, inverse probability of treatment weighting; BMI, body mass index; RAS, renin-angiotensin system; eGFR, estimated glomerular filtration rate

sulfonylurea users had the lowest rate of congestive heart failure (2.6%). Baseline characteristics were well-balanced across all treatment groups after IPTW adjustment, with maximum absolute standardized differences below 0.1 for all variables (Supplement Table 3 and Supplement Fig. 1).

Table 2 Incidence rates of atrial fibrillation

	Total	Second-line antidiabetic medications			
		SGLT2 inhibitor	Thiazolidinedione	DPP-4 inhibitor	Sulfonylurea
Number of participants	36744	3062	3062	15310	15310
Person-year	226042	17766	19182	93067	96026
Person-year after IPTW	226348	17758	19225	93143	96221
Incident atrial fibrillation					
Number of events, n (%)	774 (2.1)	50 (1.6)	68 (2.2)	305 (2.0)	351 (2.3)
Number of events after IPTW	736.32	52.88	67.78	307.39	335.27
Crude IR,1000 person-years	3.42	2.81	3.55	3.28	3.66
Weighted IR, 1000 person-years	3.37	2.98	3.53	3.30	3.48
All-cause mortality					
Number of events, n (%)	1442 (3.9)	53 (1.7)	105 (3.4)	576 (3.8)	708 (4.6)
Number of events after IPTW	1419.21	62.23	101.29	580.07	675.62
Crude IR,1000 person-years	6.38	2.98	5.47	6.18	7.37
Weighted IR, 1000 person-years	6.27	3.50	5.27	6.23	7.02

SGLT2 inhibitor, sodium-glucose cotransporter-2 inhibitor; DPP-4 inhibitor, dipeptidyl peptidase-4 inhibitor; IPTW, inverse probability of treatment weighting; IR, incidence rate

Association between different hypoglycemic drugs and incident AF

During a mean follow-up period of 6.2 years, 774 (2.1%) cases of AF occurred among 36,744 patients. Patients treated with thiazolidinediones, DPP-4 inhibitors, or sulfonylureas exhibit higher incidence rates of AF than those treated with SGLT2 inhibitors. The crude event numbers and weighted incidence rates were as follows: SGLT2 inhibitors, 50 events (2.98 per 1000 person-years); thiazolidinediones, 68 events (3.53 per 1000 person-years); DPP-4 inhibitors, 305 events (3.30 per 1000 person-years); and sulfonylureas, 351 events (3.48 per 1000 person-years). Similarly, the weighted incidence rates of all-cause mortality were higher in the thiazolidinedione, DPP-4 inhibitor, and sulfonylurea groups at 5.27, 6.23, and 7.02 per 1000 person-years, respectively, compared to 3.50 per 1000 person-years in the SGLT2 inhibitor group (Table 2). The risk of AF was significantly higher in patients treated with thiazolidinediones (SHR, 1.22; 95% CI, 1.09–1.36), DPP-4 inhibitors (SHR, 1.14; 95% CI, 1.02–1.28), and sulfonylureas (SHR, 1.20; 95% CI, 1.07–1.34) when using SGLT2 inhibitors as the reference group. However, pairwise comparisons among thiazolidinediones, DPP-4 inhibitors, and sulfonylureas revealed no significant differences in AF risk (Table 3).

Subgroup and sensitivity analyses

The association between antidiabetic medication use and AF risk was significantly modified by age, renal function, and hypertension status in the subgroup analysis. Specifically, younger individuals (< 65 years), those without hypertension, and those with relatively low renal function (eGFR < 90 mL/min/1.73 m^2) exhibited a greater increase in AF risk with thiazolidinediones, DPP-4 inhibitors, and sulfonylureas compared to SGLT2 inhibitors. However, no significant interactions were observed between sex, BMI, or smoking status (Fig. 2).

Sensitivity analyses confirmed the robustness of the main findings. Among 34,771 patients after excluding those with prior beta-blocker use, the risk of AF was higher in the thiazolidinedione (SHR, 1.23; 95% CI, 1.10–1.39), DPP-4 inhibitors (SHR, 1.13; 95% CI, 1.00–1.27), and sulfonylurea (SHR, 1.14; 95% CI, 1.01–1.28) groups than in the SGLT2 inhibitor group (Supplement Table 4). Similarly, among 31,365 patients, excluding those with prior antiplatelet use, SGLT2 inhibitors were associated with a lower risk of incident AF than thiazolidinediones, DPP-4 inhibitors, or sulfonylureas (Supplement Table 5). In addition, the risk of AF remained significantly higher in the thiazolidinedione (SHR, 1.41; 95% CI, 1.24–1.60), DPP-4 inhibitors (SHR, 1.18; 95% CI, 1.03–1.35), and

Table 3 Risk of atrial fibrillation according to different second-line antidiabetic medications

Second-line antidiabetic medications	Incident atrial fibrillation					
	SHR (95% CI)	*P*	SHR (95% CI)	*P*	SHR (95% CI)	*P*
SGLT2 inhibitor	Reference		NA		NA	
Thiazolidinedione	1.22 (1.09–1.36)	< 0.001	Reference		NA	
DPP-4 inhibitor	1.14 (1.02–1.28)	0.018	0.94 (0.85–1.04)	0.941	Reference	
Sulfonylurea	1.20 (1.07–1.34)	0.001	0.99 (0.85–1.09)	0.987	1.05 (0.95–1.16)	0.353

SGLT2 inhibitor, sodium-glucose cotransporter-2 inhibitor; DPP-4 inhibitor, dipeptidyl peptidase-4 inhibitor; SHR, sub-distribution hazard ratio; CI, confidence interval; NA, not applicable

The sub-distribution hazard ratio was calculated using the Fine–Gray competing risk model, treating all-cause mortality as a competing risk and applying the inverse probability of treatment weighting. Treatment weights were calculated using baseline variables, including age, sex, body mass index, medical aid status, alcohol consumption, smoking status, regular exercise, comorbidities (hypertension, dyslipidemia, heart failure, myocardial infarction, cerebrovascular diseases, chronic obstructive pulmonary diseases, and thyroid disease), laboratory tests (fasting glucose and estimated glomerular filtration rate), and medication use (antiplatelets, statins, RAS blockers, beta-blockers, and other antihypertensive drugs)

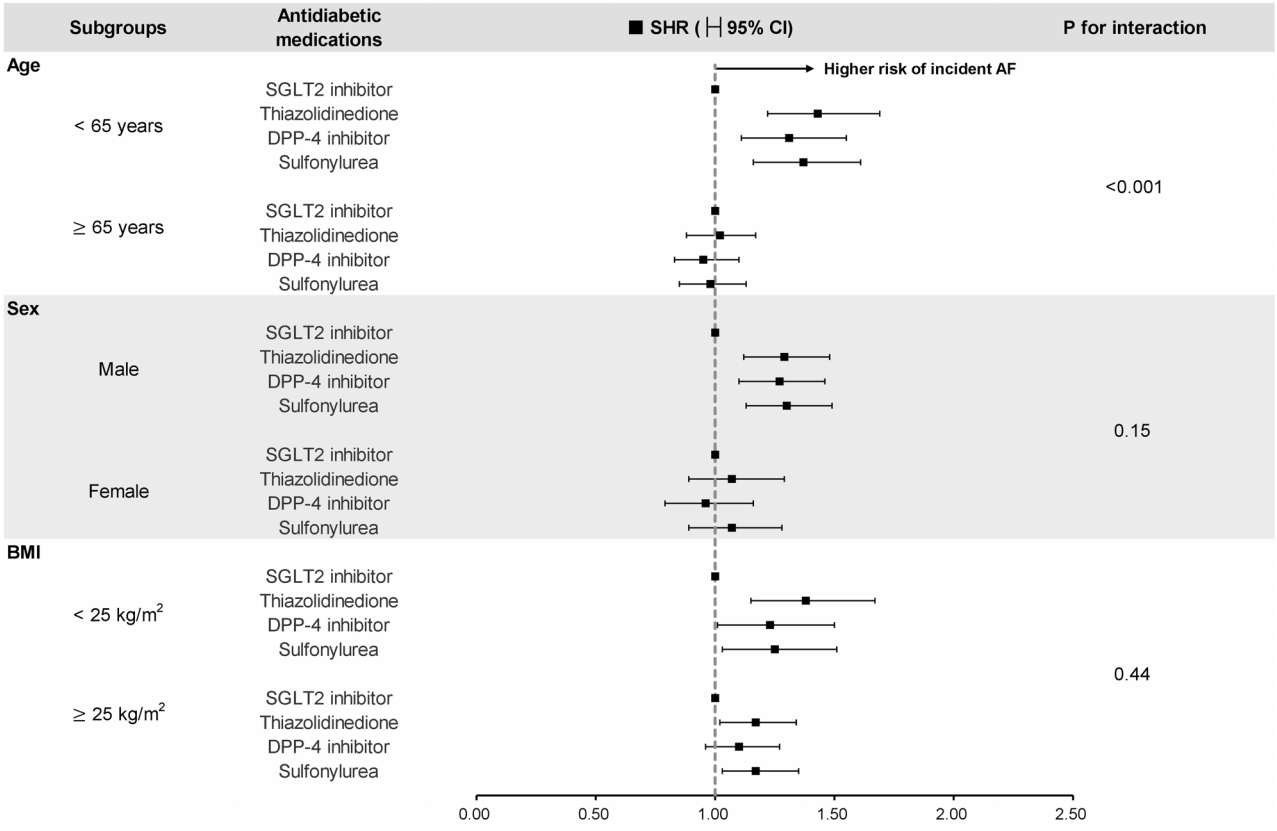

Fig. 2 Multivariable-adjusted subdistribution hazard ratios for incident atrial fibrillation according to the second-line antidiabetic medications stratified by subgroups. The subdistribution hazard ratio was calculated using the Fine–Gray competing risk model, treating all-cause mortality as a competing risk. Treatment weights were calculated using baseline variables, including age, sex, body mass index, medical aid status, alcohol consumption, smoking status, regular exercise, comorbidities (hypertension, dyslipidemia, heart failure, myocardial infarction, cerebrovascular diseases, chronic obstructive pulmonary diseases, and thyroid diseases), laboratory tests (fasting glucose and estimated glomerular filtration rate), and medication use (antiplatelets, statins, RAS blockers, beta-blockers, and other antihypertensive drugs). AF, atrial fibrillation; SHR, subdistribution hazard ratio; CI, confidence interval; SGLT2 inhibitor, sodium-glucose cotransporter-2 inhibitor; DPP-4 inhibitor, dipeptidyl peptidase-4 inhibitor; BMI, body mass index; eGFR, estimated glomerular filtration rate

sulfonylurea (SHR, 1.24; 95% CI, 1.08–1.41) groups than in the SGLT2 inhibitors group when patients who developed AF within 1 year after the index date were excluded (Supplement Table 6). The results were similar to the primary findings, regardless of the treatment duration of second-line antidiabetic medications combined with metformin, when treatment was defined as ≥ 80% adherence for 180 or 365 consecutive days (Supplement Table 7). In additional sensitivity analyses using alternative exact-matching ratios (1:1:1:1 and 1:1:3:3), the results were consistent with those of the primary analysis (Supplement Table 8), indicating that the observed associations were not materially influenced by the choice of matching ratio.

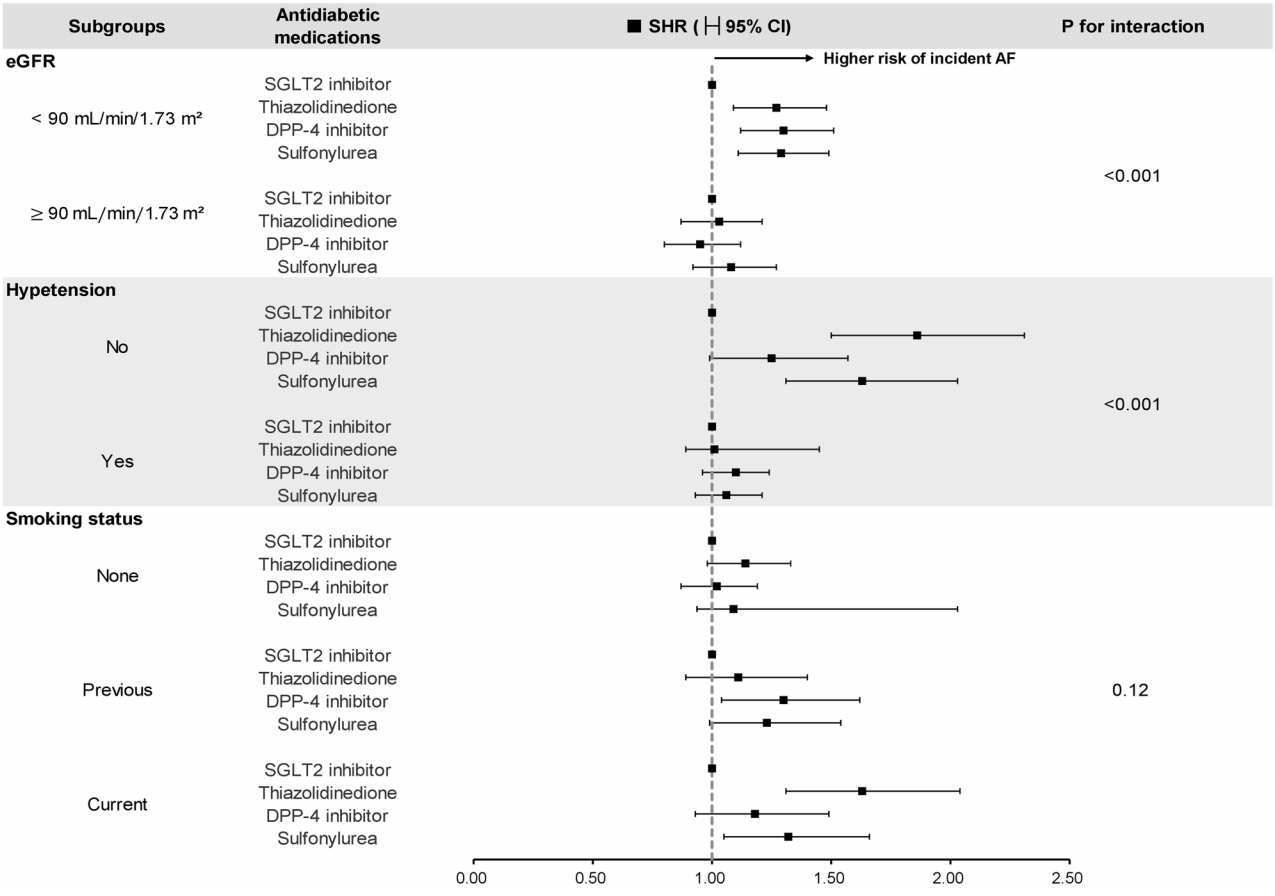

Fig. 2 (continued)

Discussion

This study used real-world data to investigate the effect of second-line antidiabetic medication on the incident AF in patients with type 2 diabetes. The findings showed a significantly lower risk of AF in patients treated with SGLT2 inhibitors than in those treated with thiazolidinediones, DPP-4 inhibitors, or sulfonylureas. No significant differences in AF risk were found in head-to-head comparisons between thiazolidinediones, DPP-4 inhibitors, and sulfonylureas. Subgroup analyses revealed no significant interactions between antidiabetic medications and sex, obesity, or smoking status in relation to incident AF. In contrast, significant effect modification was observed across the subgroups defined by age, hypertension status, and baseline renal function.

The selection of antidiabetic medications in the contemporary management of type 2 diabetes has increasingly prioritized their efficacy in reducing the risk of diabetes-related complications, including cardiovascular and kidney diseases, over traditional glycemic control [32]. This study included only new users who were simultaneously prescribed metformin and second-line antidiabetic medications, allowing for a direct comparison of the effects of these drugs. Considering that metformin, the most commonly used first-line treatment for type 2 diabetes, has been shown to decrease the risk of AF [33], and that the risk of developing AF increases with each additional year of diabetes duration [34, 35], this study evaluated the effects of second-line antidiabetic medications while controlling for the potential protective effects of metformin and mitigating the confounding influence of diabetes duration. Given the limited number of studies on the effects of second-line antidiabetic medications on the risk of AF, providing insights into their selection for AF prevention is worthwhile.

In the present study, SGLT2 inhibitors were associated with a lower risk of incident AF than thiazolidinediones, DPP-4 inhibitors, and sulfonylureas. Although SGLT2 inhibitors have demonstrated cardiorenal benefits across various conditions, such as HF and chronic kidney disease (CKD) [36–38], their effect on AF prevention remains uncertain. The Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium–Glucose Co-Transporter-2 Inhibitors (CVD-REAL) Nordic study found no significant difference in AF incidence between SGLT2 inhibitors and other glucose-lowering agents [39]. In contrast, a post-hoc analysis of the Dapagliflozin Effect on Cardiovascular Events – Thrombolysis

In Myocardial Infarction (DECLARE-TIMI) trial revealed a significant reduction in AF risk in patients treated with dapagliflozin [40]. Similarly, several observational studies and a recent meta-analysis have shown a significantly lower incidence of AF among SGLT2 inhibitor users compared with DPP-4 inhibitor users [11–13]. Similarly, the current findings showed that SGLT2 inhibitors are associated with a lower risk of incident AF than thiazolidinediones, DPP-4 inhibitors, and sulfonylureas. However, no significant differences in the risk of incident AF were observed among thiazolidinediones, DPP-4 inhibitors, and sulfonylureas.

Significant effect modification was observed across age, hypertension, and renal function subgroups in the relationship between antidiabetic medication use and AF risk. The comparative AF risk-reducing benefit of SGLT2 inhibitors versus other antidiabetic medications was attenuated in individuals with major clinical risk factors—such as advanced age or hypertension—suggesting that the comparative protective benefits may be less apparent in the presence of these strong risk factors. Given that the observed attenuation may also reflect the impact of frailty, multiple comorbidities, and age-related irreversible atrial remodeling on AF [41, 42], these findings may suggest that initiating SGLT2 inhibitors at a younger age may yield relatively greater preventive benefit on AF. However, residual confounding cannot be ruled out, as older individuals may differ in unmeasured clinical characteristics or treatment patterns; thus, these interpretations remain speculative and should be viewed with caution. Furthermore, the observed interaction between baseline renal function and the effect of antidiabetic medication indicates that SGLT2 inhibitors may have a pronounced protective effect against AF in patients with mildly to moderately decreased eGFR. Although most patients in this study had relatively well-preserved renal function, this observation may align with the results of previous meta-analyses, which have shown that absolute risk reductions for hospitalization for HF and cardiovascular death are greater among patients with CKD [43, 44]. These benefits are likely attributable to the higher baseline cardiovascular risk in this population, including a greater predisposition to AF. Several mechanisms of action of SGLT2 inhibitors, including natriuretic, anti-inflammatory, and neurohormonal regulatory actions, may account for these observations. Individuals with impaired renal function often present with volume overload, elevated left atrial pressure, and chronic activation of neurohormonal pathways, all of which promote atrial structural remodeling and arrhythmogenesis [45]. SGLT2 inhibitors enhance natriuresis and osmotic diuresis, thereby mitigating intravascular volume expansion and atrial wall stress [46]. Furthermore, SGLT2 inhibitors may further stabilize atrial electrophysiology in AF through the suppression of systemic inflammation and oxidative stress [47, 48]. By contrast, individuals with preserved renal function generally exhibit a lower baseline risk of AF and are less prone to volume overload or neurohormonal dysregulation. Therefore, the relative benefits of SGLT2 inhibitors in preventing AF may have been attenuated in this group. Nevertheless, these subgroup findings should be interpreted with caution, and prospective studies specifically designed to evaluate the differential effects of SGLT2 inhibitors in various patient populations are required.

Using large nationwide data with long-term follow-up periods, this study provides a head-to-head comparison of second-line antidiabetic medications. However, this study has some limitations. First, owing to the retrospective nature of this study, a causal relationship could not be established, and residual confounding factors may remain. Second, the diagnoses of AF and comorbidities were based on claims records, which introduced the potential for misclassification. However, previous studies have validated the operational definition of incident AF [27, 28]. Third, this study did not include data on glycemic control or diabetes-related complications such as hypoglycemia, which are associated with AF. Although fasting glucose levels were adjusted for, glycemic fluctuations and hypoglycemic events were not considered. Fourth, due to data limitations, patients who added or switched second-line antidiabetic medications during follow-up could not be fully captured. Nevertheless, to minimize potential bias from treatment changes, we conducted sensitivity analyses extending the required treatment maintenance duration to 180 and 365 days, which yielded consistent results. However, the long-term effects of treatment switching could not be comprehensively evaluated. Fifth, potential interactions between metformin and other antidiabetic medications cannot be entirely excluded. Lastly, although exact matching on age and sex prior to IPTW to strengthen internal validity and obtain more unbiased estimates within the overlapping population, the findings may have limited generalizability because the sample size decreased substantially after matching and certain subgroups—particularly underrepresented patients—may have been excluded.

Conclusion

The results of this study showed a lower risk of AF in patients using SGLT2 inhibitors than in those using thiazolidinediones, DPP-4 inhibitors, or sulfonylureas. These findings suggested that SGLT2 inhibitors might offer potential benefits in reducing the risk of AF in patients with type 2 diabetes, providing insights into the selection of optimal second-line antidiabetic medications for AF prevention.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-03024-9.

Supplementary Material 1.

Author contributions

GYH, SJH, BK, YEK, HBK, CHP, JTP, SHH, THY, SWK, MKH, and HWK involved in the study concept and design. GYH and HWK and writing a first draft of the manuscript. SJH and MKH conducted the study and edited the study protocol. All authors were involved in the analysis and interpretation of the results, reviewed and edited the manuscript, and approved the final version of the manuscript. MKH and HWK are guarantors of this work and, take the responsibility for the integrity of the data and the accuracy of the data analysis.

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Data availability

The data utilized in this study were obtained from the Korean National Health Insurance System (NHIS). Access to these data is restricted to researchers who complete the required procedures established by the NHIS. Only those who receive official approval are permitted to use the data, which can be accessed at a designated center within the approved research period. Data access requests can be made through the Health Insurance Data Service website (http://nhiss.nhis.or.kr).

Declarations

Competing interests

GYH, SJH, BK, YEK, HBK, CHP, JTP, SHH, THY, SWK, MKH, and HWK declare no competing interest relevant to this article.

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