Sodium Glucose Cotransporter 2 Inhibitors Improve Long-term Atrial Fibrillation-free Survival After Catheter Ablation

Aykun Hakgor, MD, Fatih Erkam Olgun, MD,* Atakan Dursun, MD,* Basak Catalbas Kahraman, MD,* Aysel Akhundova, MD,* Umeyir Savur, MD,* Mehmet Besiroglu, MD,* Melike Zeynep Kenger, MD,* Emir Dervis, MD,† Busra Guvendi Sengor, MD,‡ and Fethi Kilicaslan, MD**

Abstract: Although sodium–glucose cotransporter 2 inhibitors (SGLT2i) are known to reduce the incidence of atrial fibrillation (AF) and AF-related adverse events, evidence on their prognostic effect in patients undergoing catheter ablation (CA) for AF is limited. In a single center, 614 patients (mean age 58.1 ± 9.9 years, 42.2% female) who underwent CA for AF were retrospectively divided into 2 groups according to SGLT2i treatment after the index procedure and followed up for 24 months. The primary outcome of the study was AF recurrence after the first 90-day blanking period after CA. Two separate Cox regression models were constructed to determine the predictors of AF recurrence. Rates of the primary outcome were 19.4% and 35.7% in the SGLT2i and non-SGLT2i groups, respectively. According to the multivariable model 1, which was established among the clinically relevant variables that were found to be statistically significant in univariable analysis, left atrial diameter (adjusted HR: 1.087, 95% CI, 1.054–1.122, $P < 0.001$), SGLT2i therapy (adjusted HR: 0.436, 95% CI, 0.286–0.665, $P < 0.001$), and nonparoxysmal AF (adjusted HR: 1.549, 95% CI, 1.039–2.309, $P = 0.032$) were independent predictors of recurrence after ablation. In model 2, SGLT2i treatment remained an independent predictor of AF recurrence along with significant variables such as age, heart failure with reduced ejection fraction, and previous stroke (adjusted HR: 0.315, 95% CI, 0.214–0.461, $P < 0.001$). The favorable efficacy of SGLT2i on the primary outcome was maintained in subgroup analyses. SGLT2i treatment is associated with lower recurrence after CA for AF in subgroups with and without diabetes or heart failure with reduced ejection fraction and in the overall patient population, independent of AF phenotype.

Key Words: atrial fibrillation, catheter ablation, SGLT2 inhibitors, long-term outcome, risk of recurrence, cardiovascular efficacy

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From the *Department of Cardiology, Istanbul Medipol University, Medipol Mega University Hospital, Istanbul, Turkey; †Department of Cardiology, Istanbul Medipol University, Medipol Bahcelievler Hospital, Istanbul, Turkey; and ‡Department of Cardiology, Kartal Kosuyolu Training and Research Hospital, Istanbul, Turkey.

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Correspondence: Aykun Hakgor, MD, Department of Cardiology, Istanbul Medipol University, Medipol Mega University Hospital, TEM Avrupa Otoyolu Göztepe Çıkışı, No. 1, Bağcılar, Istanbul 34214, Turkey (e-mail: aykunhakgor@gmail.com).

INTRODUCTION

Atrial fibrillation (AF) is the most commonly encountered arrhythmia among the adult patient population globally, affecting over 30 million individuals.[1] Arising from complex pathophysiological mechanisms underpinned by various risk factors, AF significantly diminishes the quality of life and contributes substantially to morbidity and mortality. This is particularly because of its role in increasing the risk of ischemic stroke and causing heart failure–related adverse events.[2,3] Maintaining sinus rhythm with catheter ablation (CA) in these patients is an effective, safe, and proven superiority to antiarrhythmic drugs (AADs), which has been applied with increasing frequency in the last decade.[4,5] The application of CA in patients with AF not only enhances symptomatic relief and quality of life improvements but also offers survival benefits by reducing hospitalizations, especially in patients with heart failure with reduced ejection fraction (HFrEF).[6,7] Current guidelines for the diagnosis and treatment of AF recommend CA methods as a first-line therapy with class 1 indication for symptomatic improvement and prevention of AF progression in patients with paroxysmal and persistent AF.[8,9] However, the main concern is that despite increased clinical experience and improved device technologies, recurrence of AF occurs at rates ranging from 20% to 40% in patients undergoing CA.[10] Recurrence is associated with many adverse events in patients with AF.[11]

Sodium–glucose cotransporter 2 inhibitors (SGLT2i), including empagliflozin and dapagliflozin, have become increasingly used in recent years as oral hypoglycemic agents for the treatment of type 2 diabetes mellitus (DM).[12] Beyond their benefits in glycemic regulation, these medications have demonstrated favorable clinical outcomes across various cardiovascular conditions, notably in patients with HFrEF.[13,14] The cardiovascular benefits of SGLT2i are attributed to mechanisms such as enhancement of cardiac energy metabolism and positive remodeling, reduction of ischemia, reperfusion injury, oxidative stress and inflammation, renoprotective effects, lowering of blood pressure and blood glucose levels, elevation of erythropoietin, and facilitation of weight loss.[15,16] There is strong scientific evidence that the burden and incidence of AF is reduced in patients treated with SGLT2i for both HFrEF and DM.[17–19]

However, evidence is lacking on the effects of SGLT2i in patients with AF undergoing CA. This study aims to assess

the impact of SGLT2i on the recurrence of AF over a 24-month follow-up in patients treated with cryoballoon and radiofrequency catheter ablation (RFCA) methods.

METHODS

Study Design

This retrospective observational study included 614 patients who received CA for symptomatic AF at a tertiary care center from 2014 to 2021, ensuring comprehensive clinical data availability. Exclusion criteria included patients with history of cardiac surgery, valvular AF, congenital heart disease, hypertrophic cardiomyopathy, intracardiac thrombi, uncontrolled hyperthyroidism, severe chronic kidney disease [estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2], and severe liver failure (Child-Pugh class C). Furthermore, patients who could not use SGLT2i because of side effects, discontinued treatment or had incomplete 24-month follow-up were excluded from the study. Prescription of empagliflozin or dapagliflozin for the indication of heart failure or DM during the index hospitalization for CA or within the first 90-day blanking period after the procedure and sustained adherence to the ongoing medication during the 24-month follow-up period was considered SGLT2i use. Before the procedure, detailed clinical characteristics of the patients were noted, laboratory data from the last 15 days were recorded, and electrocardiography (ECG) was performed. A detailed transthoracic echocardiography evaluation (Vivid E9, GE, Milwaukee) was performed during the last preprocedural week, and all measurements were noted according to the recommended standard.[20] All AF definitions, procedural success, and follow-up protocols were adhered to based on current guidelines.[21]

Catheter ablation procedure

All ablation procedures were done with uninterrupted oral anticoagulation (OAC) and transoesophageal echocardiography was performed on patients who were in AF on the day of the procedure. All antiarrhythmic medications were discontinued for at least 5 half-lives before the procedure. A steerable decapolar catheter was positioned within the coronary sinus (CS). A bolus of unfractionated heparin (5.000 Units) was administered before trans-septal puncture (TSP). Access into left atrium (LA) was obtained with TSP guided by fluoroscopy. Intermittent heparin boluses were given to maintain an activated clotting time >300 after the transseptal access.

Cryoballoon Ablation

All patients underwent pulmonary vein (PV) isolation using a 28-mm cryoballoon (Arctic Front Advance; Medtronic Inc). The balloon was introduced into the PV ostium over the Achieve guidewire (Medtronic Ablation Frontiers, CA), which is used for mapping PV potentials before, during, and after cryoballoon applications. The balloon was inflated and positioned at the PV ostium. Contrast agent was injected to the distal site of the balloon to visualize PV total occlusion. A single freezing period of 3 minutes was applied for each PV. Additional cryoballoon applications were applied when PV was not isolated. If the balloon temperature exceeded −55°C, CA would be terminated. During cryo application to the right PVs, pacing was performed through the CS catheter positioned in the superior vena cava for continuous phrenic nerve stimulation. After the procedure, exit and entrance block of all PVs were confirmed by pacing maneuvers. If the patients were not in sinus rhythm after CA, cardioversion was performed. In patients who underwent AF ablation with cryoballoon, only PV isolation was performed and non-PV triggers were not ablated during the index procedure.

Radiofrequency Catheter Ablation

All ablation procedures were done under general anesthesia and performed under the guidance of a fluoroscopic, 3-dimensional electro-anatomical mapping system (CARTO3; Biosense-Webster) and transoesophageal echocardiography if needed. Double TSP was performed, and after the TSPs, two deflectable long sheath (Agilis, Abbott Medical) was placed in the LA. PentaRay (Biosense-Webster) mapping catheter was used from 1 of them to reconstruct the LA, PVs, and bipolar voltage mapping was performed. An irrigated, contact force RF catheter (ThermoCool SmartTouch; Biosense Webster) was positioned in the LA from the second deflectable long sheath. The targeted contact force ranged between 10 and 20*g*, and the energy delivery was controlled with a preset power of 40 W and a reduced setting of 35 W for the posterior wall. Maximum interlesion distance was set as 5 mm. The ablation tags were automatically generated and displayed using the Ablation Index module. The target Ablation Index was 450–500 for the nonposterior wall and 350–400 for the posterior wall. Real-time monitoring of the PV potentials was performed using the PentaRay mapping catheter. For the patients who underwent RFCA, all PVs were first isolated and then RF ablation was performed on non-PV triggers. Complete PV isolation was mandatory for all patients, whereas additional isolation of the mitral isthmus, roofline, posterior box, CS, complex fractionated atrial electrograms, and antrum of the superior vena cava was performed at the operator's discretion. Cavotricuspid isthmus ablation was additionally performed to all patients. Acute procedural success was defined as electric isolation of PVs, confirmed by entrance and exit block and a line of bidirectional block when linear ablations were performed. Non-PV triggers were confirmed using high-dose isoproterenol infusion and rapid atrial pacing. After ablation procedure, figure of eight suture was applied without protamine administration.

Almost all the patients who underwent cryoballoon ablation were first-time ablation patients, whereas most of the patients who underwent RFCA were patients with recurrent AF who had previously undergone cryo.

Postprocedural Follow-up

After successful CA, patients were monitored for 24 hours and then discharged with appropriate medical treatment. All patients received OAC for the initial 3 months postablation. Continuation of OAC therapy was tailored

based on individual CHA2DS2-VASc and hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly and drugs/alcohol (HAS-BLED) scores assessed after this period. Initially, all patients were prescribed class 1 or 3 AADs for 3 months. The decision to continue AAD therapy was subsequently left to the treating physician's discretion. If AF recurrence was detected during the first 3 months, appropriate interventions including medical or electrical cardioversion were implemented. Routine outpatient visits incorporating ECG were conducted at 1, 3, 6, 12, 18, and 24 months. If patients report any symptoms indicative of AF at any time during follow-up, an ECG was performed on the same day to confirm the presence of AF. Telehealth consultations were used as necessary. For the detection of asymptomatic AF episodes, 48-hour ambulatory rhythm Holter monitoring was conducted biannually.

Definition of Atrial Fibrillation Recurrence

AF recurrence was defined as any documented episode of AF lasting more than 30 seconds identified through ECG or Holter monitoring during the 24-month follow-up period, subsequent to the initial 90-day blanking period.

Data Collection and Ethics

Data on clinical profiles, echocardiographic assessments, and laboratory results, alongside details of procedural characteristics and pharmacological treatments, were meticulously gathered from the hospital's electronic health records. In compliance with ethical standards, written informed consent was secured from all participants before CA. This retrospective study received approval from the local university's ethics committee, adhering strictly to the ethical guidelines stipulated in the Declaration of Helsinki.

Statistical Analyses

The normality of continuous variables was assessed using the Kolmogorov–Smirnov test and histogram curve evaluations. Variables that conformed to a normal distribution were reported as mean ± SD, whereas those that did not were expressed as median and interquartile range (25th and 75th). Categorical variables were presented as numbers (n) and percentages (%). The study population was divided into 2 main groups based on the use of SGLT2i, and the differences between these groups in continuous and categorical variables were analyzed using independent t tests, Mann–Whitney U tests, Pearson χ^2 tests, or Fisher's exact test as appropriate. A 2-tailed P-value of <0.05 was set for statistical significance. The association of variables in the dataset with AF recurrence was investigated by univariable Cox regression test and hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. Two separate multivariable Cox regression models were constructed to identify independent predictors of AF recurrence, incorporating variables that were statistically significant in the univariable analysis and deemed clinically significant. Multivariable model 1 was derived by incorporating variables such as body mass index (BMI), eGFR, CHA2DS2-VASc score, AF status, left atrial diameter (LAd), and SGLT2i use. As age, hypertension, coronary artery disease (CAD), HFrEF (≤40%), and history of previous stroke/transient ischemic attack (TIA) are components of the CHA2DS2-VASc score, they were only included in model 2 with left ventricle (LV) hypertrophy and SGLT2i therapy. In opposite, the CHA2DS2-VASc score is only used in model 1. Kaplan–Meier curves were used to estimate AF-free survival after a 90-day blanking period between the 2 groups. Forest plots drawn for each subgroup were used to show the efficiency of SGLT2i on subgroups. All statistical analyses were performed using IBM SPSS Statistics, version 26 (IBM Corp, Armonk, NY).

RESULTS

General Characteristics of the Population

The comparative analysis of various characteristics of 614 patients (mean age 58.1 ± 9.9 years, 42.2% female) undergoing CA for atrial AF based on the use of SGLT2i is presented in Table 1. Demographic features and comorbid conditions revealed that the SGLT2i-using group was older with a higher BMI; as expected, the prevalence of DM, CAD, and HFrEF (≤40%) was greater in this group. The incidence of paroxysmal atrial fibrillation was lower, whereas non-PAF was higher among SGLT2i users. Another notable difference was that the mean CHA2DS2-VASc and HAS-BLED scores were significantly higher in the SGLT2i group. No significant differences were observed between the groups in gender, hypertension prevalence, previous ischemic stroke rate, eGFR, hemoglobin levels, ablation method, and OAC preferences. In addition, there was no difference in the utilization rates of AADs after blanking period between the groups. On comparing transthoracic echocardiography features, while the mean LAd was similar between groups, the SGLT2i group exhibited lower left ventricular ejection fraction, increased LV diameters, and a higher frequency of LV hypertrophy.

Predictors of AF Recurrence

During the 2-year follow-up, AF recurrence rates were 19.4% in the SGLT2i group versus 35.7% in the non-SGLT2i group ($P < 0.001$). Initial univariable Cox regression analysis identified age, BMI, hypertension, CAD, HFrEF, previous stroke/TIA, chronic obstructive pulmonary disease, eGFR, CHA2DS2-VASc and HAS-BLED scores, non-PAF, SGLT2i therapy, LAd, and LV hypertrophy as variables significantly associated with AF recurrence (Table 2). To investigate independent predictors of AF recurrence during the 2-year follow-up post-CA, 2 distinct multivariable models were established. According to model 1, LAd (adjusted HR: 1.087, 95% CI, 1.054–1.122, $P < 0.001$), SGLT2i therapy (adjusted HR: 0.436, 95% CI, 0.286–0.665, $P < 0.001$), and being non-PAF (adjusted HR: 1.549, 95% CI, 1.039–2.309, $P = 0.032$) were identified as independent predictors of postablation recurrence. In model 2, age (adjusted HR: 1.042, 95% CI, 1.023–1.060, $P < 0.001$), HFrEF (adjusted HR: 1.797, 95% CI, 1.224–2.638, $P = 0.003$), previous stroke/TIA (adjusted HR: 1.957, 95% CI, 1.240–3.090, $P = 0.004$), and SGLT2i usage (adjusted HR: 0.315, 95% CI, 0.214–0.461, $P < 0.001$) were statistically significant variables (Table 3). The 24-month Kaplan–Meier plots for AF-free survival between

TABLE 1. Comparison of Baseline Clinical, Echocardiographic, and Laboratory Characteristics of the Study Population Divided Based on SGLT2i Inhibitor Therapy

	Patients With SGLT2i (n = 211, 34.4%)	Patients Without SGLT2i (n = 403, 65.6%)	All Patients (N = 614)	*P*
Age (y)	59.8 ± 9.9	57.1 ± 9.7	58.1 ± 9.9	0.001
Gender (female)	82 (38.9)	177 (43.9)	259 (42.2)	0.228
Body mass index (kg/m^2)	27.5 ± 5.2	26.3 ± 4.9	26.7 ± 5.1	0.008
Hypertension	153 (72.5)	276 (68.5)	429 (69.9)	0.302
Type 2 diabetes mellitus	110 (52.1)	38 (9.4)	148 (24.1)	<0.001
Coronary artery disease	98 (46.4)	114 (28.3)	212 (34.5)	<0.001
HFrEF (≤40%)	77 (36.5)	36 (8.9)	113 (18.4)	<0.001
Previous stroke/TIA	21 (10)	25 (6.2)	46 (7.5)	0.094
Smoker	70 (33.2)	132 (32.8)	202 (32.9)	0.916
COPD	26 (12.3)	44 (10.9)	70 (11.4)	0.603
OSAS	16 (7.6)	6 (1.5)	22 (3.6)	<0.001
Previous CIED	31 (14.7)	14 (3.5)	45 (7.3)	<0.001
Creatinine (mg/dL)	1 (0.8–1.2)	0.9 (0.7–1.1)	0.9 (0.7–1.1)	0.081
eGFR (mL/min/1.73 m^2)	81.1 ± 24.3	85.2 ± 25.1	83.7 ± 24.8	0.151
LDL-C (mg/dL)	97.5 (69–121.7)	81 (62–110)	89 (66–111)	0.092
HbA1c (%)	7.5 ± 2.5	6.2 ± 1.9	6.7 ± 2.3	<0.001
Hemoglobin (g/dL)	13.3 ± 1.9	13.1 ± 1.7	13.2 ± 1.8	0.515
C-reactive protein (mg/dL)	8 (4–13.2)	6 (3–11)	6.7 (3–11)	0.014
CHA_2DS_2-VASc score	3.1 ± 1.4	1.9 ± 1.3	2.3 ± 1.4	<0.001
HAS-BLED score	1.8 ± 1.1	1.3 ± 0.9	1.5 ± 0.9	<0.001
Paroxysmal AF	124 (58.8)	291 (72.2)	415 (67.6)	
Non-paroxysmal AF	87 (41.2)	112 (27.8)	199 (32.4)	0.001
Cryoballoon PVI	184 (87.2)	361 (89.6)	545 (88.8)	
RF catheter ablation	27 (12.8)	42 (10.4)	69 (11.2)	0.376
Beta-blocker	158 (74.9)	241 (59.8)	399 (65)	<0.001
Class 1 or 3 AADs after blanking period	71 (33.6)	112 (27.8)	183 (29.8)	0.132
ACEi/ARB/ARNi	166 (78.7)	250 (62)	416 (67.8)	<0.001
Spironolactone	54 (25.6)	27 (6.7)	81 (13.2)	<0.001
Empagliflozin	93 (44.1)			
Dapagliflozin	118 (55.9)	—	—	—
Insulin	51 (24.2)	14 (3.5)	65 (10.6)	<0.001
NOACs	162 (76.8)	304 (75.4)	466 (75.9)	
Vit-K antagonists	21 (10)	27 (6.7)	48 (7.8)	
None	28 (13.2)	72 (17.9)	100 (16.3)	0.157
LVEF	52.3 ± 13.5	60.5 ± 8.2	57.7 ± 11.1	<0.001
LAd (mm)	41.6 ± 7.1	40.5 ± 7.1	40.9 ± 7.2	0.079
LVEDd (mm)	50.6 ± 8.3	46.9 ± 4.6	48.2 ± 6.4	<0.001
LVESd (mm)	35.7 ± 11.2	31.3 ± 7.4	32.8 ± 9.2	<0.001
LV hypertrophy	70 (33.2)	94 (23.3)	164 (26.7)	0.009

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARNi, angiotensin receptor neprilysin inhibitor; CIED, cardiac implantable electronic device; HbA1c, glycated hemoglobin; LDL-C, low-density lipoprotein cholesterol; LVEDd, left ventricle end-diastolic diameter; LVEF, left ventricle ejection fraction; LVESd, left ventricle end-systolic diameter; NOACs, novel oral anticoagulants; OSAS, obstructive sleep apnea syndrome; PVI, pulmonary vein isolation; Vit-K, vitamin K.

SGLT2i users and nonusers showed a distinct separation favoring the SGLT2i group (log-rank $P < 0.001$) (Fig. 1). Finally, the additive effect of SGLT2i treatment in reducing AF recurrence after CA in the general patient population seems to be maintained across nearly all subgroups (Fig. 2).

DISCUSSION

This extensive single-center retrospective observational study has demonstrated that the use of SGLT2i is associated with lower recurrence of AF after CA in patients with both paroxysmal and non-paroxysmal AF, after a 90-day blanking period over a 2-year follow-up. Subgroup analyses revealed that this favorable effect preserved in patients both with and without DM and HFrEF. However, no statistically significant outcome was reached in the nondiabetic group. Other clear predictors of AF recurrence in this cohort include advanced age, increased LAd, non-PAF status, and HFrEF (≤40%).

SGLT2i, which primarily was introduced into clinical practice for its antidiabetic efficiency, has shown beneficial

TABLE 2. Univariable Cox Regression Hazard Analyses for AF Recurrence

	Unadjusted HR	CI 95%	*P*
Age (y)	1.044	1.027–1.062	<0.001
Gender (female)	0.954	0.713–1.277	0.752
Body mass index (kg/m^2)	1.074	1.044–1.104	<0.001
Hypertension	1.404	1.006–1.960	0.046
Type 2 diabetes mellitus	0.712	0.495–1.024	0.067
Coronary artery disease	1.356	1.011–1.820	0.042
HFrEF (≤40%)	1.461	1.036–2.061	0.031
Previous stroke/TIA	1.895	1.214–2.958	0.005
Smoker	1.282	0.951–1.727	0.103
COPD	1.573	1.052–2.352	0.027
OSAS	1.673	0.884–3.164	0.114
Previous CIED	1.549	0.953–2.520	0.078
eGFR (mL/min/1.73 m^2)	0.986	0.979–0.992	<0.001
C-reactive protein (mg/dL)	0.990	0.976–1.004	0.157
CHA_2DS_2-VASc score	1.181	1.076–1.296	<0.001
HAS-BLED score	1.440	1.248–1.662	<0.001
Non-paroxysmal AF	2.580	1.933–3.443	<0.001
RF catheter ablation (Cryo as reference)	0.599	0.347–1.032	0.065
Beta-blocker therapy	1.075	0.793–1.457	0.641
Class 1 or 3 AADs after ablation	1.257	0.926–1.706	0.142
ACEi/ARB/ARNi therapy	1.330	0.963–1.836	0.083
Spironolactone therapy	1.366	0.919–2.030	0.123
SGLT2i therapy	0.493	0.348–0.697	<0.001
LVEF (%)	0.989	0.977–1.001	0.084
LAd (mm)	1.106	1.087–1.125	<0.001
LVEDd (mm)	1.018	0.995–1.040	0.122
LVESd (mm)	1.007	0.991–1.024	0.404
LV hypertrophy	1.396	1.025–1.902	0.034

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARNi, angiotensin receptor neprilysin inhibitor; CIED, cardiac implantable electronic device; LVEDd, left ventricle end-diastolic diameter; LVESd, left ventricle end-systolic diameter; OSAS, obstructive sleep apnea syndrome.

clinical outcomes in cardiovascular diseases. Although initial studies on the effects of these drugs on AF provided controversial results, significant reduction in AF incidence was identified in post hoc analyses of the Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial.[17,18] These findings were supported by a meta-analysis of 16 randomized studies showing that SGLT2i decrease AF incidence and all-cause mortality risk in patients with DM.[22] Furthermore, the largest meta-analysis to date, encompassing approximately 75,000 diabetic and nondiabetic patients, demonstrated that SGLT2i reduced the incidence of AF and atrial flutter by 25% compared with placebo.[23] In addition, SGLT2i is known to significantly reduce the AF burden and AF-related adverse events across various patient groups.[18]

Despite the above-mentioned robust scientific evidence of SGLT2i on AF, data on its effects on the prognosis of patients undergoing AF ablation are relatively limited and no large prospective study has yet been available. A randomized study involving 80 patients diagnosed with type 2 DM treated with tofogliflozin and anagliptin over a 12-month follow-up demonstrated significant reduction in AF recurrence in the tofogliflozin group, presenting pioneering data in this field.[24] After this, a retrospective study of 326 patients showed that dapagliflozin decreased atrial arrhythmia recurrence over a 36-month follow-up in patients with type 2 DM treated with RFCA.[25] Although these studies exclusively included patients with AF with a diagnosis of DM, the first study to involve nondiabetic patients was conducted by Noh HJ et al, which covered 272 patients and presented 18-month follow-up results. In this study, the dapagliflozin group exhibited lower rates of atrial arrhythmias after a 3-month blanking period in both the general and the propensity score–matched populations (HR: 0.22, 95% CI, 0.11–0.44, $P < 0.001$).[26] Although the level of statistical significance differs (HR: 0.49, 95% CI, 0.34–0.69, $P < 0.001$), the effect of SGLT2i treatment on the primary outcome is similar between our study and the series of Noh et al. Differences between these studies may be attributable to variations in patient numbers, CA preferences, and demographic characteristics of the study populations. Although the percentage of DM, mean eGFR, and left ventricular ejection fraction were similar between the study groups, our study featured younger age and lower LAd, as well as higher rates of paroxysmal atrial fibrillation and cryoablation. Furthermore, despite similar subgroup analysis results, our study uniquely

TABLE 3. Multivariable Cox Regression Analyses Investigating Independent Predictors of AF Recurrence

Multivariable Model 1			
	Adjusted HR	**CI 95%**	***P***
Body mass index (kg/m^2)	1.015	0.970–1.062	0.518
eGFR (mL/min/1.73 m^2)	0.994	0.987–1.001	0.087
CHA2DS2-VASc score	1.077	0.945–1.227	0.266
Non-paroxysmal AF	1.549	1.039–2.309	0.032
LAd (mm)	1.087	1.054–1.122	<0.001
SGLT2i therapy	0.436	0.286–0.665	<0.001
Multivariable Model 2			
	Adjusted HR	**CI 95%**	**P**
Age (y)	1.042	1.023–1.060	<0.001
Hypertension	1.151	0.813–1.629	0.429
Coronary artery disease	1.174	0.861–1.603	0.311
HFrEF (≤40%)	1.797	1.224–2.638	0.003
Previous stroke/TIA	1.957	1.240–3.090	0.004
COPD	1.272	0.843–1.920	0.252
LV hypertrophy	1.147	0.826–1.593	0.412
SGLT2i therapy	0.315	0.214–0.461	<0.001

demonstrates that SGLT2i effectively reduces AF recurrence across with and without HFrEF patient groups, supported by a larger patient cohort and extended follow-up duration, thereby highlighting its potential as a valuable therapeutic option in a broader clinical context.

In a recent study using propensity score matching, SGLT2i use was shown not only to reduce the need for post-CA cardioversion, redo AF ablation, and class 1 or 3 AADs in diabetic AF patients, but also to significantly reduce clinical deterioration because of heart failure, ischemic stroke, all-cause mortality, and hospitalizations at 12-month follow-up after ablation.[27] The most comprehensive data to date comes from a meta-analysis of 525 patients reported from China, which demonstrated that SGLT2i use led to a 37% reduction in AF recurrence during an 18-month follow-up in patients who had undergone CA.[28] Subgroup analyses revealed that SGLT2i provided greater benefits, particularly in patients with a high BMI (≥24 kg/m^2), persistent AF, and those with AF duration exceeding 1 year. Furthermore, this meta-analysis identified LAd as another independent predictor of AF recurrence.[28] In our current study, focusing primarily on the efficacy of SGLT2i, model 1 identified LAd and non-PAF, whereas Model 2 highlighted age, HFrEF ≤40%, and history of stroke as statistically significant predictors of primary outcome. Existing literature further supports that AF phenotype, LA diameter, and volume are the main determinants of recurrence after ablation.[29–31]

Multifactorial mechanisms are thought to be behind the favorable effects of SGLT2i on AF recurrence. These include the management of body weight, blood pressure, blood glucose levels, and intravascular volume control.[15] Moreover, accelerated reduction in atrial fibrosis, adverse atrial remodeling, and thinning of epicardial fat tissue, as

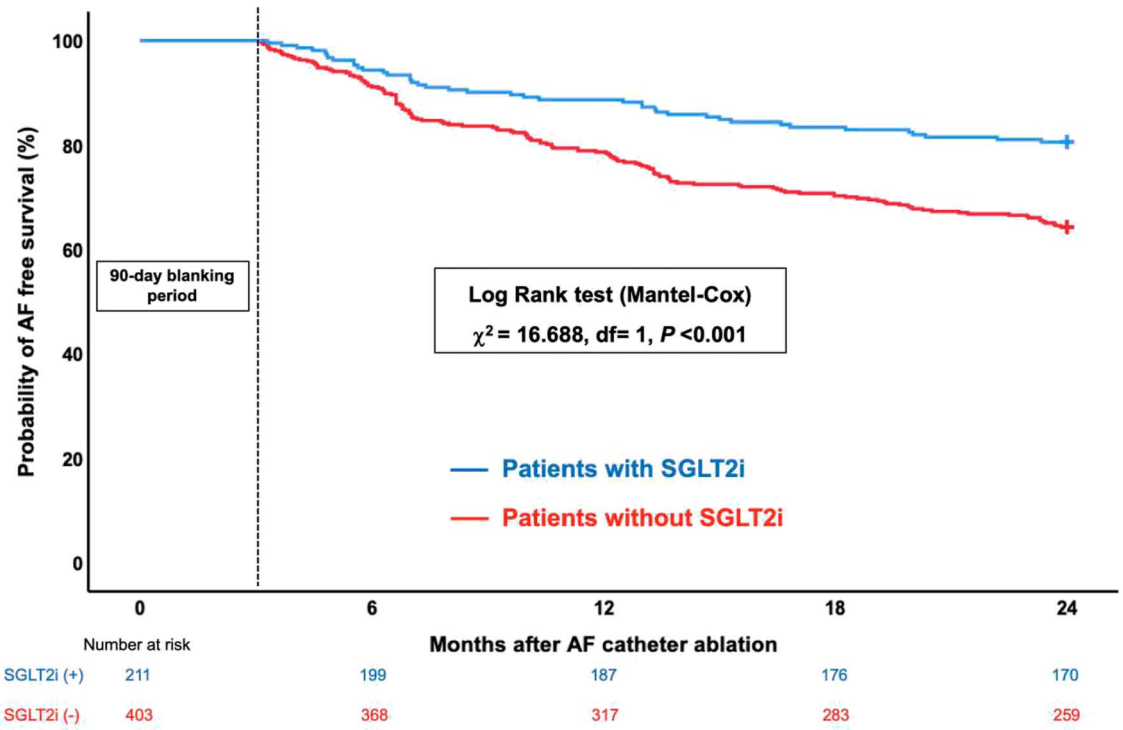

FIGURE 1. 24-month Kaplan–Meier AF-free survival plots according to SGLT2i therapy after index procedure. AF, atrial fibrillation; df, degree of freedom; SGLT2i, sodium-glucose cotransporter 2 inhibitors.

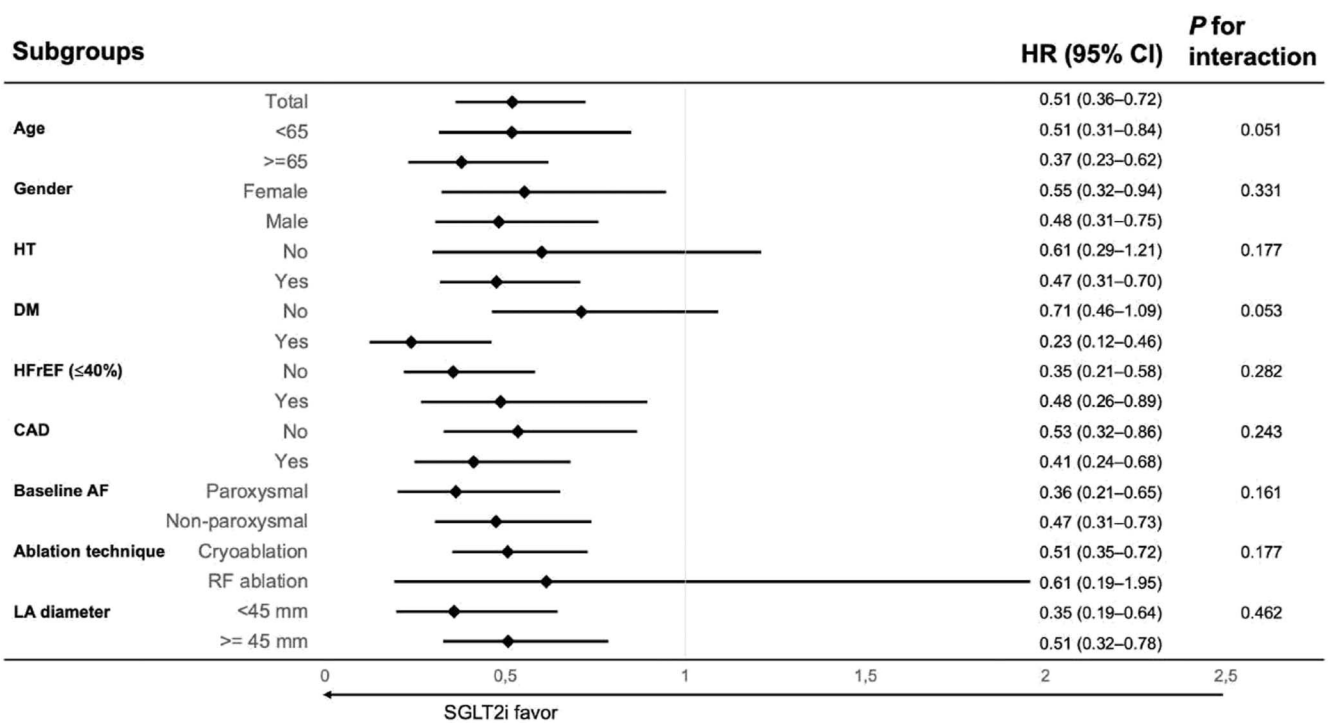

FIGURE 2. Forest plots generated for subgroups. AF, atrial fibrillation; CAD, coronary artery disease; CI, confidence interval; DM, diabetes mellitus; HFrEF, heart failure reduced ejection fraction; HR, hazard ratio; HT, hypertension; LA, left atrium; RF, radiofrequency; SGLT2i, sodium-glucose cotransporter 2 inhibitors.

demonstrated in various animal models, contribute to the decreased risk of AF development.[23,32–34]

CONCLUSIONS

This study demonstrated that in patients with different AF phenotypes undergoing CA, the use of SGLT2i after the index procedure contributed to the maintenance of sinus rhythm by reducing AF recurrence at 24-month follow-up. According to the results of subgroup analysis, SGLT2i continues to exert these favorable effects regardless of the presence of increased LAd (≥45 mm) and HFrEF (≤40%), particularly in patients with type 2 DM. Although the prognostic impact of SGLT2i seems beneficial in nondiabetic patients as well, sufficient data have not yet been accumulated for this group. Nevertheless, the remarkable results of this study may suggest that clinicians could use SGLT2 in appropriate patients to improve treatment efficacy after AF ablation and may guide future studies that may be planned in this manner. However, for broader use of SGLT2i in this indication, especially among nondiabetic groups and patients with preserved ejection fraction heart failure, support and validation through randomized-prospective studies are necessary.

Study Limitations

The primary limitation of this study is its single-center, retrospective design, which may introduce unmeasured confounding factors. Although ECG and Holter monitoring were performed during specified periods to detect AF recurrence, recurrence detection was primarily based on symptomatic presentation. The study did not use implantable electronic devices or increasingly popular smartwatches for AF screening, potentially overlooking asymptomatic AF episodes. The majority of the ablation techniques used were cryoballoon, with RFCA constituting only 11.2% of cases, which might have affected the recurrence rates in an unquantifiable way. Furthermore, although the demographic characteristics were largely similar, the numbers of patients using SGLT2i and those not using were not closely matched, and the lack of propensity score matching also constitutes another limitation related to the study design.

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