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ORIGINAL RESEARCH

A Prospective Cohort Study on the Impact of SGLT2 Inhibitors on the 12-Month Recurrence Risk of Atrial Fibrillation After Catheter Ablation

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Background: Catheter ablation (CA) effectively maintains sinus rhythm in atrial fibrillation (AF) patients, but its postoperative recurrence rate remains high (20–40%), necessitating safe and effective adjuvant therapies. Sodium-glucose cotransporter 2 inhibitors (SGLT2i) have cardioprotective effects, yet high-quality evidence on their value and impact on AF recurrence post-CA is insufficient.
Methods: This single-center observational study prospectively enrolled AF patients undergoing first-time cardiac radiofrequency CA (Jan 2020-Dec 2023). Patients were split into the SGLT2i group (106 cases, 10mg daily dapagliflozin/empagliflozin) and the control group (324 cases). 1:3 propensity score matching (PSM, 13 variables including gender, age, BMI) balanced baselines. Kaplan-Meier analysis compared 12-month AF-free survival; univariate and multivariate Cox models analyzed SGLT2i-AF recurrence association.
Results: A total of 430 patients were enrolled, with an overall 12-month AF recurrence rate of 21.63% (93/430). Kaplan-Meier analysis demonstrated higher 12-month AF-free survival in the SGLT2i group (total cohort Log-rank P = 0.019; PSM cohort Log-rank P = 0.016). Multivariate Cox analysis confirmed SGLT2i use was independently associated with a reduced risk of AF recurrence (total cohort: HR = 0.459, 95% CI = 0.228–0.926, P = 0.030; PSM cohort: HR = 0.458, 95% CI = 0.223–0.939, P = 0.033).
Conclusion: Postoperative SGLT2i use correlates with lower 12-month AF recurrence risk in first-time CA patients, suggesting SGLT2i as a potential adjuvant therapy. Given the observational nature of this study, these findings should be considered hypothesis-generating. Large-scale multicenter randomized controlled trials are needed for verification.

Keywords: atrial fibrillation, SGLT2 inhibitors, radiofrequency catheter ablation, recurrence, propensity score matching analysis

Introduction

Atrial fibrillation (AF), the predominant type of sustained cardiac arrhythmia, currently affects over 60 million individuals globally, a number projected to rise substantially due to population aging.[1,2] This condition imposes a substantial burden by significantly elevating the risk of stroke, heart failure, and all-cause mortality,[3,4] while concurrently imposing immense costs on healthcare systems globally.[5] Radiofrequency catheter ablation (RFCA) is a key therapy for drug-refractory symptomatic arrhythmias that restores sinus rhythm by creating localized lesions to electrically isolate arrhythmogenic triggers, primarily in the pulmonary veins.[6] However, the long-term success of RFCA is limited by a high recurrence rate of 20–40% within the first year, with even higher rates thereafter.[6,7] Recurrence not only signifies the return of debilitating symptoms such as palpitations, dyspnea, and exercise intolerance, but it also frequently necessitates redo ablation procedures or long-term antiarrhythmic drug therapy, both of which carry inherent risks and side effects.[8,9] While antiarrhythmic drugs (AADs) demonstrate short-term efficacy in reducing early recurrence during

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the 3-month blanking period after CA, their long-term benefit for sinus rhythm maintenance remains conflicting among studies, with the overall effect on 1-year arrhythmia-free survival being modest at best.[10]

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are the first glucose-lowering agents proven as a cornerstone in cardiovascular therapeutics. Large-scale, randomized controlled trials (eg., EMPA-REG OUTCOME, DAPA-HF) unequivocally established that SGLT2i markedly lower the risk of heart failure hospitalizations and cardiovascular mortality, with these benefits extending to patients with and without diabetes.[11,12] Emerging evidence suggests that SGLT2i may exert direct cardioprotective effects beyond glycemic control, including attenuation of systemic inflammation and reduction of myocardial fibrosis, as demonstrated in the EMPA-TROPISM trial,[13] and direct modulation of human atrial potassium channels and stabilization of intracellular calcium homeostasis.[14–16] These pleiotropic mechanisms—targeting electrical, structural, and autonomic remodeling—are particularly relevant to atrial arrhythmogenesis, as inflammation and fibrosis play key roles in the atrial substrate remodeling that promotes AF recurrence after CA.[17] Consequently, while a protective effect of SGLT2i against new-onset AF has been established in broad patient populations (eg., with diabetes or heart failure), underscoring their value in primary prevention,[18–21] far less is known from prospective studies about their role in secondary prevention after rhythm control procedures. Therefore, this prospective study aims to determine whether SGLT2i use is associated with reduced AF recurrence with a 12-month follow-up after CA.

Methods

Study Population

The data for this prospective study were sourced from patients undergoing first-time RFCA for AF between January 2020 and December 2023 at the Third Affiliated Hospital of Nanjing Medical University. Figure 1 presents the study flowchart detailing patient screening, enrollment, and group allocation procedures.

Inclusion required: (1) age 18–90 years (undergoing initial RFCA procedure); (2) AF confirmed by 12-lead ECG or Holter monitoring (arrhythmia documentation); (3) AF type as paroxysmal (terminating spontaneously within 48 hours) or persistent (continuing >7 days, including after cardioversion) (consistent with guideline definitions). Patients were excluded for any of the following criteria: (1) contraindication or known allergy to oral anticoagulants; (2) a history of any valvular surgery (including biological valve prostheses), significant native valvular heart disease (eg., moderate to severe aortic or mitral stenosis), congenital heart disease, hyperthyroidism, hypothyroidism, or type 1 diabetes; (3) severe hepatic insufficiency (Child-Pugh class C or aminotransferase levels >3 times the upper limit of normal) or severe renal insufficiency (eGFR <30 mL/min/1.73 m^2); (4) experience of major cardiovascular events (eg., acute myocardial infarction or stroke) within 3 months prior to enrollment; or (5) unwillingness to participate in the follow-up.

Patients assigned to the SGLT2i group were prescribed a daily dose of 10 mg of either dapagliflozin or empagliflozin, with treatment initiation typically occurring within 24–48 hours after CA, upon confirmation of postoperative stability. To ensure a uniform treatment baseline and avoid immortal time bias, patients with prior exposure to SGLT2i before the ablation were excluded from the analysis. The intended treatment duration was at least 12 months, unless contraindicated. For the primary analysis, adherence to the SGLT2i regimen was defined as a Proportion of Days Covered (PDC) of ≥ 80% during the 12-month postoperative period. In our study, we chose this cut-off as it is a widely accepted and validated metric in pharmacoepidemiology for assessing medication adherence across various chronic disease medications, including cardiovascular drugs.[22,23] While we agree that drug-specific validation would be ideal, the PDC ≥80% threshold serves as a robust standard to differentiate between adherent and non-adherent patients in claims database analyses, minimizing misclassification bias. The control group consisted of patients who were not prescribed any SGLT2i medication at discharge but could receive other antihyperglycemic agents (eg., metformin, glinides, DPP-4 inhibitors, sulfonylureas, alpha-glucosidase inhibitors, or insulin) as part of their type 2 diabetes management. No GLP-1 receptor agonists were used in the study cohort, reflecting the local prescribing patterns during the enrollment period.

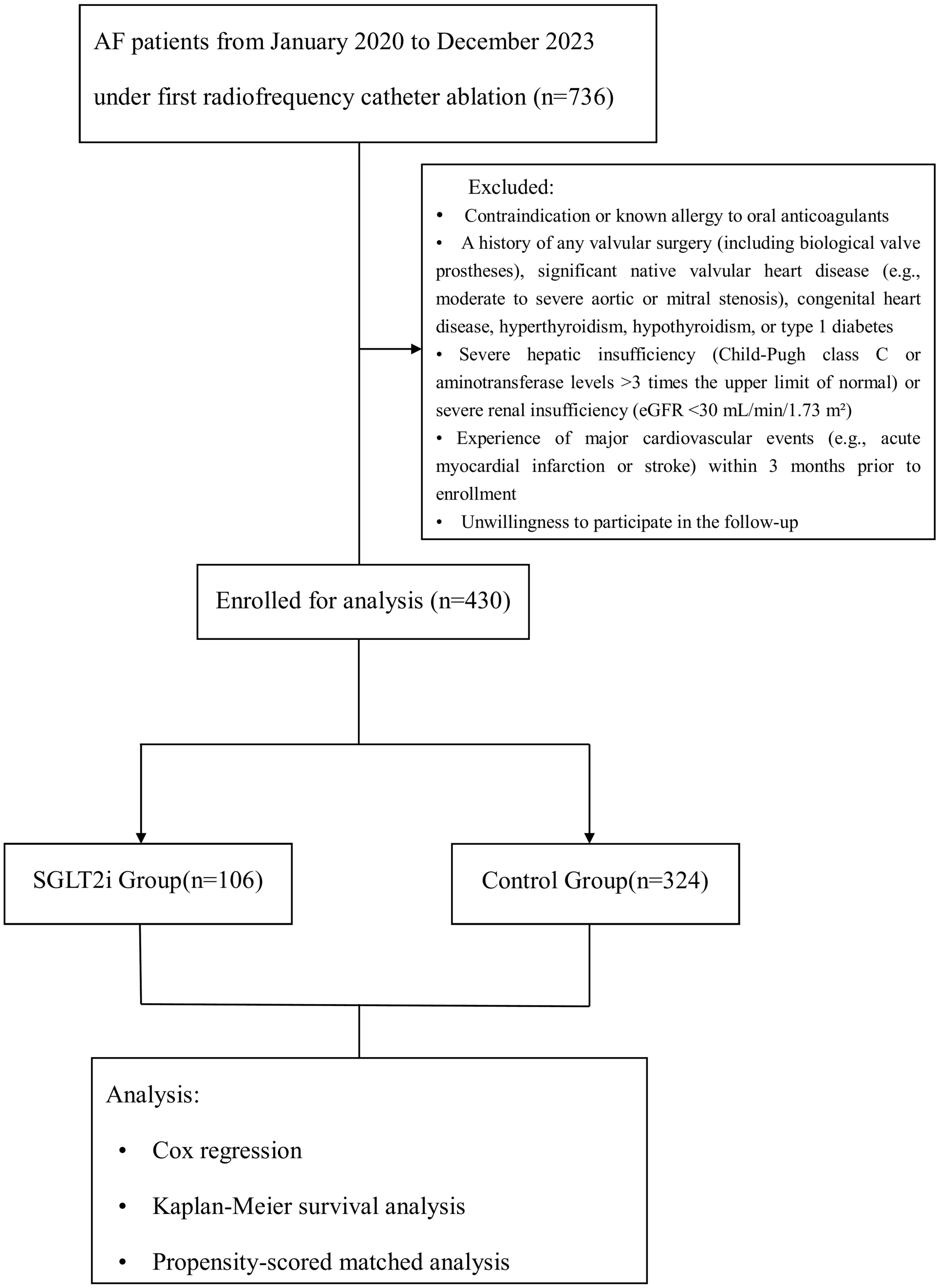

Figure 1 Consort flowchart of patient enrollment, exclusion, and group allocation.

Catheter Ablation

Consistent with protocol guidelines, preprocedural management included a minimum three-week course of oral anticoagulation prior to the procedure.[24] Subsequent transesophageal echocardiography (TEE) examinations systematically ruled out the presence of left atrial thrombi in all cases.[25,26] Prior to the intervention, any antiarrhythmic medications were discontinued for a duration exceeding five elimination half-lives.[27]

The procedure was initiated with bilateral femoral vein access. Under fluoroscopic guidance, two 8.5-F steerable sheaths (SL1, Abbott Laboratories) were advanced into the left atrium via transseptal puncture. Systemic anticoagulation was achieved with intravenous heparin, titrated to maintain an activated clotting time (ACT) of 300–350 seconds. An atrial geometry was reconstructed using a three-dimensional electroanatomic mapping system (CARTO3, Biosense

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Webster) and a high-density mapping catheter (Pentaray, Biosense Webster). Three board-certified electrophysiologists, each with substantial experience in contact-force guided ablation (>300 AF procedures, >20 cases using SmartTouch), performed the interventions. An AI-optimized protocol guided the ablation workflow. Circumferential pulmonary vein isolation was achieved using a SmartTouch catheter (Biosense Webster, CA, USA) with real-time contact force (5–30 g) monitoring and titrated radiofrequency power (30–45 W). Sequential lesions were applied with 4-mm spacing to ensure continuity. AI-derived, anatomically stratified ablation index targets were set as follows: anterior wall 500, roof 400–450, and posterior/inferior areas 350–400.

All patients underwent standard circumferential pulmonary vein isolation (PVI). Based on the operator's intraoperative findings, the subsequent surgical intervention comprised superior vena cava isolation, posterior wall ablation of the BOX, and/or a tailored set of linear ablations (potentially involving the left atrial roof, mitral isthmus, left atrial anterior wall, tricuspid isthmus, and left atrial septal lines), followed by further substrate modification as needed. If a sustained arrhythmia persisted after isolation, synchronized direct-current cardioversion (200 J biphasic) was applied. Substrate modification was subsequently performed in patients where high-density mapping identified left atrial low-voltage zones (< 0.5 mV). The surgical objective was the confirmed isolation of pulmonary veins and additional linear lesions, defined by the absence of pulmonary vein potentials and no reconnection during isoproterenol (2–4 μg/min) and adenosine triphosphate (ATP, 20–40 mg) challenge.

Follow-Up and Outcome

After CA, patients received at least three months of anticoagulant therapy,[28] with the continuation of this therapy depending on the patient's follow-up status. Patients were monitored after the ablation procedure at 3, 6, 9, and 12 months through outpatient clinic visits and 24-hour Holter monitoring. For suspected arrhythmia, chest tightness, or syncope during follow-up, order an immediate 12-lead ECG for diagnosis.

The study defined AF recurrence as any documented AF episode exceeding 30 seconds in duration that occurred after the 3-month blanking period.[29] This blanking period accounts for early arrhythmias attributed to transient procedural inflammation and edema, which are not considered indicative of true recurrence.[30]

Statistical Analysis

All analyses were performed in two complementary populations. First, we conducted analyses in the entire cohort as the primary exploratory analysis, adjusting for potential confounders using multivariable Cox proportional hazards models. Second, to address potential confounding by indication and mitigate baseline imbalances between the SGLT2i and non-SGLT2i groups, we performed a 1:3 propensity score matching (PSM). This propensity score-matched analysis served as a sensitivity analysis to validate the robustness of the findings from the primary exploratory analysis.

Data are presented as mean ± standard deviation for normally distributed continuous variables, median (interquartile range) for skewed data, and frequency (percentage) for categorical variables. Group comparisons were performed using Student's *t*-test, Mann–Whitney *U*-test, or Pearson's χ^2-test, as appropriate. Variables demonstrating a univariate association ($p < 0.05$) were incorporated into the multivariable Cox proportional hazards model. Survival probabilities were estimated using the Kaplan-Meier method and compared with the Log rank test. PSM was applied to reduce potential confounding. Statistical analyses were carried out with IBM SPSS Statistics (v27.0) and R programming environment (version 4.4.3). A two-tailed p-value < 0.05 was considered statistically significant.

Missing data were observed for several variables, with proportions all below 7.5% (NT-proBNP: 7.44%; TG: 1.16%; LAD: 1.16%; LVEF: 0.93%; Cr: 0.70%; HbA1c: 0.47%). Given this low level of missingness, the values were handled using the Multiple Imputation by Chained Equations (MICE) approach, implemented via the R package "mice". Five imputed datasets were created via predictive mean matching (continuous variables) and logistic regression (categorical variables), with convergence ensured by 50 iterations per imputation. A random seed was set at 500 to guarantee reproducibility. In accordance with our pre-specified analytical plan, a single imputed dataset was randomly selected (in this instance, the fifth) for the primary analysis once the post-imputation missingness was confirmed to be below a pre-defined threshold of 10%. This strategy was implemented to ensure analytical reproducibility while avoiding unnecessary computational complexity. We confirmed that the distributions of key covariates in the randomly selected fifth dataset were substantively comparable to those in the other imputed datasets and the original data.

PSM was performed using the MatchIt package in R. Covariates for multivariable adjustment and PSM were selected based on clinical relevance and established risk factors for AF recurrence after CA, as identified in prior studies,[31–34] as well as factors potentially influencing SGLT2i prescription to minimize confounding by indication.[35,36] The propensity score was estimated via a logistic regression model that incorporated these covariates. Specifically, we matched on sex, age, BMI, diabetes, sleep apnea hypoventilation syndrome (SAHS), coronary heart disease (CHD), left atrial diameter (LAD), left ventricular ejection fraction (LVEF), and the use of diuretics, angiotensin receptor-neprilysin inhibitors (ARNI), beta-blockers, and statins, in addition to the ablation strategy (PVI alone). Nearest neighbor matching was applied with a 1:3 ratio without replacement, employing a caliper width of 0.2 SD of the logit propensity score to ensure comparability. To compare baseline characteristics, we calculated the standardized mean difference (SMD).

Results

Overall, 430 patients with AF undergoing RFCA were included in the study. The mean age was 69 years, and 53.3% were male. Regarding AF type, 53.7% had paroxysmal AF, 46.3% had persistent AF. Common comorbidities included hypertension (69.3%), diabetes (44.9%), CHD (24.0%), and stroke (8.8%). Mean LAD was 43.7±5.6 mm, whereas the median LVEF was 58.0% (IQR, 54.2–62.0). Detailed baseline characteristics of the study population before and after PSM are summarized in Supplementary Table S1. Of these, 93 patients (21.63%) experienced AF recurrence within 12 months postoperatively. Before PSM, patients were divided into two groups based on SGLT2i use: SGLT2i group (n = 106) and control group (n = 324). The crude recurrence rate was 13.2% (14/106) in the SGLT2i group versus 24.4% (79/324) in the control group. However, significant baseline imbalances existed between the two groups. Compared with controls, the SGLT2i group had higher BMI, HbA1c, WBC, NT-proBNP, LAD, and a higher prevalence of persistent AF, type 2 diabetes, SAHS, and CHD, but lower LVEF (all P < 0.05; Table 1). With respect to medication use and ablation strategy, the SGLT2i group showed higher proportions of diuretics, ARNI, beta-blockers, statins, DPP-4 inhibitors, and alpha-glucosidase inhibitors, as well as a more frequent posterior wall ablation of the BOX and a lower rate of PVI alone (all P < 0.05; Table 2). These imbalances necessitated PSM to adjust for potential confounding.

Table 1 Baseline Characteristics

	Before Matching			**After Matching**		
	Ctrl Group (n=324)	**SGLT2i Group (n=106)**	**p-value**	**Ctrl Group (n=159)**	**SGLT2i Group (n=83)**	**p-value**
Male	171 (52.8)	58 (54.7)	0.728	89 (56)	45 (54.2)	0.794
Age (years)	68 (62,73)	70 (63,74)	0.126	70 (65,75)	69 (63,73.5)	0.433
BMI (kg/m^2)	24.8±3.1	26.5±3.4	< 0.001	25.7±3	26.1±3.3	0.274
Diagnosis			0.014			0.825
Paroxysmal AF	185 (57.1)	46 (43.4)		79 (49.7)	40 (48.2)	
Persistent AF	139 (42.9)	60 (56.6)		80 (50.3)	43 (51.8)	
Duration(years)	2 (0.3,4)	1 (0.2,4)	0.369	2 (0.2,4.5)	1 (0.2,4)	0.273
Smoke	60 (18.5)	19 (17.9)	0.891	32 (20.1)	14 (16.9)	0.540
Drink	35 (10.8)	12 (11.3)	0.882	17 (10.7)	10 (12.0)	0.750
Diabetes	112 (34.6)	81 (76.4)	< 0.001	108 (67.9)	62 (74.7)	0.274
SAHS	14 (4.3)	11 (10.4)	0.021	9 (5.7)	7 (8.4)	0.41
Hypertension	221 (68.2)	77 (72.6)	0.391	124 (78)	59 (71.1)	0.235
CHD	67 (20.7)	36 (34.0)	0.005	46 (28.9)	27 (32.5)	0.563
Stroke	28 (8.6)	10 (9.4)	0.803	19 (11.9)	8 (9.6)	0.588
Hyperlipidemia	74 (22.8)	15 (14.2)	0.055	37 (23.3)	14 (16.9)	0.246
HbA1c (%)	6 (5.6,6.5)	6.7 (6.2,7.6)	< 0.001	6.4 (5.9,7)	6.8 (6.2,7.8)	0.001

(*Continued*)

Table 1 (Continued).

	Before Matching			After Matching		
	Ctrl Group (n=324)	**SGLT2i Group (n=106)**	**p-value**	**Ctrl Group (n=159)**	**SGLT2i Group (n=83)**	**p-value**
WBC (×10^9/L)	6.2 (5.2,7.5)	6.5 (5.9,7.7)	0.038	6.2 (5.4,7.6)	6.6 (6,7.7)	0.092
NEUT (%)	63.1±9.3	64.2±8.5	0.295	63.7±9.2	64.7±8.6	0.407
NT-proBNP (pg/mL)	386 (124.8,789.8)	618.5 (236.5,1340)	< 0.001	483 (146.5,1070)	547 (196,1340)	0.229
Cr (umol/L)	71 (63,82)	74.5 (61.5,86.8)	0.587	75 (63,85)	72 (57.5,86.5)	0.288
TG (mmol/L)	1.3 (0.9,1.9)	1.3 (1.0,1.8)	0.842	1.3 (1,1.9)	1.3 (1,1.8)	0.620
LAD(mm)	43±5.5	45.9±5.3	< 0.001	44.4±5.3	45.2±5.3	0.273
LVEF (%)	59 (55,63)	56.5 (51.2,61)	< 0.001	58 (54,62)	57 (53,62)	0.589

Notes: Values are expressed as mean ± SD, median (IQR), or n (%).

Abbreviations: BMI, body mass index; SAHS, sleep apnea-hypopnea syndrome; CHD, coronary heart disease; HbA1c, hemoglobin A1C; WBC, white blood cell; NEUT, neutrophil percentage; NT-proBNP, N-terminal pro-brain natriuretic peptide; Cr, creatinine; TG, triglyceride; LAD, left atrial diameter; LVEF, left ventricular ejection fraction.

Table 2 Medications and Ablation Type Data

	Before Matching			After Matching		
	Ctrl Group (n=324)	**SGLT2i Group (n=106)**	**p-value**	**Ctrl Group (n=159)**	**SGLT2i Group (n=83)**	**p-value**
Medications						
Diuretic	27 (8.3)	33 (31.1)	< 0.001	27 (17)	19 (22.9)	0.266
ANRI	32 (9.9)	37 (34.9)	< 0.001	30 (18.9)	18 (21.7)	0.602
Beta-blocker	129 (39.8)	58 (54.7)	0.007	78 (49.1)	45 (54.2)	0.446
Statins	187 (57.7)	83 (78.3)	< 0.001	122 (76.7)	64 (77.1)	0.947
Propafenone	7 (2.2)	2 (1.9)	1	3 (1.9)	2 (2.4)	1
Amiodarone	91 (28.1)	30 (28.3)	0.966	46 (28.9)	20 (24.1)	0.423
ACEI/ARB	123 (38)	37 (34.9)	0.572	59 (37.1)	34 (41)	0.558
Metformin	47 (14.5)	22 (20.8)	0.128	47 (29.6)	19 (22.9)	0.269
Glinides	5 (1.5)	3 (2.8)	0.414	5 (3.1)	2 (2.4)	1
DPP4i	4 (1.2)	6 (5.7)	0.017	3 (1.9)	5 (6)	0.127
Sulfonylurea	21 (6.5)	8 (7.5)	0.704	21 (13.2)	7 (8.4)	0.27
Alpha-glucosidase inhibitors	21 (6.5)	18 (17)	0.001	21 (13.2)	16 (19.3)	0.213
Insulin	11 (3.4)	9 (8.5)	0.058	10 (6.3)	8 (9.6)	0.346
Ablation type						
PVI alone	225 (69.4)	54 (50.9)	< 0.001	100 (62.9)	44 (53)	0.137
SVC	41 (12.7)	18 (17)	0.261	20 (12.6)	15 (18.1)	0.249
Linear ablation	25 (7.7)	12 (11.3)	0.251	12 (7.5)	9 (10.8)	0.387
BOX	34 (10.5)	24 (22.6)	0.001	25 (15.7)	16 (19.3)	0.484
Further substrate modification	15 (4.6)	3 (2.8)	0.58	7 (4.4)	3 (3.6)	1
Intraoperative Electrical Cardioversion	126 (38.9)	50 (47.2)	0.132	74 (46.5)	34 (41)	0.407

Abbreviations: ANRI, angiotensin receptor-enkephalinase inhibitor; ACEI, angiotensin-converting enzyme inhibitor; ARB, aldosterone receptor blocker; DPP4i, dipeptidyl peptidase 4 inhibitors; PVI, pulmonary vein isolation; SVC, superior vena cava.

After 1:3 PSM with a caliper of 0.2, 23 patients were excluded due to lack of suitable matches, yielding a matched cohort of 83 SGLT2i users and 159 controls. In this matched cohort, all baseline characteristics were well balanced between groups, with absolute standardized mean differences (SMDs) below 0.1 for all covariates (Supplementary Figure S1). Although a residual imbalance in HbA1c persisted, it was reduced compared with the pre-match cohort. Within the PSM cohort, the AF recurrence rate was 12.0% (10/83) in the SGLT2i group versus 25.2% (40/159) in the control group (P = 0.017).

Figure 2 presents the Kaplan-Meier curve for freedom from AF recurrence in the total cohort before PSM. The SGLT2i group showed a higher 12-month AF-free survival (86.8% versus 75.6%; Log-rank P = 0.019; Figure 2). After PSM, the Kaplan-Meier curve in Figure 3 demonstrates superior AF-free survival with SGLT2i in the PSM cohort (12-month: 88.0% vs 74.8%; log-rank P=0.016).

Factors associated with AF recurrence were evaluated by Cox proportional hazards models (Table 3). Univariate analysis indicated that SGLT2i therapy was associated with a reduced risk of AF recurrence (HR: 0.513, 95% CI: 0.291–0.906, P = 0.021). Based on these results, two multivariate models were constructed. Model 1, which incorporated adjustments for sex, age, BMI, diagnosis, NT-proBNP, LAD, and LVEF, demonstrated that SGLT2i administration maintained an independent correlation with decreased AF recurrence (adjusted HR: 0.462, 95% CI: 0.251–0.850, P = 0.013). Model 2 incorporated additional covariates, including diabetes, SAHS, CHD, HbA1c,

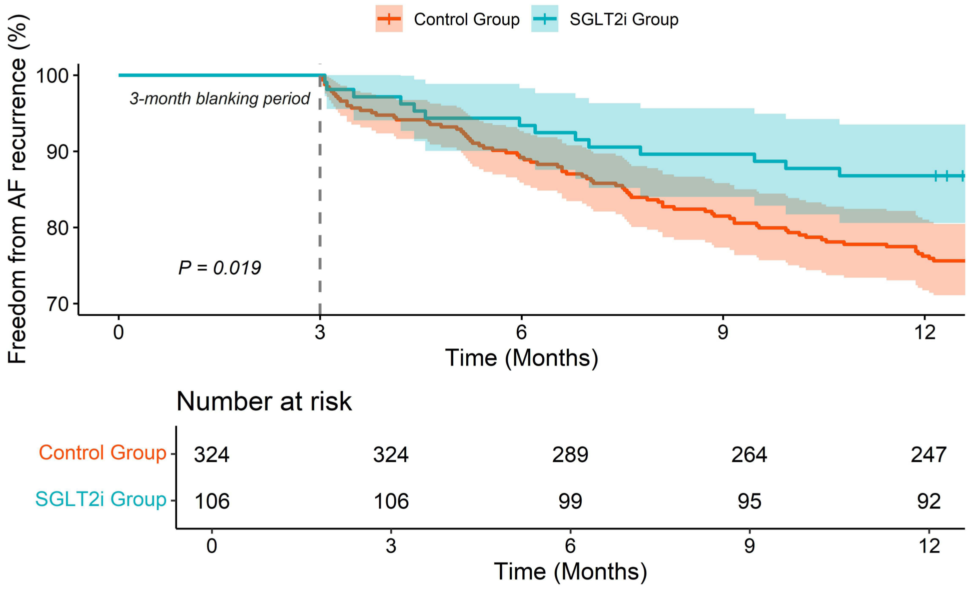

Figure 2 Freedom from AF recurrence survival curve in the total cohort (Pre-PSM) during the 12-month post-ablation follow-up.

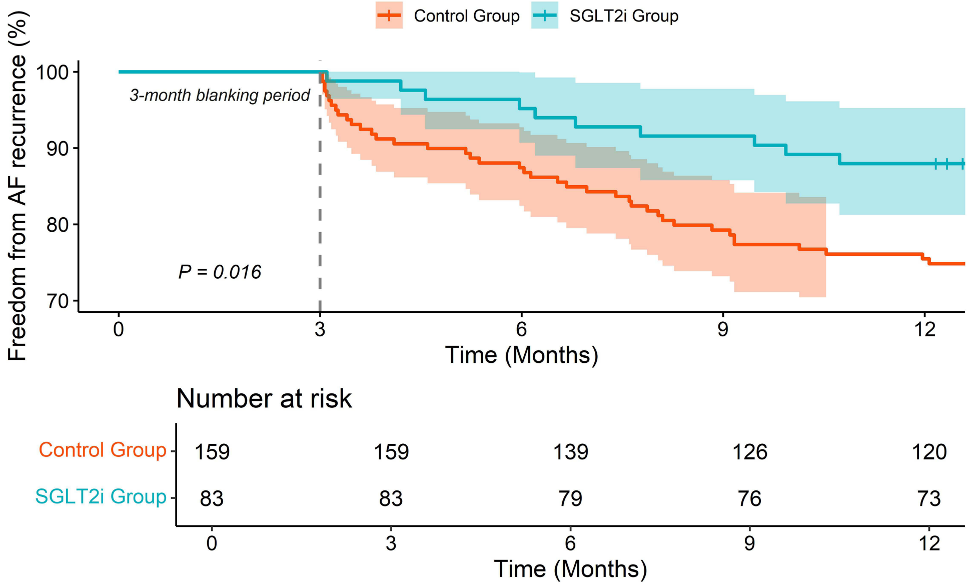

Figure 3 Freedom from AF recurrence survival curve in the propensity score-matched cohort (Post-PSM) during the 12-month post-ablation follow-up.

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Table 3 Univariate and Multivariate COX Regression Analysis for Total AF Recurrence

Variables	Univariate Analysis		Multivariate Analysis			
			Model 1		**Model2**	
	HR (95% CI)	**p-value**	**aHR* (95% CI)**	**p-value**	**aHR# (95% CI)**	**p-value**
Sex	0.815(0.543–1.224)	0.325	0.798(0.523–1.217)	0.294	0.765(0.497–1.179)	0.225
Age	0.985(0.963–1.007)	0.183	0.985(0.962–1.009)	0.219	0.992(0.967–1.018)	0.546
BMI	0.985(0.926–1.049)	0.645	0.986(0.920–1.056)	0.680	0.997(0.927–1.072)	0.933
Diagnosis	2.001(1.318–3.037)	0.001	1.968(1.215–3.188)	0.006	1.843(1.114–3.051)	0.017
Diabetes	0.592(0.385–0.911)	0.017			0.987(0.551–1.769)	0.965
SAHS	0.951(0.386–2.341)	0.913			1.021(0.391–2.663)	0.967
CHD	0.635(0.371–1.089)	0.099			0.743(0.410–1.348)	0.328
HbA1c	0.701(0.546–0.900)	0.005			0.733(0.518–1.035)	0.078
WBC	0.989(0.877–1.116)	0.862			1.001(0.885–1.133)	0.981
NT-proBNP	1(1–1)	0.603	1(1–1)	0.929	1(1–1)	0.570
LAD	1.017(0.979–1.055)	0.387	1.005(0.960–1.052)	0.830	1(0.954–1.0480)	0.993
LVEF	0.982(0.957–1.007)	0.161	0.986(0.957–1.015)	0.340	0.999(0.968–1.032)	0.968
SGLT2i	0.513(0.291–0.906)	0.021	0.462(0.251–0.850)	0.013	0.459(0.228–0.926)	0.030
Diuretic	1.501(0.887–2.540)	0.130			1.821(0.918–3.614)	0.087
ANRI	1.261(0.745–2.134)	0.387			1.237(0.626–2.444)	0.541
Beta-blocker	1.127(0.749–1.694)	0.567			1.108(0.721–1.703)	0.640
Statins	0.691(0.459–1.039)	0.076			0.896(0.568–1.413)	0.637
PVI alone	0.972(0.636–1.487)	0.896			1.192(0.676–2.103)	0.544
BOX	1.526(0.902–2.582)	0.115			1.350(0.640–2.845)	0.430
DPP4i	0.432(0.060–3.100)	0.404			1.232(0.156–9.720)	0.843
Alpha-glucosidase inhibitors	0.536(0.218–1.321)	0.175			1.195(0.421–3.392)	0.737

Notes: Values are presented as hazard ratios (95% confidence intervals). Model 1: *Hazard ratios were adjusted for sex, age, BMI, diagnosis, NT-proBNP, LAD, and LVEF. Model 2: #Hazard ratios were adjusted for Model 1+diabetes, SAHS, CHD, HbA1c, WBC, diuretic, ANRI, Beta-blocker, Statins, PVI alone, Box, DPP4i, and Alpha-glucosidase inhibitors.

Abbreviations: CI, confidence interval; HR, hazard ratio; aHR, adjusted hazard ratio.

WBC, diuretic, ANRI, Beta-blocker, Statins, PVI alone, Box, DPP4i, and Alpha-glucosidase inhibitors based on model 1. After adjustment for these potential confounders, multivariate Cox regression identified SGLT2i as an independent protective factor, associated with a 54.1% lower risk of AF recurrence (adjusted HR: 0.459, 95% CI: 0.228–0.926, P = 0.030; Table 3).

To identify predictors of AF recurrence post-PSM, Cox regression was performed (Table 4). In univariate analysis, SGLT2i use was correlated with a lower recurrence risk (HR: 0.438, 95% CI: 0.219–0.876, P = 0.020). Adjusting for the effects of sex,

Table 4 Univariate and Multivariate COX Regression Analysis for Risk Factors Associated with AF Recurrence in the Propensity-Scored Matched Cohort

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	**p-value**	**aHR* (95% CI)**	**p-value**
Sex	0.854(0.490–1.488)	0.578	0.688(0.382–1.240)	0.214
Age	0.983(0.954–1.014)	0.286	0.983(0.952–1.015)	0.299
BMI	1.003(0.919–1.095)	0.943		
Diagnosis	2.267(1.251–4.107)	0.007	1.602(0.842–3.047)	0.151
Duration	1.091(1.036–1.149)	0.001	1.071(1.016–1.129)	0.011
Diabetes	0.411(0.236–0.716)	0.002	0.821(0.370–1.824)	0.628
SAHS	0.931(0.290–2.992)	0.905		
HbA1c	0.621(0.447–0.864)	0.005	0.789(0.546–1.141)	0.208

(*Continued*)

Table 4 (Continued).

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	**p-value**	**aHR* (95% CI)**	**p-value**
NT-proBNP	1(1–1)	0.098		
LAD	1.052(0.997–1.110)	0.062		
LVEF	0.971(0.940–1.003)	0.074		
SGLT2i	0.438(0.219–0.876)	0.020	0.458(0.223–0.939)	0.033
Diuretic	2.023(1.104–3.705)	0.023	1.236(0.613–2.490)	0.554
Amiodarone	2.204(1.256–3.865)	0.006	1.602(0.873–2.940)	0.128
Metformin	0.395(0.177–0.877)	0.023	0.552(0.230–1.324)	0.183

Notes: Values are presented as hazard ratios (95% confidence intervals). *Hazard ratios were adjusted for sex, age, diagnosis, duration, diabetes, HbA1c, diuretic, amiodarone, and metformin.
Abbreviations: CI, confidence interval; HR, hazard ratio; aHR, adjusted hazard ratio.

age, diagnosis, duration, diabetes, HbA1c, diuretic, amiodarone, and metformin, multivariate results suggested that SGLT2i reduced the risk of AF recurrence by 54.2% (adjusted HR: 0.458, 95% CI: 0.223–0.939, P = 0.033). To further assess whether variations in ablation strategies influenced this association, we performed an additional analysis adjusting for all ablation strategies (Supplementary Table S2). After this adjustment, SGLT2i use remained significantly associated with reduced AF recurrence (HR: 0.450; 95% CI: 0.217–0.932; P = 0.032), virtually identical to the main analysis. Notably, none of the individual ablation techniques were significantly associated with recurrence (all P > 0.05), indicating that in our well-balanced matched cohort, variations in ablation strategies do not independently predict outcomes or confound the SGLT2i effect.

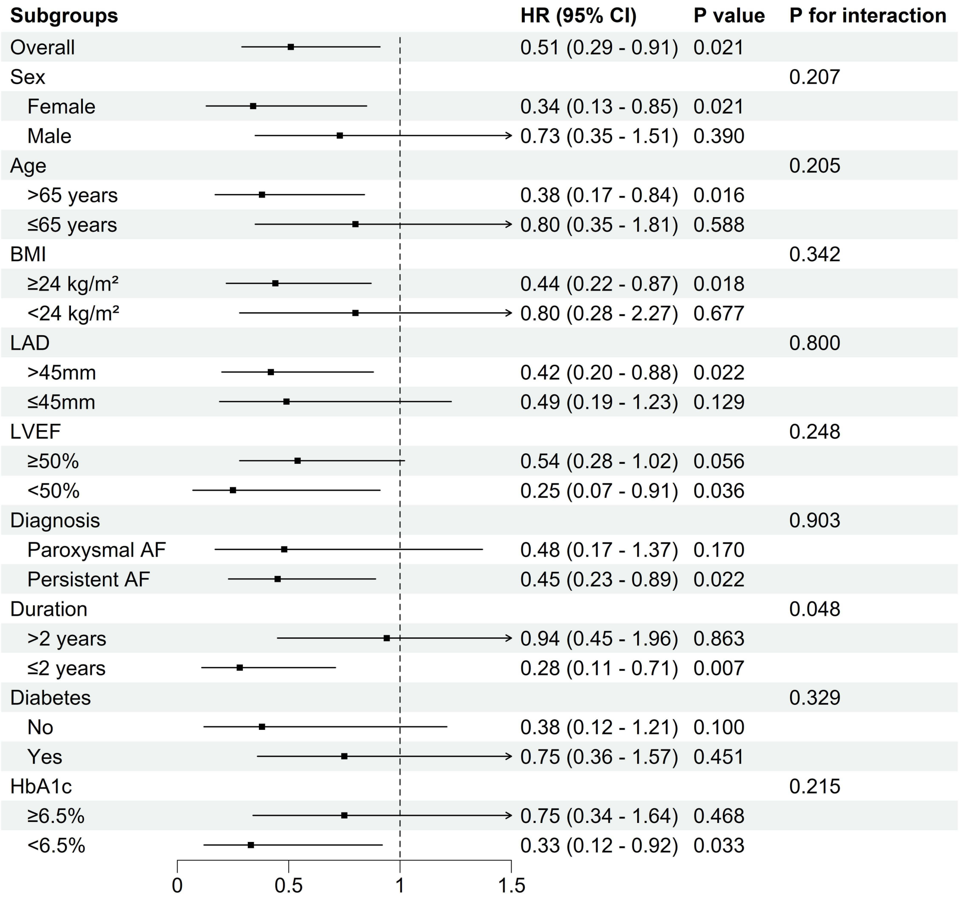
Subgroup analysis was performed to examine the treatment benefits of SGLT2i in various patient characteristics, including sex, age, BMI, LAD, LVEF, diagnosis, duration, diabetes, and HbA1c level (Figure 4). A significant reduction in AF recurrence after CA was observed with SGLT2i use in the overall cohort (HR: 0.51, 95% CI: 0.29–0.91, p = 0.021). However, due to the modest sample sizes within certain strata, all subgroup analyses should be interpreted as exploratory, as the width of the confidence intervals reflects the reduced precision of these estimates. Stratified by the median AF duration of 2.0 years, a significant interaction was observed (P for interaction = 0.048), revealing a greater benefit in patients with a shorter AF history (≤ 2 years; HR: 0.28, 95% CI: 0.11–0.71, P = 0.007) than in those with longer disease duration (> 2 years; HR: 0.94, 95% CI: 0.45–1.96, P = 0.863).

While formal tests for interaction did not reach statistical significance for most characteristics, the pattern of hazard ratios—with point estimates favoring SGLT2i across numerous subgroups including females (HR: 0.34, 95% CI: 0.13–0.85, P = 0.021), Age > 65 years (HR: 0.38, 95% CI: 0.17–0.84, P = 0.016), BMI ≥ 24 kg/m^2 (HR: 0.44, 95% CI: 0.22–0.87, P = 0.018), LAD > 45 mm (HR: 0.42, 95% CI: 0.20–0.88, P = 0.022), LVEF < 50% (HR: 0.25, 95% CI: 0.07–0.91, P = 0.036), persistent AF (HR: 0.45, 95% CI: 0.23–0.89, P = 0.022), and HbA1c < 6.5% (HR: 0.33, 95% CI: 0.12–0.92, P = 0.033)—is suggestive of a broadly consistent treatment effect. However, given the exploratory nature of these analyses and the wide confidence intervals indicative of imprecise estimates (as noted above), these findings should be interpreted with caution. The lack of significance in other subgroups (eg., males, Age ≤ 65 years, BMI < 24 kg/m^2, LAD ≤ 45 mm, LVEF ≥ 50%, Paroxysmal AF, with or without diabetes, HbA1c ≥ 6.5%), coupled with the non-significant interaction tests, may be attributable to limited statistical power rather than a definitive absence of benefit. These observations are hypothesis-generating and warrant validation in larger, adequately powered prospective studies.

Discussion

In this single-center prospective study, SGLT2i use conferred a 54% lower risk of AF recurrence after CA after adjusting for baseline HbA1c. This indicates that the beneficial effect is not mediated by glycemic control alone, which aligns with the mechanism of SGLT2i's cardioprotection independent of hypoglycemia.[11,12,18,37]

Our findings address an evidence gap regarding SGLT2i's antiarrhythmic effects in general AF populations. Previous research has primarily focused on diabetic cohorts, but our study extends the findings of the Korean retrospective study[38] (n = 272) by using



Subgroups	HR (95% CI)	P value	P for interaction
Overall	0.51 (0.29 - 0.91)	0.021	
Sex			0.207
Female	0.34 (0.13 - 0.85)	0.021	
Male	0.73 (0.35 - 1.51)	0.390	
Age			0.205
>65 years	0.38 (0.17 - 0.84)	0.016	
≤65 years	0.80 (0.35 - 1.81)	0.588	
BMI			0.342
≥24 kg/m²	0.44 (0.22 - 0.87)	0.018	
<24 kg/m²	0.80 (0.28 - 2.27)	0.677	
LAD			0.800
>45mm	0.42 (0.20 - 0.88)	0.022	
≤45mm	0.49 (0.19 - 1.23)	0.129	
LVEF			0.248
≥50%	0.54 (0.28 - 1.02)	0.056	
<50%	0.25 (0.07 - 0.91)	0.036	
Diagnosis			0.903
Paroxysmal AF	0.48 (0.17 - 1.37)	0.170	
Persistent AF	0.45 (0.23 - 0.89)	0.022	
Duration			0.048
>2 years	0.94 (0.45 - 1.96)	0.863	
≤2 years	0.28 (0.11 - 0.71)	0.007	
Diabetes			0.329
No	0.38 (0.12 - 1.21)	0.100	
Yes	0.75 (0.36 - 1.57)	0.451	
HbA1c			0.215
≥6.5%	0.75 (0.34 - 1.64)	0.468	
<6.5%	0.33 (0.12 - 0.92)	0.033	

Figure 4 Subgroup analysis of the effect of SGLT2i use on AF recurrence after ablation. Horizontal lines represent 95% confidence intervals. Arrows indicate that the confidence interval extends beyond the axis limit.

a larger prospective cohort (n = 430), adjusting for more confounders—including biomarkers (NT-proBNP, HbA1c, WBC), comorbidities (SAHS), concomitant medications, and ablation strategies (PVI alone, Box ablation)—and included a substantial proportion of non-diabetic patients (23.6% of the SGLT2i group). This design confirms that the anti-recurrence effect of SGLT2i is independent of glycemic status and applicable to a broader patient population.

The biological plausibility of our findings is supported by multiple mechanistic pathways. In the post-CA setting, SGLT2i may exert anti-recurrence effects by targeting two key pathological processes: 1) reducing post-ablation atrial inflammation and oxidative stress,[39] which prevents reconnection of pulmonary veins; 2) improving left atrial remodeling (eg., reducing LAD[40]), which decreases the substrate for AF maintenance. This is particularly relevant because post-CA recurrence is often driven by PV reconnection or persistent atrial remodeling.[6]

These effects align with documented SGLT2i benefits including suppression of inflammatory pathways, reduction of oxidative stress,[41,42] and mitigation of glucotoxicity-related myocardial injury.[43,44] Emerging evidence further suggests direct electrophysiological benefits through modulation of myocardial sodium and calcium handling.[45]

To further contextualize our findings, it is important to acknowledge that the cardiovascular benefits of SGLT2i extend to patient populations beyond those traditionally studied in diabetes trials. Recent data indicate favorable effects in patients with valvular heart disease, including aortic stenosis, potentially through improved ventricular remodeling and hemodynamic profiles.[46] Furthermore, SGLT2i have demonstrated consistent benefits across the broad spectrum of heart failure, including preserved and mildly reduced ejection fraction, through mechanisms such as modulation of myocardial energetics, inflammation, and fibrosis.[47] This expanding literature on SGLT2i-mediated cardiovascular protection, independent of glycemic status, reinforces the biological plausibility of our observed association between SGLT2i use and reduced AF recurrence.

AF duration was an independent predictor of arrhythmia recurrence following RFCA in multivariate analysis. This finding aligns with the established literature, which consistently links increased AF burden with progressive atrial remodeling and worse ablation outcomes.[40] Sustained AF induces electrophysiological and structural alterations in the atria, creating a substrate that is more resistant to the durable success of ablation therapy. Specifically, electrical remodeling, characterized by action potential shortening and refractory period adaptation, promotes AF stability. Concurrently, structural remodeling, involving diffuse interstitial fibrosis and atrial dilation, provides the anatomical foundation for re-entrant circuits.[48] Consequently, patients with long-standing AF exhibit a more advanced diseased substrate, making permanent pulmonary vein isolation and the reversal of this remodeling process significantly more challenging.

This evidence underscores the critical importance of early rhythm-control intervention. The EARLY-AF trial demonstrated superior outcomes for cryoablation as a first-line therapy compared to AADs, highlighting the benefit of intervening before significant therapeutic delay.[49] Our results reinforce this paradigm, suggesting that patients referred for ablation earlier in their disease course may derive the greatest benefit. Future studies integrating precise quantification of atrial fibrosis via late-gadolinium enhancement cardiac MRI with clinical metrics like AF duration could further refine risk stratification and enable truly personalized therapeutic strategies.[50]

Our results converge with accumulating clinical evidence from major cardiovascular outcome trials. The EMPA-REG, DELIVER, and DAPA-HF trials established SGLT2i's cardioprotective properties,[51–53] while the DECLARE-TIMI 58 trial specifically demonstrated reduced AF risk in high-risk diabetics.[54] Subsequent evidence from the China-AF Registry[55] and recent meta-analyses[56–58] has corroborated these antiarrhythmic benefits across diabetic and non-diabetic populations. Collectively, these findings position SGLT2i as a valuable adjunctive therapy to CA, with the potential to improve long-term rhythm outcomes in a broad spectrum of AF patients.

However, the proposed anti-inflammatory, anti-remodeling, and electrophysiological mechanisms, while plausible, remain speculative in the absence of direct mechanistic data from our study. Therefore, our conclusions should be interpreted with appropriate caution. Our study demonstrates that SGLT2i use is significantly associated with reduced AF recurrence after ablation, independent of glycemic control. While this association is supported by a robust and evolving body of literature on the pleiotropic cardiovascular effects of SGLT2i, it does not prove a definitive antiarrhythmic mechanism.

Limitations

First, to ensure matching quality, 23 patients were excluded as they lacked suitable controls within the stringent 0.2 caliper. This rigorous process, resulting in a well-balanced cohort of 83 SGLT2i and 159 control patients, underscores the reliability of the observed association. Future studies with even larger samples will be valuable to further solidify these findings. Second, as a single-center study, our findings may be limited by the homogeneous patient population (eg., 92.09% of patients were Han Chinese). This specific setting served to strengthen internal validity through reduced variability in clinical practice. In particular, the uniform absence of GLP-1 receptor agonist use, reflecting local prescribing patterns, removed a significant confounding factor and provided a unique opportunity to isolate the effect of SGLT2i. Third, our study excluded patients with significant native valvular heart disease and those with prosthetic valves. Given the known interaction between valvular pathology, atrial remodeling, and AF recurrence, our findings may not be generalizable to these populations. Furthermore, although patients with significant valvular disease were excluded, we cannot rule out the potential influence of mild valvular abnormalities on atrial remodeling and AF recurrence. Future studies with comprehensive echocardiographic phenotyping may further elucidate this relationship. Further research is needed to validate our results in patients with valvular AF. Fourth, while our subgroup analyses suggest potential heterogeneity in treatment effect across certain clinical characteristics (eg., AF duration), these findings must be interpreted with caution. The limited number of patients in subgroups such as those with low BMI or reduced LVEF resulted in wide confidence intervals and insufficient statistical power to detect modest but clinically meaningful differences. These analyses are hypothesis-generating and require validation in larger, prospectively designed studies. Future multicenter RCTs should include diverse ethnic groups and assess long-term outcomes (eg., 2-year recurrence, major bleeding events) to confirm the safety and efficacy of SGLT2i as adjuvant therapy. Fifth, as with any observational study using PSM, the possibility of residual confounding remains an inherent limitation. Specifically, the imbalance in HbA1c levels after matching suggests that unmeasured confounders related to glycemic control, such as duration of diabetes or details of prior anti-diabetic regimens, may not have been fully accounted for. This persistent difference could indicate residual differences in underlying cardiometabolic disease severity or cardiovascular risk factor management between the groups. Consequently, our findings should be interpreted as demonstrating an association rather than a causal effect. Well-designed prospective studies and randomized controlled trials are warranted to confirm these findings and further elucidate the benefits of SGLT2i in patients with AF. Sixth, it should also be noted that our study excluded patients with significant native valve disease or prosthetic valves. Therefore, the findings may not be generalizable to the broader population of AF patients with concomitant valvular heart disease, in whom atrial remodeling mechanisms may differ.

Conclusions

Postoperative SGLT2i use correlates with lower 12-month AF recurrence risk in first-time CA patients, suggesting SGLT2i as a potential adjuvant therapy. Given the observational nature of this study, these findings should be considered hypothesis-generating. Large-scale multicenter randomized controlled trials are needed for verification.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author, Qingjie Wang, upon reasonable request.

Ethics

This study was conducted in strict accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all participants, and the study protocol was reviewed and approved by the Ethics Committee of The Third Affiliated Hospital of Nanjing Medical University (No.KY339-01).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests.

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