Original Article

Sodium-glucose cotransporter-2 inhibitors protect against atrial fibrillation in patients with heart failure

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Background: Heart failure (HF) often complicates atrial fibrillation (AF) and conversely, AF frequently complicates HF. Furthermore, the coexistence of both conditions significantly increases the risk of cardiovascular complications. Sodium-glucose cotransporter-2 (SGLT-2) inhibitors have been demonstrated to decrease hospitalizations for HF and reduce cardiovascular death. Therefore, this study evaluated the effects of SGLT-2 inhibitors on AF in patients with HF.

Methods: A total of 903 patients with HF were enrolled in this study. Basic patient data including demographic characteristics, medical history, cardiovascular medications, and results of biochemical tests were collated. Logistic regression analysis was performed to examine the association between SGLT-2 inhibitors and the risk of AF. The effects of SGLT-2 inhibitors on AF were further analyzed according to subgroups.

Results: Patients treated with SGLT-2 inhibitors experienced a lower prevalence of AF (8.4% *vs.* 12.1%, P<0.001) compared to patients without SGLT-2 treatment. Controlling for potential confounders revealed that SGLT-2 inhibitors decreased the risk of AF by 24% [odds ratio (OR): 0.76; 95% confidence interval (CI): 0.70–0.85; P<0.001]. The effect of SGLT-2 inhibitors on AF was consistent in patients aged < 65 years and patients aged ≥65 years (OR =0.82 and 95% CI: 0.71–0.88 *vs.* OR =0.84 and 95% CI: 0.77–0.92, respectively; P interaction =0.501). Similarly, neither gender, body mass index (BMI), estimated glomerular filtration rate (eGFR), nor the New York Heart Association (NYHA) classification affected the protective effect of SGLT-2 inhibitors.

Conclusions: SGLT-2 inhibitors reduced the risk of AF in patients with HF, and the effect was consistent irrespective of age, gender, BMI, eGFR, and NYHA classification.

Keywords: Sodium-glucose cotransporter-2 inhibitors (SGLT-2 inhibitors); atrial fibrillation (AF); heart failure (HF)

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Introduction

Cardiac structural or functional damage can result in heart failure (HF) which is characterized by a series of typical symptoms and signs including dyspnea, fatigue, ankle swelling, and limited physical capacity, with preserved left ventricular ejection fraction and reduced ejection fraction (1,2). Globally, millions of patients suffer from HF and it is associated with poor quality of life, high morbidity and mortality, as well as substantial medical costs to society (3). Atrial fibrillation (AF) is the most common arrhythmia in HF patients and occurs in more than half of all individuals

with HF (2).

AF is associated with several pathophysiological mechanisms, including atrial electrical, structural remodeling, and glycemic fluctuations (3). In such patients, AF increases the risk of hospitalization, stroke, and all-cause mortality (4). AF and HF commonly coexist and the prevalence of both conditions is expected to rise with the aging population world-wide (5). Despite a plethora of advances in the field of AF and HF over the past 2 decades (6), it remains uncertain which medications can provide optimal long-term outcome for patients with coexisting AF and HF.

The sodium-glucose cotransporter-2 (SGLT-2) is mainly expressed in the kidneys and is responsible for the reabsorption of sodium (Na^+) and glucose in the renal tubules (7). Inhibition of SGLT-2 increases the urinary glucose excretion and augments natriuresis in patients with type 2 diabetes (T2DM) (8). Thus, SGLT-2 inhibitors have emerged as novel glucose-lowering medications. Furthermore, SGLT-2 inhibitors have been shown to be beneficial for HF hospitalizations in T2DM patients by lowering cardiac pre-load and reducing pulmonary congestion (9,10). In fact, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) both recommend the use of SGLT-2 inhibitors in T2DM patients with HF (11). In addition, two large international randomized trials demonstrated that SGLT-2 inhibitors can significantly lower the risk of deteriorating HF, as well as reducing cardiovascular mortality in HF patients with reduced ejection fraction (HFrEF) (12,13). Recently, evidence of a real-world study showed that SGLT-2 inhibitors reduced the risk of new-onset AF in T2DM patients, and subgroup analysis revealed that the use of SGLT-2 inhibitors was associated with a lower risk of new-onset AF in T2DM patients with congestive heart failure compared to those without congestive heart failure (14). Furthermore, studies have shown that SGLT-2 inhibitors can also promote weight loss, lower blood pressure, and reduce inflammation and oxidative stress independent of the effect on blood glucose (7). Since oxidative stress and inflammation play essential roles in the development and progression of AF (15), SGLT-2 inhibitors may be associated with the risk of AF in HF patients. Therefore, this study investigated the association between SGLT-2 inhibitors and the risk of AF in patients with HF. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/apm-21-2694).

Methods

Study participants

In this retrospective observational study, patients aged 18 years and over, who were admitted to the First Affiliated Hospital of Anhui Medical University for HF between January 2016 and December 2020, were recruited. The diagnose of HF was determined by systematic medical history review, physical examination, and laboratory tests. The diagnose of AF was determined by medical history and electrocardiogram which was performed after the initial consultation. Patients with unknown cardiomyopathy, uncontrolled arrhythmia, mental disorders, malignant carcinoma, or severe kidney or liver dysfunction were excluded from the study. Finally, a total of 903 patients with HF were enrolled, including 78 participants with AF and 825 participants without AF. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics board of the First Affiliated Hospital of Anhui Medical University (No. 2016-004) and informed consent was taken from all the patients.

Data collection

Basic patient data including age, gender, weight, height, smoking status, systolic blood pressure (SBP), diastolic blood pressure (DBP), previous medical history, and cardiovascular medications were collated via a standardized data collection form. The main SGLT-2 inhibitors used were dapagliflozin, empagliflozin, and canagliflozin. HF was classified according to the New York Heart Association (NYHA) classification system (16), however, the type of AF was not classified.

Venous blood samples were collected from patients after a 10-hour overnight fast. Samples were tested for levels of hemoglobin A1c (HbA1c), triglyceride (TG), low density lipoprotein cholesterol (LDL-C), uric acid (UA), estimated glomerular filtration rate (eGFR), and B-type natriuretic peptide (BNP). All tests were performed in our hospital.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD), or median (interquartile range, IQR). Continuous variables were compared using Student's *t*-tests or nonparametric tests. Categorical variables are presented as frequencies and percentages and compared using

Table 1 A comparison of the basic characteristics of heart failure patients with and without atrial fibrillation

Indexes	AF group (N=78)	No AF group (N=825)	P value
Age, years	65.6±6.7	63.4±6.4	<0.001
Female, n (%)	34 (43.6)	378 (45.8)	<0.001
Smoking, n (%)	17 (21.8)	126 (15.3)	0.117
BMI, kg/m^2	25.4±4.2	23.7±3.6	0.002
Duration of HF, years	6.5±2.1	4.3±3.7	0.009
History of coronary heart disease, n (%)	35 (44.9)	218 (26.4)	<0.001
History of cerebrovascular disease, n (%)	11 (14.1)	58 (7.0)	0.014
History of diabetes, n (%)	18 (23.1)	115 (14.0)	0.021
Cardiovascular medication, n (%)			
Beta-blocker	62 (79.5)	486 (58.9)	<0.001
ACE inhibitors or ARB	65 (83.3)	618 (74.9)	0.031
Antiplatelet	35 (44.9)	388 (47.0)	0.314
Anticoagulant	51 (65.4)	16 (1.9)	<0.001
SBP, mmHg	129±17	135±11	<0.001
DBP, mmHg	69±10	74±13	0.012
HbA1c, %	7.6±2.0	7.4±1.7	0.087
TG, mmol/L	1.69 (0.79, 2.04)	1.77 (0.91, 2.21)	0.176
LDL-C, mmol/L	2.71±1.05	2.47±1.22	0.214
UA, μmol/L	371±89	322±91	<0.001
eGFR, mL/min/1.73 m^2	79.8±14.2	88.2±15.8	0.003
BNP, pg/mL	1,801±304	1,208±279	<0.001

AF, atrial fibrillation; BMI, body mass index; HF, heart failure; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; UA, uric acid; eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide.

the Chi-square test among different groups. The study participants with HF were divided into two groups based on the AF status and the NYHA classification. Logistic regression analysis was used to evaluate the independent association of SGLT-2 inhibitors and the risk of AF in HF patients, after controlling for potential confounders including age, gender, BMI, duration of HF, coronary heart disease, cerebrovascular disease, diabetes, cardiovascular medication, blood pressure, HbA1c, UA, eGFR, and BNP. The effect of SGLT-2 inhibitors on AF was also assessed according to subgroups based on age, gender, BMI, eGFR, and NYHA classification. Two-tailed P values <0.05 were considered statistically significant. Statistical analysis was performed using the SPSS Statistics 21.0 software (IBM SPSS, Armonk, NY).

Results

Basic characteristics of participants by AF status and NYHA classification

A total of 903 participants, including 412 (45.6%) females, were enrolled in this study. The mean age of the patients was 64.6±9.5 years and the mean BMI was 24.1±4.7 kg/m^2. *Table 1* shows the clinical characteristics of patients with AF compared to patients without AF. Patients with AF were older and predominantly male and had a higher prevalence of coronary heart disease, cerebrovascular disease, and diabetes. In addition, AF patients used beta-blockers,

Table 2 A comparison of patient characteristics based on the NYHA classification

Indexes	NYHA I/II (N=723)	NYHA III/IV (N=180)	P value
Age, years	66.1±6.2	68.4±7.7	<0.001
Female, n (%)	332 (45.9)	80 (44.4)	0.301
Smoking, n (%)	122 (16.9)	21 (11.7)	0.116
BMI, kg/m^2	23.7±3.2	24.5±3.9	0.021
Duration of HF, years	4.7±2.9	6.4±3.1	<0.001
History of coronary heart disease, n (%)	196 (27.1)	57 (31.7)	<0.001
History of cerebrovascular disease, n (%)	60 (8.3)	9 (5.0)	0.247
History of diabetes, n (%)	98 (13.6)	35 (19.4)	0.081
Cardiovascular medication, n (%)			
Beta-blocker	442 (61.1)	106 (58.9)	0.412
ACE inhibitors or ARB	558 (77.2)	125 (69.4)	0.034
Antiplatelet	306 (40.9)	117 (65.0)	<0.001
Anticoagulant	34 (4.7)	33 (18.3)	<0.001
SBP, mmHg	129±15	134±17	0.009
DBP, mmHg	70±11	75±12	0.027
HbA1c, %	7.4±1.3	7.7±1.8	0.081
TG, mmol/L	1.77 (0.82–2.09)	1.74 (0.94–2.17)	0.325
LDL-C, mmol/L	2.55±1.41	2.17±1.20	0.011
UA, μmol/L	342±77	355±81	0.112
eGFR, mL/min/1.73 m^2	86.5±11.7	79.6±13.7	0.007
BNP, pg/mL	1308±401	1798±311	<0.001

NYHA, New York Heart Association; AF, atrial fibrillation; BMI, body mass index; HF, heart failure; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; UA, uric acid; eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide.

anticoagulants, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers (ARB) more frequently than individuals without AF. Patients with AF were more likely to have a higher BMI, blood pressure, UA, eGFR, and BNP compared to patients without AF. There were no differences in the smoking history, use of antiplatelet agents, nor levels of HbA1c, TG, and LDL-C between the two groups.

Patients were categorized according to the NYHA classification, namely, the NYHA I/II group and the NYHA III/IV group. *Table 2* summarizes the characteristics of study participants by NYHA classification. In general, HF patients with NYHA III/IV were older and heavier. There were also more likely to have a longer duration of HF, a history of coronary heart disease, a higher level of blood pressure, and higher levels of LDL-C and BNP compared to subjects with NYHA III/IV. In contrast, HF patients with NYHA III/IV had lower levels of eGFR. However, patients in the NYHA I/II group and the NYHA III/IV group had comparable circulating concentrations of HbA1c, TG, and UA.

Risk for AF with SGLT-2 inhibitors

The prevalence of AF increased with ascending NYHA classification (*Figure 1A*; P=0.016). The incidence of AF in patients with NYHA I classification was 8.1%, compared to 10.2% in NYHA II patients, 14.2% in NYHA III patients,

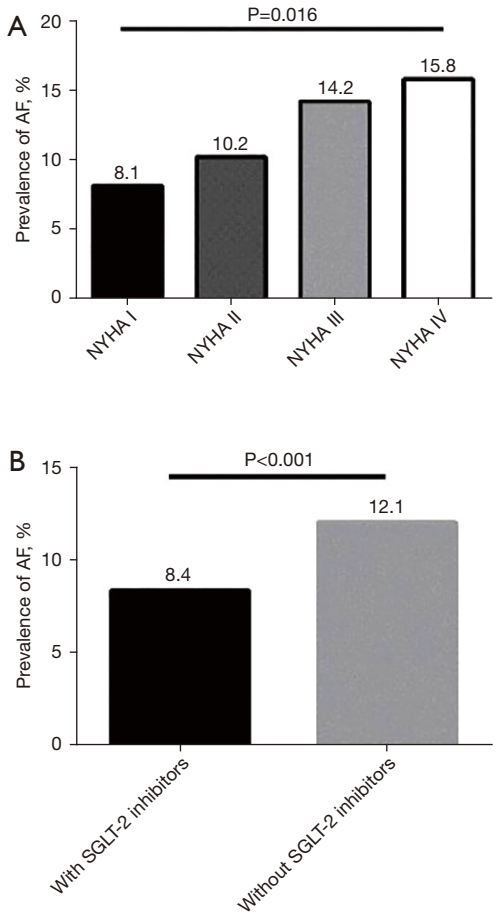

Figure 1 The prevalence of atrial fibrillation among different subgroups. (A) The prevalence of AF in patients with different NYHA classification; (B) the prevalence of AF in patients treated with or without SGLT-2 inhibitors. AF, atrial fibrillation; NYHA, New York Heart Association; SGLT-2, sodium-glucose co-transporter 2.

and 15.8% in the NYHA IV group. Administration of SGLT-2 inhibitors significantly lowered the prevalence of AF compared to patients who did not use SGLT-2 inhibitors (8.4% *vs.* 12.1%, P<0.001) (*Figure 1B*). After controlling for potential confounders, logistic regression analysis revealed that the use of SGLT-2 inhibitors was independently associated with a lower risk of AF (*Table 3*). Model 1 shows the analysis adjusted for age and gender, and Model 2 shows the results adjusted for age, gender, BMI, duration of HF, coronary heart disease, cerebrovascular disease, diabetes, and cardiovascular medication. Model 3 represents model 2 further adjusted for blood pressure, HbA1c, UA, eGFR, and BNP (OR =0.76; 95% CI: 0.70–0.85; P<0.001).

Subgroup analysis

The effect of SGLT-2 inhibitors on AF was further analyzed according to subgroups (*Table 4*). The effect of SGLT-2 inhibitors on AF in patients aged <65 years was comparable to that of patients aged ≥65 years (OR =0.82 and 95% CI: 0.71–0.88 *vs.* OR =0.84 and 95% CI: 0.77–0.92; P=0.501). Similarly, neither gender, BMI, nor the level of eGFR had any consequence on the effect of SGLT-2 inhibitors on AF. Moreover, the effect of SGLT-2 inhibitors on AF was not modified by NYHA classification (OR =0.76 and 95% CI: 0.70–0.85 for NYHA I/II *vs.* OR =0.73 and 95% CI: 0.67–0.89 for NYHA III/IV; P interaction =0.104).

Discussion

This observational study demonstrated that SGLT-2 inhibitors were independently associated with a decreased risk of AF among patients with HF. After adjusting for potential confounders, the effect of SGLT-2 inhibitors on AF remained significant. Of note, the effect of SGLT-2 inhibitors was found to be consistent in patients aged <65 years and patients aged ≥65 years. In addition, NYHA classification did not modify the effect of SGLT-2 inhibitors on AF in patients with HF. The ability of SGLT-2 inhibitors to reduce the incidence of AF was independent of gender, BMI, and eGFR.

HF has been identified as an independent risk factor for AF, possibly by inducing atrial fibrosis and atrial ionic remodeling (17). Individuals with HF and AF have increased risk of cardiovascular complications (4). Both hypertensive heart disease and diabetes mellitus are commonly observed in HF patients, and are associated with a higher prevalence of AF. The possible mechanisms causally linking HF with AF is complex, and may include mechanical stress, inflammation, and electrical remodeling (6).

SGLT-2 inhibitors suppress the active reabsorption of sodium and glucose at the level of the proximal renal tubule, and this may lead to a reduction in blood pressure, blood glucose, and body weight (18). In the cardiovascular outcome trials, dapagliflozin was shown to reduce the worsening of HF events in patients with HF (12), while empagliflozin reduced the risk of cardiovascular death or hospitalization for HF (13). However, there is currently a paucity of data suggesting a relationship between SGLT-2 inhibitors and AF in HF patients. This study demonstrated the protective effect of SGLT-2 inhibitors against AF in patients with HF.

Table 3 The effect of SGLT-2 inhibitors on atrial fibrillation after controlling for potential confounders

	Without SGLT-2 inhibitors	With SGLT-2 inhibitors		P value
		ORs	95% CI	
Univariate analysis	1.00 (Reference)	0.64	0.60–0.72	<0.001
Model 1	1.00 (Reference)	0.68	0.64–0.75	<0.001
Model 2	1.00 (Reference)	0.72	0.67–0.77	<0.001
Model 3	1.00 (Reference)	0.76	0.70–0.85	<0.001

Model 1 is adjusted for age and gender. Model 2 is adjusted for age, gender, BMI, duration of HF, coronary heart disease, cerebrovascular disease, diabetes, and cardiovascular medication. Model 3 is adjusted for all the factors in Model 2, plus blood pressure, HbA1c, UA, eGFR, and BNP. BMI, body mass index; HF, heart failure; HbA1c, hemoglobin A1c; UA, uric acid; eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide; SGLT-2, sodium-glucose co-transporter 2.

Table 4 Effect of SGLT-2 inhibitors on atrial fibrillation by subgroups

Subgroups	Without SGLT-2 inhibitors	With SGLT-2 inhibitors		P Interaction
		ORs	95% CI	
Age				0.501
<65 years	1.00 (Reference)	0.82	0.71–0.88	
≥65 years	1.00 (Reference)	0.84	0.77–0.92	
Gender				0.217
Male	1.00 (Reference)	0.79	0.70–0.87	
Female	1.00 (Reference)	0.83	0.76–0.90	
BMI, kg/m^2				0.341
<28	1.00 (Reference)	0.75	0.70–0.83	
≥28	1.00 (Reference)	0.80	0.76–0.88	
eGFR, mL/min/1.73 m^2				0.612
≥90	1.00 (Reference)	0.80	0.72–0.89	
60–90	1.00 (Reference)	0.77	0.70–0.87	
<60	1.00 (Reference)	0.74	0.67–0.82	
NYHA classification				0.104
I/II	1.00 (Reference)	0.76	0.70–0.85	
III/IV	1.00 (Reference)	0.73	0.67–0.89	

SGLT-2, sodium-glucose co-transporter 2; BMI, body mass index; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; SGLT-2, sodium-glucose co-transporter 2.

To date, there is conflicting data regarding the protective effect of SGLT-2 inhibitors. A systematic review and meta-analysis (n=3,157,259) conducted by Li *et al.* concluded that SGLT-2 inhibitors did not reduce the risk of AF in patients with T2DM compared to other glucose lowering medications (19). Similarly, the CVD-REAL Nordic study, a multinational observational analysis, found no significant difference between SGLT2 inhibitors and other anti-hyperglycemic medications in terms of the incidence of AF in patients with T2DM (20). In contrast, a meta-analysis conducted by Okunrintemi *et al.* involving eight cardiovascular and renal outcomes, showed that SGLT-

2 inhibitors significantly lowered the incidence of AF regardless of the presence or absence of diabetes (relative risk: 0.79; 95% CI: 0.67–0.93) (21). In a recent study of pharmacovigilance databases, AF was reported more frequently in patients taking diabetic drugs compared to patients taking SGLT2 inhibitors (22). In view of these conflicting results, more real-world data are required to verify the protective effect of SGLT-2 inhibitors against AF and the clinical feasibility of SGLT-2 inhibitors warrants further investigation.

Several potential mechanisms have been proposed for the protective effect of SGLT-2 inhibitors against AF in patients with HF. SGLT-2 inhibitors can protect the heart from glucotoxicity, as well as reduce the pre-load, decongestion, and filling pressures through peculiar diuretic actions, which may further reduce atrial dilation. SGLT-2 inhibitors may exert a protective effect by improving atrial structural and electrical remodeling and ameliorating mitochondrial function (23). A recent retrospective analysis demonstrated that SGLT-2 inhibitors have beneficial effects on ventricular repolarization indices including the QT interval and the T peak-to-end (Tp-e)/QT ratio (24), which may be protective against AF occurrence. Clinical data have also demonstrated that SGLT-2 inhibitors are associated with a reduction in epicardial adipose tissue volume (25), which is a biologically highly active tissue that contributes to the development and progression of AF (26). Furthermore, SGLT-2 inhibitors may affect calcium (Ca^{2+}) cycling, Na^{+} balance, and inflammatory and energy balance, all of which play essential roles in the incidence and severity of AF (27).

To the best of our knowledge, this is the first study to evaluate the effect of SGLT-2 inhibitors on AF in HF patients. There were some limitations to this investigation. First, as the study did not distinguish between persistent AF and paroxysmal AF, it remains unclear whether the protective effect of SGLT-2 inhibitors might be affected by the type of AF. Second, the lack of serial electrocardiograms and Holter monitoring means it was not possible to quantify the burden of AF. Third, we regarded the BNP other than NT-proBNP as the biomarker of HF in this study. Compared with BNP, the NT-proBNP is mainly filtered by glomerulus, thus the NT-proBNP concentrations is greatly affected by renal function. HF patients may have a decrease in estimated glomerular filtration rate, so we chose the BNP other than NT-proBNP. Fourth, a causal relationship between SGLT-2 inhibitor use and AF risk could not be established due to the observational nature of this study design. Future randomized clinical trials are warranted to further investigate the protective effect of SGLT-2 inhibitors on the incidence of AF.

In conclusion, SGLT-2 inhibitors reduced the risk of AF in patients with HF, and this protective effect was not altered by age, gender, BMI, eGFR, nor NYHA classification.

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Footnote

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Data Sharing Statement: Available at https://dx.doi.org/10.21037/apm-21-2694

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-2694). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics board of the First Affiliated Hospital of Anhui Medical University (No. 2016-004) and informed consent was taken from all the patients.

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