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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

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Abstract

Purpose: Sodium glucose cotransporter 2 inhibitor (SGLT2i) reduced the risk of hard cardiovascular endpoints in type 2 diabetes mellitus (T2DM) patients with/without established cardiovascular diseases. Whether SGLT2i is associated with a lower risk of new-onset atrial fibrillation (AF) in T2DM patients is unclear. We aimed to evaluate the risk of new-onset AF associated with the use of SGLT2i compared to dipeptidyl peptidase-4 inhibitors (DPP4i) among a longitudinal cohort of diabetic patients.

Methods: We used medical data from a multi-center healthcare provider in Taiwan, which included a total of 21,480 and 22,989 patients treated with SGLT2i and DPP4i, respectively, from June 1, 2016 to December 31, 2018. We used propensity-score weighting to balance covariates across study groups. Patients were followed up from the drug index date until the occurrence of new-onset AF, discontinuation of the index drug, or the end of the study period, whichever occurred first.

Results: Overall, 56%, 42%, and 2% of the patients were treated with empagliflozin, dapagliflozin, and canagliflozin, respectively. Most patients in the DPP4i group were prescribed with linagliptin (51%), followed by sitagliptin (24%), saxagliptin (13%), vildagliptin (8%) and alogliptin (4%). The use of SGLT2i was associated with a lower risk of new-onset AF compared with DPP4i after propensity-score weighting [adjusted hazard ratio: 0.69; 95% confidential interval: 0.64-0.74; $P < 0.001$]. Subgroup analysis revealed that the use of SGLT2i was associated with a lower risk of new-onset AF compared with DPP4i across several subgroups including old age, the presence of congestive heart failure, cardiovascular disease, overweight patients, hemoglobin A1c 8%, and chronic kidney disease. The advantage of SGLT2i over DPP4i persisted with different SGLT2i (dapagliflozin or empagliflozin) and either low- or standard-dose SGLT2i.

Conclusions: SGLT2i was associated with a lower risk of new-onset AF compared with DPP4i among T2DM patients in real-world practice.

Background

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia worldwide, and it is associated with higher risks of ischemic stroke, heart failure hospitalization and mortality.[1-3] Diabetes mellitus (DM) is associated with higher risks of ischemic cardiovascular events and mortality, and also a 40% higher risk of AF in the general population.[4, 5] Pathophysiological mechanisms including atrial electrical, structural, autonomic remodeling, oxidative stress, inflammation, and glycemic fluctuations have been suggested to explain the association between DM and occurrence of AF.[6, 7] Sodium-glucose cotransporter 2 inhibitor (SGLT2i) is a new class of anti-diabetic drug which inhibit sodium and glucose reabsorption in proximal tubules of the kidney and thereby lower blood glucose in patients with type 2 diabetes mellitus (T2DM).[8] Three randomized placebo controlled trials have shown that SGLT2i (including canagliflozin, dapagliflozin, and empagliflozin) reduced the risk of hard cardiovascular endpoints in T2DM patients with/without established cardiovascular diseases.[9-11] SGLT2i has been shown to have multiple pleiotropic effects of glucose-independent and direct cardiac protection, including mitigating inflammation, oxidative stress, endothelial dysfunction, and left ventricular dysfunction, which may improve atrial remodeling and thus reduce the risk of AF. Although these randomized controlled trials have shown firm evidence of the benefits of SGLT2i with regards to ischemic cardiovascular diseases and mortality, all-cause mortality, and heart failure hospitalizations in patients with a high cardiovascular risk, whether SGLT2i themselves reduce the risk of atrial arrhythmia or AF is unclear. The primary aim of the present study was to investigate whether SGLT2i is associated with a decreased risk of incident AF compared with dipeptidyl peptidase-4 inhibitor (DPP4i) in T2DM patients in a real-world setting.

Methods

Database

The study was based in part on data from the Chang Gung Research Database provided by Chang Gung Memorial Hospital (CGMH). The interpretation and conclusions contained herein do not represent the position of Chang Gung Memorial Hospital (CGMH). This study was approved by the Institutional Review Board of the Chang Gung Medical Foundation. We conducted this retrospective observational study using patient data from the CGMH Medical System. The CGMH Medical System is composed of three major teaching hospitals and four tertiary care medical centers with a total of 10,050 beds and around 280,000 admissions per year, and it is currently the largest healthcare provider in Taiwan.[12, 13] The advantage of the CGMH medical database is that detailed data on diagnoses, interventions, medications, laboratory examinations, and imaging are available for each patient.[13, 14] The identification number of each patient is encrypted and de-identified using a consistent encryption procedure; therefore, the need for informed consent was waived for this study.

Study design and outcome

The flowchart of the study design and patient enrollment is shown in **Figure 1**. The CGMH Research Database was retrospectively searched for patients 20 years of age in whom new-onset T2DM was diagnosed from January 1, 2001 to December 31, 2018 (n = 382,839). Patients who did not use any ant-diabetic drugs (n = 95,622) were excluded from the present study. We also excluded patients with a diagnosis of AF before a diagnosis of T2DM (n = 8,898). Among the 258,319 patients treated with any anti-diabetic drug without a diagnosis of AF, those who had a first prescription for a SGLT2i (approval date: June 1, 2016) were enrolled in the present study (n = 21,480). Of the other 236,839 patients who received other non-SGLT2i treatments, 22,989 had a first prescription for a DPP4i after June 1, 2016. The study outcome was defined as the diagnosis of AF (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 427.31 from January 1, 2010, to December 31, 2015, and ICD-10-CM code I48 from January 1, 2016, to December 31, 2018) in at least one inpatient or outpatient department visit. For each group, the index date was defined as the first date of a prescription for a SGLT2i or DPP4i after June 1, 2016. The follow-up period was defined as the period from the index date until the occurrence of new-onset AF, discontinuation of the index drug, mortality, or the end of the study period (December 31, 2018), whichever occurred first.

Covariates

Baseline characteristics referred to any claims record with the above diagnoses or medication codes prior to the drug index date. The ischemic etiology of the T2DM patients was defined by one of the following criteria: 1) ≥75% luminal diameter stenosis of the main epicardial coronary artery; 2) history of myocardial infarction or coronary revascularization; and 3) myocardial ischemia or infarction documented in myocardial perfusion imaging. A history of any prescription medicine was confined to medications taken at least once within 3 months preceding the index date. Important laboratory data listed in **Table 1** were based on the measurements performed within 1 year before the drug index date.

Statistical analysis

We used the propensity score method to simulate the effect of a randomized clinical trial for observational cohort data and to estimate the study outcomes of study groups [15]. The inverse probability of treatment weights of propensity scores was used to balance covariates across the four groups. The weights were derived to obtain estimates representing average treatment effects in the treated. All of the covariates listed in **Table 1** were included in the propensity models. Incidence rates were estimated using the total number of study outcomes during the follow-up

period divided by person-years at risk. The risk of time-dependent study outcomes for two study groups was obtained using survival analysis (Kaplan-Meier method and log-rank test for univariate analysis and Cox proportional hazards regression for multivariate analysis). The balance of covariates at baseline among the study groups was assessed using the absolute standardized mean difference (ASMD) rather than statistical testing, because balance is a property of the sample and not of an underlying population. Another advantage of using ASMD is that it is not influenced by sample size. An ASMD value ≤ 0.1 was defined as indicating a negligible difference in potential confounders between two study groups (**Table 1**). Statistical significance was defined as a *P*-value < 0.05. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

A total of 21,480 SGLT2i users and 22,989 DPP4i users were eligible for the study. Among the SGLT2i users, 12,016 (56%), 9,071 (42%), and 393 (2%) were treated with empagliflozin, dapagliflozin, and canagliflozin, respectively. Most of the DPP4i users were prescribed with linagliptin (n = 11,719, 51%), followed by sitagliptin (n = 5,452, 24%), saxagliptin (n = 2,960, 13%), vildagliptin (n = 1,994, 8%), and alogliptin (n = 86, 44%).

Table 1 summarizes the baseline demographic characteristics, comorbidities, and medications of the two groups. Before propensity score weighting, the SGLT2i group had higher prevalence rates of ischemic heart disease, hypertension, dyslipidemia and chronic liver disease, and lower prevalence rates of stroke history and diagnosed cancer. The SGLT2i group had higher serum hemoglobin, hemoglobin A1c (HbA1c) and estimated glomerular filtration rate (eGFR) than the DPP4i group. For baseline medications, the SGT2i group had a higher prescription rate of anti-platelet agents, statins, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and concomitant anti-diabetic agents including sulfonylureas, metformin, and glitazones than the DPP4i group (ASMD > 0.1). After propensity-score weighting, the two study groups were well-balanced in most characteristics (most ASMD < 0.1).

The SGLT2i users were associated with a lower risk of new-onset AF compared with the DPP4i users, both before and after propensity-score weighting [adjusted hazard ratio (aHR): 0.69; 95% confidential interval (CI): 0.64-0.74; *P* < 0.001]. There was a clear separation of event curves for new-onset AF between these two groups both before and after propensity score weighting adjustments (**Figure 2)**. Subgroup analysis revealed that the use of SGLT2i was associated with a lower risk of new-onset AF compared with the use of DPP4i in all subgroups (**Figure 3**). Furthermore, the use of SGLT2i was associated with greater reductions in new-onset AF events in subgroups including male sex, no previous history of stroke, body mass index (BMI) < 25 kg/m^2, eGFR < 60 ml/min/1.73 m^2, and concomitant use of renin-angiotensin system blockers or metformin (*P* interaction < 0.05).

In addition, the advantage of SGLT2i over DPP4i in lowering the risk of incident AF persisted with different SGLT2i (dapagliflozin or empagliflozin) and both low-dose (empagliflozin 10 mg or dapagliflozin 5 mg once daily) and standard-dose (empagliflozin 25 mg or dapagliflozin 10 mg once daily) SGLT2i treatment. Moreover, the use of dapagliflozin was associated with a greater reduction in new-onset AF events than empagliflozin when compared with DPP4i (*P* interaction < 0.001) (**Figure 4**).

Discussion

To the best of our knowledge, this is the largest observational study to specifically evaluate the risk of new-onset AF in T2DM patients treated with SGLT2i versus DPP4i. Our results showed that the use of SGLT2i was associated with a significantly lower risk of new-onset AF compared to DPP4i among T2DM patients. The benefits in reducing the risk of new-onset AF with SGLT2i over DPP4i persisted in several important subgroups including old age, presence of heart failure or cardiovascular disease, obesity, impaired renal function, and elevated HbA1c levels. In addition, the

advantages of SGLT2i over DPP4i in lowering the risk of new-onset AF persisted with different SGLT2i drugs (dapagliflozin or empagliflozin) and both low and standard doses of SGLT2i.

T2DM is an important risk factor for ischemic stroke and the development of new-onset AF.[15] An animal study demonstrated that diabetic rat atria had greater interstitial fibrosis, lower connexin 40 expression, and decreased conduction velocity. In addition, the diabetic atria showed electrical remodeling with prolongation of action potential duration (APD), an increase in spatial dispersion and frequency-dependent shortening of APD, and increased incidence of APD alternans.[16] All of these factors facilitated the formation of re-entry associated atrial arrhythmia. Other studies have also reported adrenergic activation and heterogeneous sympathetic innervation in diabetic hearts, suggesting that neural remodeling may play a crucial role in diabetes-related atrial arrhythmia.[17] Furthermore, T2DM itself is associated with several chronic diseases including hypertension, chronic kidney disease, and heart failure, all of which further increase the risk of incident AF.

SGLT2i is a new class of anti-hyperglycemic agents that inhibit glucose absorption by the proximal tubules of the kidney, resulting in glycosuria.[18] SGTL2i has been shown to reduce blood sugar levels, blood pressure, body weight, albuminuria, lipid profile, arterial stiffness, and endothelial function via an insulin-independent mechanism in T2DM patients.[19] Moreover, SGLT2i has been shown to have impressive cardioprotective and renoprotective effects. The main mechanisms of their cardioprotective effects are improvements in cardiac cell metabolism and ventricular loading conditions, inhibition of Na^+/H^+ exchange in myocardial cells, alterations in adipokine and cytokine production, and reductions in cardiac cell necrosis and cardiac fibrosis.[20] SGLT2i has also been shown to reduce sympathetic overdrive, which plays an important role in the development of AF.[21]

Other diabetes medications including metformin, thiazolidinedione (TZD), and DPP4i, may also be associated with a lower risk of AF. A previous study of a nationwide, population-based dynamic cohort indicated that the use of metformin was associated with a decreased risk of AF in T2DM patients who were not using other antidiabetic drugs, probably by attenuating atrial cell tachycardia-induced myolysis and oxidative stress.[22] Another study indicated that the use of DPP4i as second-line antidiabetic drugs was associated with a lower risk of AF compared with other second-line antidiabetic drugs among T2DM patients treated with metformin in real-world practice.[23] TZD is an insulin sensitizer that also have anti-inflammatory and anti-oxidative effects, and they might decrease the risk of AF compared with other antidiabetic drugs. *Pallisgaard et al.* reported that the use of TZD was associated with a 24% reduction in the risk of incident AF compared with other antidiabetic drugs as second-line treatment among T2DM patients.[24] However, no significant differences in the risk of incident AF with use of TZD were reported in the PROactive, RECORD, and BARI 2D trials.[25-27]

Three large randomized controlled trials, EMPA-REG OUTCOME (empagliflozin), CANVAS Program (canagliflozin), and DECLARE–TIMI 58 (dapagliflozin) demonstrated that three SGLT2i significantly reduced the risk of heart failure hospitalization in T2DM patients with/without established cardiovascular diseases compared with the current standard-of-care diabetes management.[9-11] Furthermore, the DAPA-HF trial indicated that dapagliflozin treatment reduced the risk of worsening heart failure or cardiovascular death by 26% compared to placebo among patients with heart failure and a reduced ejection fraction of < 40%, regardless of the presence or absence of T2DM.[28] However, despite the potential improvements in atrial remodeling mediated by SGLT2i, few clinical studies have investigated the relationship between the use of SGLT2i and the risk of AF, and the results have been inconsistent. A meta-analysis of 35 eligible randomized controlled trials (canagliflozin, nine; empagliflozin, eight; dapagliflozin, 18), showed that SGLT2i significantly reduced all-cause mortality, major adverse cardiac events, non-fatal myocardial infarction, and heart failure hospitalization in T2DM patients compared to placebo. However, no significant difference was noted in the occurrence of stroke, unstable angina, or AF (odd ratio: 0.61; [95% CI 0.31-1.19]; $P = 0.15$).[29] The CVD-REAL Nordic

study also indicated that dapagliflozin was associated with lower risks of cardiovascular events and all-cause mortality but a neutral risk of AF (HR: 0.92; [95% CI 0.76-1.12]; *P* = 0.414) compared with DPP-4is in a real-world clinical setting.[30, 31] Conversely, post-hoc analysis of the DECLARE-TIMI 58 trial indicated that dapagliflozin reduced the risk of AF/atrial flutter (AFL) by 19% (HR: 0.81; [95% CI 0.68-0.95]; *P* = 0.009) and the number of total AF/AFL events by 23% compared to placebo in 17,160 T2DM patients, regardless of the presence or absence of AF/AFL, established cardiovascular disease, or heart failure at baseline. To the best of our knowledge, no previous studies have compared the risk of AF between SGLT2i and DPP4i treatment or other oral hypoglycemic agents among T2DM patients. Further prospective and randomized studies are necessary to clarify our results.

In this study, dapagliflozin seemed to result in a greater reduction in new-onset AF events than empagliflozin when compared with DPP4i (*P* interaction < 0.001) (**Figure 4**)**.** Several possible mechanisms may explain this difference between these two SGLT2is. Empagliflozin has greater SGLT2 to SGLT1 selectivity (2500-fold) than dapagliflozin (1200-fold).[32] Previous studies have shown that SGLT1 receptors are predominantly found in the human intestine, and that higher SGLT1 receptor selectivity can lower variations in postprandial blood glucose.[33, 34] In addition, other studies have suggested an association between higher blood glucose variability and a higher risk of new-onset AF in T2DM patients.[35, 36] In addition, dapagliflozin has longer lasting pharmacological effects such as sodium excretion and osmotic diuresis, and this may reduce blood pressure variability.[34, 37] Higher blood pressure variability has been associated with a higher risk of developing AF in the general population, especially in high-risk subjects including those with an old age and the presence of concomitant T2DM or chronic kidney disease.[38] Finally, although both SGLT2is seemed to reduce the risk of heart failure, a previous study indicated that dapagliflozin may have greater effects on reducing heart failure compared to empagliflozin.[39] Future studies are required to investigate the differences in risk reduction of new-onset AF between different SGLT2i.

Study Limitations

There are several limitations to the present study. First, we did not have serial ECG data to help identify whether the patients diagnosed with AF had persistent or paroxysmal AF related to acute illnesses such as hyperthyroidism or infection. Moreover, we lacked data of other unmeasured confounding factors such as the physicians' choice of medications, use of tobacco or alcohol, race, and family history. Second, long-term outcome comparisons such as 5 or 10 years of follow-up were not included in this study as SGLT2i is a relatively new drug compared to other antidiabetic drugs. Third, this was a retrospective and observational study. The clinical characteristics of the patients were different across SGLT2i and DPP4i groups. Although we adjusted for several important parameters relevant to clinical outcomes by using propensity score weighting models, residual unmeasured confounders were still probably present. We suggest that future prospective randomized studies are needed to determine whether our findings are applicable to T2DM patients. Fourth, we did not analyze the relative risk of AF for canagliflozin versus DPP4i in the subgroup analysis due to a very limited number of patients (n = 393, 2%) and short follow-up period (approved after March 1, 2018) in the present study. Further studies are needed to investigate whether the treatment benefits of empagliflozin and dapagliflozin in lowering the risk of new-onset AF can be extrapolated to canagliflozin. Lastly, we only investigated Asian patients, and whether our results can be extrapolated to other races remains unclear.

Conclusions

The use of SGLT2i was associated with a lower risk of incident AF compared DPP4i among T2DM patients, irrespective of underlying comorbidities or different SGLT2i in a large real-world setting.

Abbreviations

ACEI = angiotensin-converting enzyme inhibitor

AF = atrial fibrillation

ACEI = angiotensin-converting enzyme inhibitor

ACR = albumin to creatinine ratio

ALT = alanine aminotransferase;

ARB = angiotensin receptor blocker

ARNI = angiotensin receptor-neprilysin inhibitor

ASMD = absolute standardized mean difference

AMI = acute myocardial infarction

APT = antiplatelet agent

BMI = body mass index

CKD = chronic kidney disease;

DBP = diastolic blood pressure

DM = diabetes mellitus

DPP4i = dipeptidyl peptidase-4 inhibitor

eGFR = estimated glomerular filtration rate

HbA1c = hemoglobin A1c

HDL = high-density lipoprotein

IHD = ischemic heart disease

LDL = low-density lipoprotein

MRA = mineralocorticoid Receptor Antagonist

PAD = peripheral artery disease

PSW = propensity score weighting

SBP = systolic blood pressure

SGLT2i = sodium glucose cotransporter-2 inhibitor

SU = sulfonylurea

T2DM = type 2 diabetes mellitus

Declarations

Ethics approval and consent to participate

The study protocol complies with the Declaration of Helsinki and was approved by the Institutional Review Board of the Chang Gung Medical Foundation.

Disclosures

The authors have nothing to disclose.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed in the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

AWCL and CCC contributed equally to the study and manuscript. AWCL, CCC, and YHC contributed to the conception and design of the study, analysis and interpretation of the data, wrote the manuscript, and approved submission. YWK contributed to the data acquisition and analysis. YWK and CYH collected the data. YWK and PHC contributed to analysis of data and provided critical revision of the paper. YHC and PHC provided critical revision of the paper for important intellectual content. All authors read and approved the final manuscript.

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Table

Table 1 Clinical characteristics of the patients with type 2 diabetes treated with SGLT2is and DPP4is

	Before PSW			After PSW		
	SGLT2i (n = 21480)	DPP4i (n = 22989)	ASMD	SGLT2i (n = 48264.9)	DPP4i (n = 41837.7)	ASMD
ical characteristics						
e (years)	59.15±11.99	65.34±13.10	0.066	61.46±12.47	64.17±13.21	0.211
male	41.6%	44.8%	0.066	46.6%	40.9%	0.116
hemic heart logy	10.3%	7.2%	0.110	10.6%	10.2%	0.014
pertension	64.4%	47.9%	0.337	57.8%	55.2%	0.054
slipidemia	68.6%	38.0%	0.643	51.4%	50.1%	0.026
rebral cular idents	5.5%	8.2%	0.111	9.9%	8.0%	0.065
ngestive rt failure	5.0%	5.1%	0.007	7.9%	6.0%	0.074
ronic lung ease	2.4%	3.6%	0.074	4.4%	4.2%	0.011
ronic liver ease	23.8%	15.4%	0.214	19.5%	19.5%	<0.001
ronic kidney ease	17.1%	17.9%	0.023	19.5%	19.1%	0.011
ripheral ery disease	1.0%	1.4%	0.029	1.9%	1.5%	0.030
ut	9.6%	8.3%	0.045	9.5%	8.9%	0.022
lignancy	7.7%	12.0%	0.147	10.6%	11.0%	0.012
l signs						
ight (cm)	161.83±13.43	159.72±13.85	0.155	160.51±12.99	160.49±14.33	0.002
dy weight)	74.14±15.83	67.52±32.28	0.261	70.09±15.50	69.69±33.95	0.015
MI (kg/m^2)	27.95±4.90	26.22±12.02	0.188	26.90±4.89	26.71±12.69	0.020
stolic blood ssure nHg)	139.03±19.94	138.87±22.23	0.008	138.51±20.81	138.19±22.01	0.015
astolic blood ssure nHg)	78.28±12.10	76.72±13.14	0.124	77.04±12.37	77.07±12.95	0.003
art rate m)	84.71±13.76	83.97±14.91	0.052	84.62±14.15	84.55±14.91	0.005
eline laboratory data						
A1c (%)	8.83±1.71	8.37±2.09	0.239	8.65±1.78	8.67±2.21	0.007
moglobin dL)	13.61±2.01	12.27±2.34	0.615	12.50±2.35	12.73±2.42	0.098
telet count 00/ul)	234.78±77.30	232.80±94.34	0.023	233.55±87.55	233.39±93.05	0.002
FR /min/1.73	92.67±31.25	75.13±42.17	0.473	82.79±34.69	84.68±59.12	0.039
T (U/L)	35.35±46.56	33.30±52.15	0.041	33.63±49.23	34.73±54.02	0.021
iglycerides /dL)	187.87±242.53	171.75±173.45	0.076	191.48±301.31	196.27±328.93	0.015
L (mg/dL)	94.96±32.05	98.32±36.06	0.099	97.58±35.77	96.23±35.12	0.038
L (mg/d)	43.55±11.48	42.77±13.15	0.063	42.80±11.87	42.62±13.16	0.014

ic acid /dL)	5.85±1.65	6.18±2.06	0.178	6.23±2.02	6.07±2.00	0.078
R	254.04±790.26	471.87±1504.20	0.181	521.09±1373.90	383.04±1238.44	0.106
eline medications						
i-platelet nts	33.7%	26.5%	0.158	32.5%	31.3%	0.026
tins	58.5%	36.1%	0.459	44.9%	45.4%	0.011
ofibrate	9.9%%	5.3%	0.175	7.3%	7.8%	0.020
timibe	12.3%%	6.0%	0.217	8.7%	8.4%	0.013
ı-ydropyridine Bs	5.3%%	5.0%	0.015	5.2%	6.4%	0.049
ydropyridine Bs	16.3%%	20.3%	0.103	21.3%	19.4%	0.048
a-blockers	34.8%	26.9%	0.170	32.2%	30.4%	0.039
EIs or ARBs ARNIs	59.4%	44.2%	0.308	53.2%	51.6%	0.033
As	3.7%	3.8%	0.007	6.0%	4.6%	0.064
p diuretics	7.9%	1.8%	0.130	13.5%	12.5%	0.030
azide	0.8%	1.0%	0.021	1.2%	1.0%	0.025
ates	6.9%	6.2%	0.027	8.1%	8.1%	0.001
oxin	1.4%	1.2%	0.025	2.0%	1.4%	0.044
i-diabetic nts						
Js	62.5%	36.9%	0.529	48.0%	50.6%	0.052
Metformin	87.2%	59.3%	0.663	68.9%	71.2%	0.050
Glinides	3.3%	6.2%	0.139	6.5%	5.3%	0.049
itazones	22.8%	4.8%	0.539	12.5%	12.7%	0.007
Acarbose	7.7%	7.1%	0.327	12.1%	13.3%	0.037
nsulin	16.7%	21.4%	0.122	22.9%	22.6%	0.008

ACEI = angiotensin-converting enzyme inhibitor; ACR = albumin to creatinine ratio; ALT = alanine aminotransferase; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; MBI = body mass index; CCB = calcium channel blocker; DPP4i = dipeptidyl peptidase-4 inhibitor; eGFR = estimated glomerular filtration rate; HBA1c = hemoglobin A1c; HDL = high density lipoprotein; LDL = low density lipoprotein; MRA = mineralocorticoid receptor antagonist; PSW = propensity score weighting; SGLT2i = sodium glucose co-transporter-2 inhibitor; SU = sulfonylurea

Data are expressed as mean ± standard deviation or as percentage %.

Figures

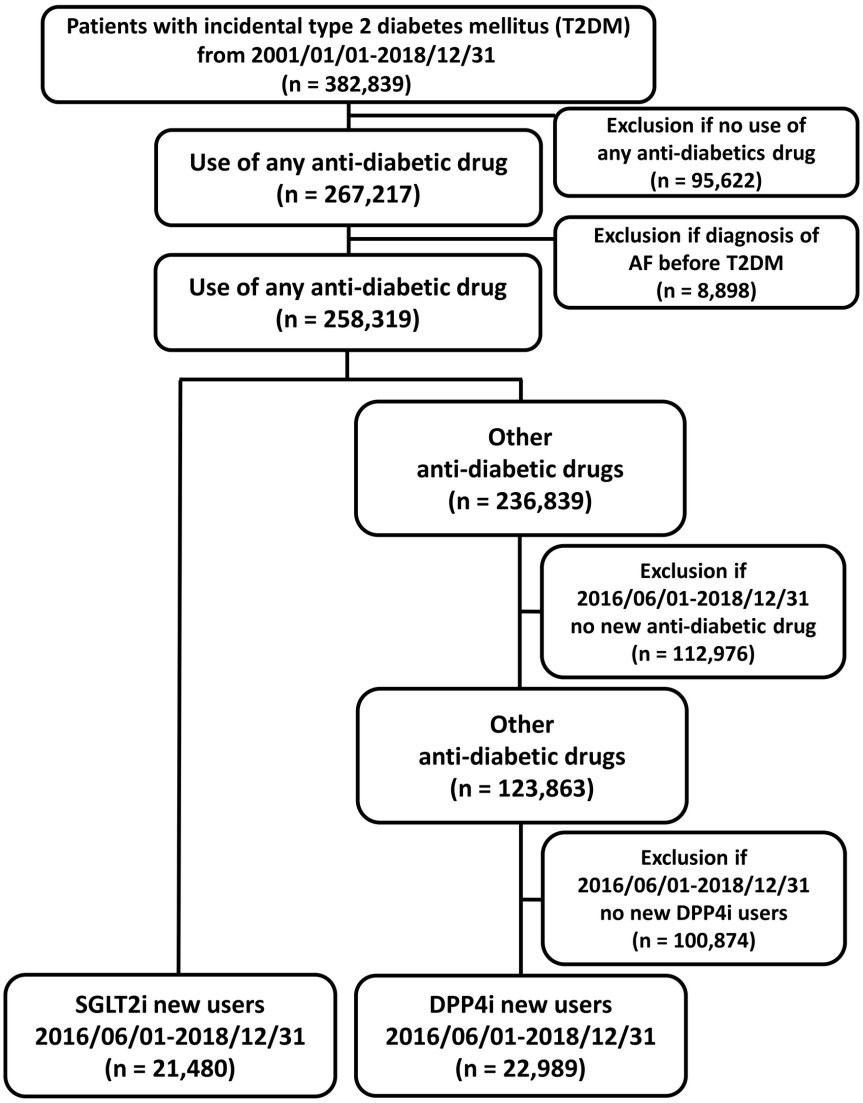

Figure 1

Enrollment of patients with type 2 diabetes mellitus (T2DM) treated with sodium glucose cotransporter 2 inhibitors (SGLT2i) versus dipeptidyl peptidase-4 inhibitors (DPP4i) A total of 21,480 T2DM patients treated with SGLT2i were compared with 22,989 patients treated with DPP4i from June 1, 2016 to December 31, 2018. AF = atrial fibrillation; DPP4i = dipeptidyl peptidase-4 inhibitor; SGLT2i = sodium glucose cotransporter 2 inhibitor; T2DM = type 2 diabetes mellitus

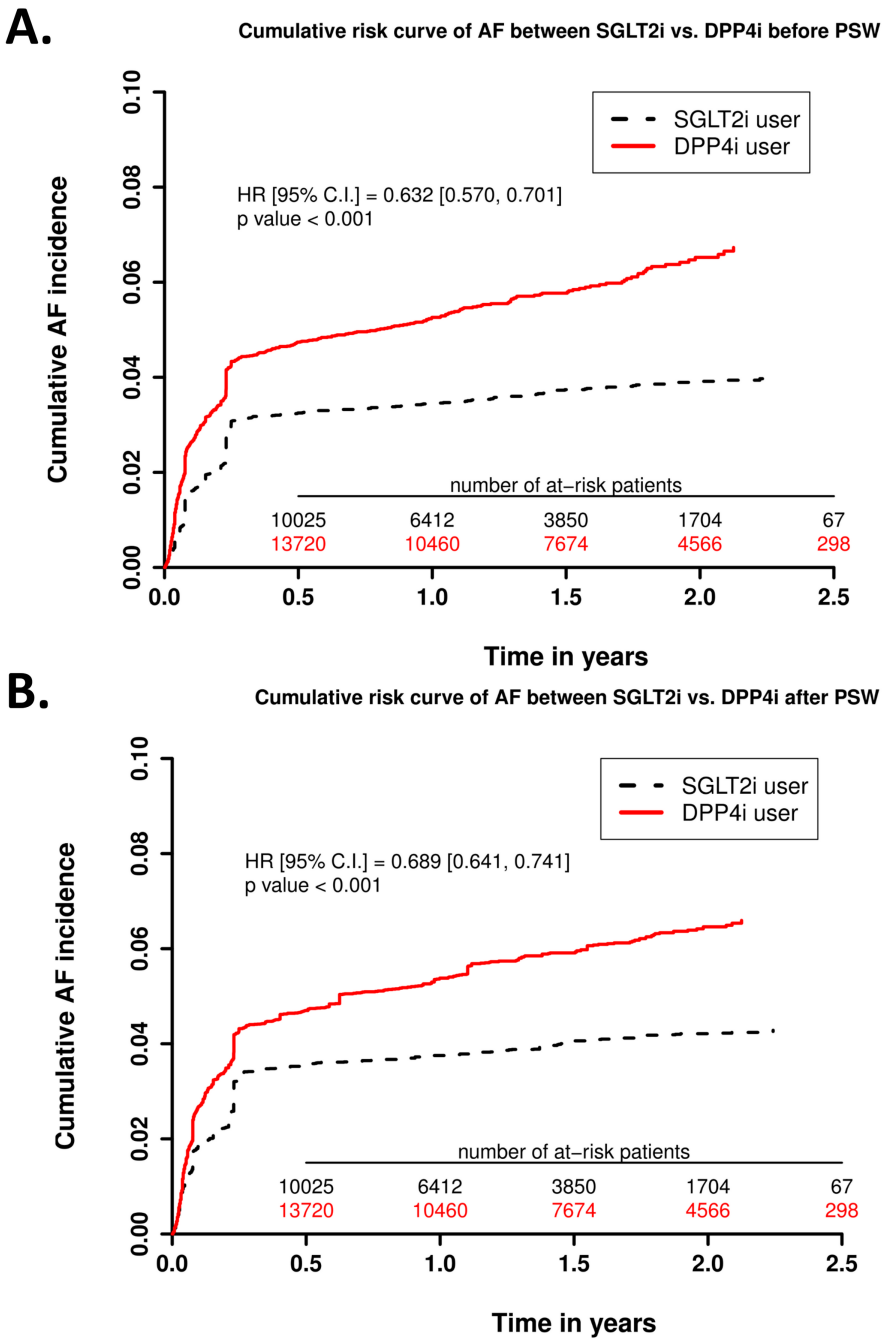

Figure 2

Cumulative risk curve of incident atrial fibrillation (AF) for the study cohorts treated with SGTL2i versus DPP4i before and after propensity-score weighting (PSW) SGLT2i showed a significantly lower cumulative risk of new-onset AF compared with DPP4i in T2DM patients before and after PSW. aHR = adjusted hazard ratio; CI = confidential interval; PSSW = propensity-score stabilized weighting Other abbreviations as in Figure 1

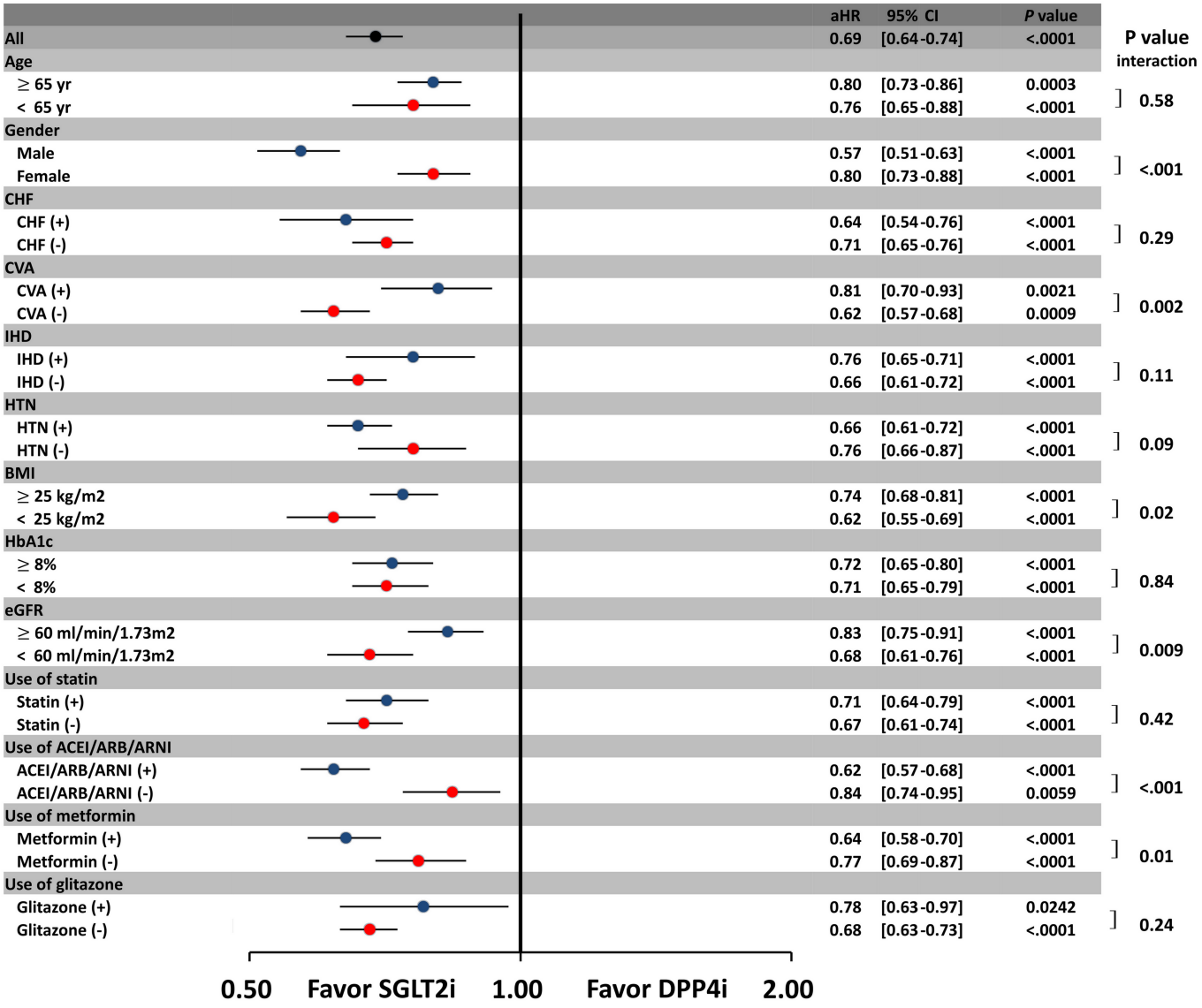

Figure 3

Subgroup analysis of forest plot of adjusted hazard ratio (aHR) for SGLT2i versus DPP4i among T2DM patients after PSW. Subgroup analysis showed consistent results for a lower risk of incident AF for SGLT2i vs. DPP4i among T2DM patients aged ≥ 65 years, and those with congestive heart failure (CHF), cerebral vascular disease (CVA), ischemic heart disease (IHD), hypertension (HTN), body mass index (BMI) ≥ 25 kg/m2, hemoglobin A1c (HbA1c) ≥ 8%, estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m2, and the use of concomitant medications as the main analysis. Of note, the use of SGLT2i reduced the number of new-onset AF events in subgroups including male sex, no previous history of stroke, BMI < 25 kg/m2, eGFR < 60 ml/min/1.73 m2, concomitant use of renin-angiotensin system blockers and metformin (P interaction < 0.05). ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; BMI = body mass index; CHF = congestive heart failure; CVA = cerebral vascular disease; eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1c; HTN = hypertension; IHD = ischemic heart disease Other abbreviations as in Figure 1 and 2

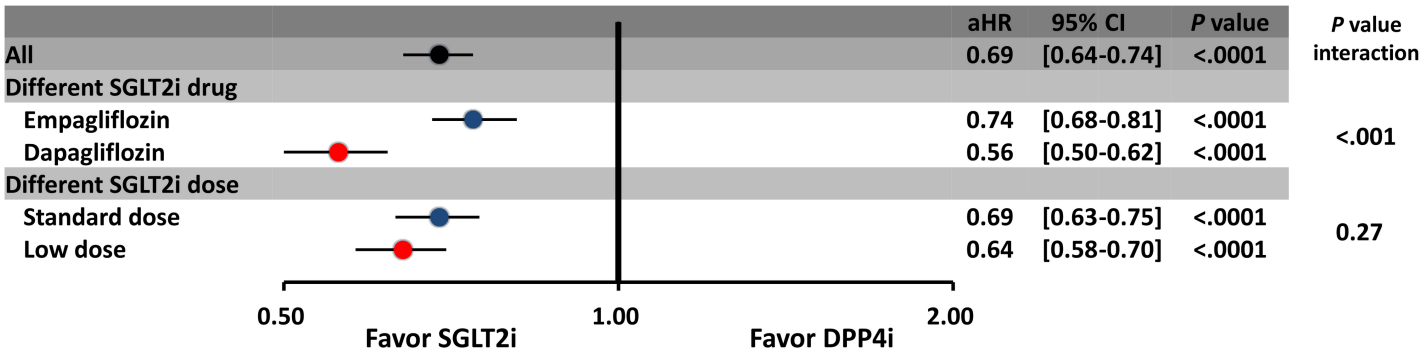

Figure 4

Subgroup analysis of forest plot of aHR for SGLT2is versus DPP4is among T2DM patients treated with different SGLT2i or different SGLT2i dosages after PSW. The benefits of SGLT2i over DPP4i in lowering the risk of incident AF persisted with different SGLT2i (dapagliflozin or empagliflozin) and both low- (empagliflozin 10 mg or dapagliflozin 5 mg once daily) and standard-dose (empagliflozin 25 mg or dapagliflozin 10 mg once daily) SGLT2i treatment. The abbreviations as in Figure 3