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Long-term efficacy of sodium-glucose cotransporter 2 inhibitor therapy in preventing atrial fibrillation recurrence after catheter ablation in type 2 diabetes mellitus patients☆

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ABSTRACT

Background: Sodium-glucose cotransporter 2 inhibitors (SGLT2i) reduce new-onset atrial fibrillation (AF) in patients with type 2 diabetes mellitus (T2DM). We aimed to determine the long-term effects of SGLT2i on atrial tachyarrhythmia recurrence after catheter ablation (CA) in T2DM patients.

Methods: This retrospective study enrolled consecutive patients with T2DM undergoing CA for AF between January 2016 and December 2021. Patient baseline demographic characteristics and use of anti-diabetic and anti-arrhythmic medications were analyzed. Echocardiographic parameters were obtained one day and 6 months after CA.

Results: Our study population comprised 122 patients (70% paroxysmal AF). The baseline patient characteristics were similar between the SGLT2i-treated group (n = 45) and the non-SGLT2i-treated group (n = 77) except for stroke. At 6-month follow-up, body-mass index (BMI) was significantly decreased and left ventricular ejection fraction (LVEF) was significantly increased only in the SGLT2i group. E/e' was decreased 6 months after CA in both groups. During a mean follow-up of 33.7 ± 21.6 months, 22 of 122 patients had atrial tachyarrhythmia recurrence. The long-term atrial tachyarrhythmia-free survival rate was significantly higher in the SGLT2i-treated patients, and multivariate analysis revealed that AF type and SGLT2i use were independently associated with atrial tachyarrhythmia recurrence after CA.

Conclusion: The use of SGLT2i and AF type were independent risk factors associated with atrial tachyarrhythmia recurrence after CA in T2DM patients with AF. This result was at least partly due to the pleiotropic effects of SGLT2i on BMI reduction and left ventricular function improvement.

1. Introduction

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia encountered in daily clinical practice. Type II diabetes mellitus

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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(T2DM) has been identified as a risk factor for AF, with T2DM patients having a 34% greater risk of developing AF [1]. Patients with T2DM and incident AF are at increased risk of myocardial infarction, heart failure (HF), and even mortality [2]. Structural, electrical, and electromechanical remodeling of the atria are suggested to be involved in the underlying mechanism of AF development in patients with diabetes [3]. Poor glycemic control reflected by higher serum hemoglobin A1c (HbA1c) level is reported to increase the risk of incident AF in patients with diabetes, with an adjusted hazard ratio (HR) of 1.14 per 1% increase in HbA1c level [4]. Several classes of antidiabetic medications are associated with a decreased risk of AF, including metformin, dipeptidyl peptidase-4 inhibitors (DPP4i), and thiazolidinediones (TZD) [3–5]. Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are a new class of antidiabetic agents that inhibit glucose reabsorption in the proximal convoluted tubules of the kidney, thereby increasing urinary glucose excretion and lowering the plasma glucose in patients with T2DM [6]. SGLT2i have been proved to reduce the risks of poor cardiovascular outcomes, especially HF and all-cause mortality [7,8]. SGLT2i suppress pro-inflammatory pathways and improve mitochondrial function, resulting in reduced atrial remodeling in animal models and *ex vivo* experiments [9,10]. Consequently, SGLT2i have been reported to prevent AF occurrence in observational studies, subgroup analyses, and meta-analyses [11–13].

Catheter ablation (CA) is a common treatment strategy for symptomatic AF refractory to anti-arrhythmic medications. However, the long-term success rate is only 50–80% in several cohorts [14,15]. Metformin and pioglitazone have been shown to reduce the risk of AF recurrence after CA [16,17]. A recent prospective, randomized controlled study by Kishima et al. [18] demonstrated that lower rate of SGLT2i use, higher prevalence rate of non-paroxysmal AF, elevated brain natriuretic peptide, higher urinary albumin-creatinine ratio, larger left atrial diameter (LAD), elevated E wave, lower left ventricular ejection fraction (LVEF), and lower rate of cryoballoon ablation were associated with AF recurrence post CA during 1-year follow-up. In addition, tofogliflozin (SGLT2i) achieved greater suppression of AF recurrence after CA in patients with T2DM than anagliptin (DPP4i). However, multivariate analysis was not able to identify any independent risk factor because of a small number of patients in that study. In addition, whether SGLT2i prevent atrial tachyarrhythmia recurrence during long-term follow-up is still unknown. Therefore, the aim of this study was to investigate whether the use of SGLT2i is an independent factor associated with improved long-term outcomes in patients with T2DM undergoing CA for AF in comparison with other anti-diabetic medications, especially DPP4i.

2. Methods

2.1. Study population

We retrospectively collected data of consecutive patients with T2DM undergoing CA for anti-arrhythmics–refractory AF between Jan 2016 and Dec 2021 at our institution. Baseline patient characteristics, including patient demographics, comorbidities, laboratory data, echocardiographic parameters, and medications were obtained for all patients. In accordance with the HRS/EHRA/ECAS expert consensus statement [19], paroxysmal AF was defined as AF that terminates spontaneously or with intervention within 7 days of onset; and non-paroxysmal AF is defined as continuous AF that is sustained beyond 7 days of onset. Patients with an estimated glomerular filtration rate (eGFR) $<$ 30 mL/min according to the Cockcroft-Gault equation or those for whom antidiabetic medications were unnecessary were excluded. Patients were classified based on whether they did or did not receive SGLT2i (the SGLT2i and non-SGLT2i groups, respectively), including empagliflozin, dapagliflozin, and canagliflozin, after they underwent CA for AF. Patients who received SGLT2i therapy before CA but discontinued SGLT2i treatment after CA were classified as non-SGLT2i group. We also classified patients

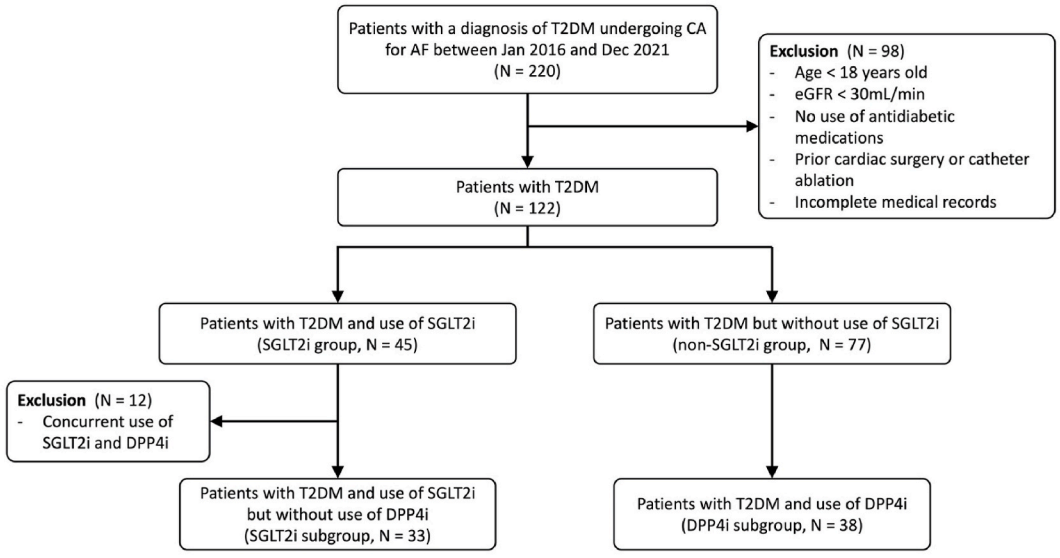

Fig. 1. Flow diagram of the study cohort. T2DM, Type 2 diabetes mellitus; eGFR, estimated glomerular filtration rate; SGLT2i, sodium-glucose cotransporter 2 inhibitor; DPP4i, dipeptidyl peptidase-4 inhibitor.

into the SGLT2i subgroup and DPP4i subgroup according to the use of SGLT2i or DPP4i, respectively. Patients with concurrent use of SGLT2i and DPP4i were excluded from the subgroups. The flow diagram of patient cohort was shown in Fig. 1. This study was approved by the Institution Review Board of Chang Gung Memorial Hospital (IRB No. 202200258B0), and individual consent for this retrospective analysis was waived.

2.2. Electrophysiological study and CA procedure

AF ablation was performed using a three-dimensional electroanatomical mapping system (CARTO, Biosense Webster, Diamond Bar, CA, USA) as previously reported [15]. Briefly, all patients underwent CA under general anesthesia and endotracheal intubation. All anti-arrhythmic drugs were discontinued at least five half-lives before CA except amiodarone, which was discontinued at least 3 months before procedure. Oral anticoagulants were also discontinued 2 days pre-procedure, and subcutaneous low-molecular-weight heparin was used to bridge the procedure until oral anticoagulants were resumed following the procedure. Intravenous heparin was administered to maintain an activated clotting time >300 s. A 3.5-mm open-tip irrigated catheter (NaviStar Thermo-Cool, Biosense Webster) was percutaneously introduced through the right femoral vein for mapping and ablation. Circumferential pulmonary vein isolation (CPVI) with confirmation of entrance block was verified in all patients. Linear ablation, especially across low-voltage area to eliminate arrhythmogenic atrial tissues as well as to create lines of block to prevent reentry formation [15], was performed at the operator's discretion if AF persisted or left atrial tachycardia occurred after CPVI. External cardioversion was performed to restore sinus rhythm if atrial tachyarrhythmias were not terminated by CA.

2.2.1. Echocardiography

Echocardiographic images were obtained on the next day after CA. These examinations were performed using a commercially available ultrasound scanner (Vivid 9, General Electric Medical Health, Waukesha, WI, USA) with a 2.5-MHz phased-array transducer. Standard echocardiographic measurements were obtained in accordance with the current guidelines of the American Society of Echocardiography/European Association of Cardiovascular Imaging [20]. Mitral inflow was recorded between the tips of the mitral leaflets by pulsed-wave Doppler at the apical position. Peak velocities of early (E) and atrial (A) diastolic filling were measured. Color Tissue Doppler imaging was obtained in the apical 4-chamber view. Peak early diastolic (e') myocardial velocities were measured within a 6-mm circular sample volume at the septal and lateral mitral annular positions. Ratios of E/e' were calculated for both the septal E/e' and lateral E/e' [21].

2.3. Follow up and the definition of recurrence

Patients were follow-up at 1 week, 1 month, 3 months, 6 months and every 3–6 months after CA or whenever required because of AF symptoms. Twelve-lead electrocardiograms and 24-h Holter ambulatory electrocardiograms were recorded after CA and when the patients had symptoms of palpitation. After 3-month blanking period, any episode of atrial tachyarrhythmia lasting longer than 30 s on a 12-lead ECG, Holter monitoring, or pacemaker/implantable cardioverter-defibrillator interrogation during a follow-up visit was considered as recurrence. Anti-arrhythmic drugs were prescribed to patients with recurrent atrial tachyarrhythmia. Repeat CA was advocated in patients who remained symptomatic despite the use of anti-arrhythmic drugs.

2.4. Statistical analysis

Continuous variables are expressed as the mean ± standard deviation, and categorical variables are presented as the number with percentage in brackets. Continuous variables were compared using Student's t-test and paired data were compared using paired *t*-test. Categorical variables were compared using the chi-square test or Fisher's exact test. Atrial tachyarrhythmia-free survival was analyzed using the Kaplan–Meier method, with statistical significance between groups assessed using the Log-rank test. Univariate and multivariate Cox regression analyses were performed to identify predictors of atrial tachyarrhythmia recurrence and the interaction of predictors on the efficacy of SGLT2i therapy in preventing recurrence of atrial tachyarrhythmia. The HR and 95% confidence interval (CI) were calculated for each variable. For all analyses, differences were considered statistically significant at $p < 0.05$. Statistical analyses were performed using SPSS software ver. 25.0 (IBM, Armonk, NY, USA).

3. Results

3.1. Baseline characteristics in groups with and without SGLT2i

We retrospectively evaluated 220 consecutive patients with T2DM who underwent CA for anti-arrhythmics–refractory AF. Fourteen patients with eGFR <30 mL/min, 38 patients not taking antidiabetic medication, 15 patients with previous cardiac surgery or catheter ablation and 31 patients with incomplete medical records were excluded, yielding a cohort of 122 patients with diabetes (73% male; mean duration of AF before CA, 3.46 ± 3.51 years; mean age, 62.1 ± 9.4 years). Eighty-six patients (70%) had paroxysmal AF. During a mean follow-up of 33.7 ± 21.6 months (median: 27.6 months), 22 of 122 patients (18%) had atrial tachyarrhythmia recurrence. Table 1 presents the baseline clinical characteristics and antidiabetic and anti-arrhythmic medication use of the study population. There were no significant differences in age, gender, AF type, AF duration, body-mass index (BMI), CHA_2DS_2-VASc scores, HbA1c, creatinine, eGFR, and underlying medical diseases between the two groups, but a higher percentage of stroke was noted in the

non-SGLT2i group ($p = 0.026$). In the SGLT2i group, a higher percentage of patients used TZD ($p = 0.005$) and sulfonylureas ($p = 0.041$) and a lower percentage of patients used DPP4i ($p = 0.014$). In the SGLT2i group, SGLT2i treatment was initiated 5.6 ± 4.4 months before CA and the mean duration of SGLT2i treatment was 33.2 ± 16.0 months. No significant differences were observed in the use of metformin, glucagon-like peptide-1 agonists, α-glucosidase inhibitors, insulin, or anti-arrhythmic medications. The SGLT2i group had a statistically significant reduction in BMI from 28.6 ± 4.2 kg/m^2 to 27.2 ± 3.9 kg/m^2 in 6 months after CA ($p < 0.001$) compared to the non-SGLT2i group (from 27.3 ± 3.9 kg/m^2 to 26.9 ± 5.0 kg/m^2, $p = 0.343$). CPVI was achieved in all patients both in the SGLT2i and non-SGLT2i groups. Additional ablation strategies, such as linear ablation or cavotricuspid isthmus ablation, did not differ between the two groups.

The baseline patient characteristics were not significantly different between the SGLT2i subgroup and the DPP4i subgroup, except for the use of sulfonylurea, which was higher in the SGLT2i subgroup (Table 2).

3.2. Echocardiographic parameters in with and without SGLT2i

Table 3 summarized the echocardiographic parameters obtained 1 day and 6 months after CA. The echocardiographic parameters obtained 1 day and 6 months post CA did not differ significantly between the two groups. At 6-month follow-up echocardiography, significant decreases were observed in LAD, septal E/e', lateral E/e', and average E/e' in both groups, but only the SGLT2i group

Table 1
Comparison of baseline characteristics and medications between the SGLT2i and non-SGLT2i groups.

	Total		SGLT2i group		Non-SGLT2i group		P value
Clinical characteristics							
Patient number	122		45		77		
Age (years)	62.1 ± 9.4		60.1 ± 10.6		63.2 ± 8.6		.097
Gender (Male, %)	89 (73%)		35 (78%)		54 (70%)		.359
Type of AF							.909
Paroxysmal	86 (70%)		32 (71%)		54 (70%)		
Persistent	36 (30%)		13 (29%)		23 (30%)		
AF duration (years)	3.46 ± 3.51		3.09 ± 3.10		3.67 ± 3.73		.380
BMI (kg/m^2)		P value*		P value*		P value*	
Baseline	27.8 ± 4.7		28.6 ± 4.2		27.3 ± 3.9		.148
6 months after CA	27.1 ± 4.6	<.001	27.2 ± 3.9	<.001	26.9 ± 5.0	.343	.763
CHA_2DS_2-VASc score	2.9 ± 1.3		2.8 ± 1.2		2.9 ± 1.3		.752
HbA1c (%)	6.7 ± 0.8		6.8 ± 0.7		6.6 ± 0.8		.166
Creatinine (mg/dL)	0.98 ± 0.32		1.01 ± 0.32		0.97 ± 0.33		.581
eGFR (ml/min)	84.6 ± 27.4		83.3 ± 24.1		85.4 ± 29.3		.691
Underlying diseases							
Hypertension	93 (76%)		36 (80%)		57 (74%)		.455
Dyslipidemia	73 (60%)		26 (58%)		47 (61%)		.723
Hyperthyroidism	16 (13%)		7 (16%)		9 (12%)		.541
LV systolic dysfunction	13 (11%)		6 (13%)		7 (9%)		.547
CAD	19 (16%)		10 (22%)		9 (12%)		.122
Stroke	9 (7%)		0 (0%)		9 (12%)		.026
RHD	1 (1%)		0 (0%)		1 (1%)		>.999
SSS	7 (6%)		3 (7%)		4 (5%)		.708
COPD	2 (2%)		0 (0%)		2 (3%)		.531
Smoking	15 (12%)		6 (13%)		9 (12%)		.789
Anti-diabetic medications							
Metformin	90 (74%)		36 (80%)		54 (70%)		.232
DPP4 inhibitors	50 (41%)		12 (27%)		38 (49%)		.014
Thiazolidinediones	18 (15%)		12 (27%)		6 (8%)		.005
GLP-1 agonists	4 (3%)		1 (2%)		3 (4%)		>.999
Sulfonylureas	33 (27%)		17 (38%)		16 (21%)		.041
α-glucosidase inhibitors	7 (6%)		3 (7%)		4 (5%)		.708
Insulin	6 (5%)		1 (2%)		5 (7%)		.412
Anti-arrhythmic medications							
Class Ic	46 (38%)		14 (31%)		32 (42%)		.251
Class III	44 (36%)		13 (29%)		31 (40%)		.207
Beta-blocker	79 (65%)		32 (71%)		47 (61%)		.261
Ablation Strategies							
CPVI	122 (100%)		45 (100%)		77 (100%)		NA
Linear ablation	51 (42%)		19 (42%)		32 (42%)		.943
Cavotricuspid isthmus	96 (79%)		36 (80%)		60 (78%)		.787

*Comparison between baseline and 6 months after catheter ablation.

AF, atrial fibrillation; BMI, body-mass index; CA, catheter ablation; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CPVI: circumferential pulmonary vein isolation; DPP4, dipeptidyl peptidase-4; eGFR: estimated glomerular filtration rate; GLP-1: glucagon-like peptide-1; HbA1c, hemoglobin A1c; LV systolic dysfunction: left ventricular ejection fraction <50%; NA: not available; RHD: rheumatic heart disease; SGLT2i: sodium-glucose cotransporter 2 inhibitors; SSS: sick sinus syndrome.

Table 2
Comparison of baseline characteristics and medications between the SGLT2i and DPP4i subgroups.

	SGLT2i subgroup		DPP4i subgroup		P value
Clinical characteristics					
Patient number	33		38		
Age (years)	59.2 ± 11.3		63.5 ± 9.1		.084
Gender (Male, %)	26 (79%)		26 (68%)		.325
Type of AF					.956
Paroxysmal	25 (76%)		29 (76%)		
Persistent	8 (24%)		9 (24%)		
AF duration (years)	3.0 ± 2.8		3.3 ± 3.6		.659
BMI (kg/m^2)		P value*		P value*	
Baseline	28.4 ± 4.2		26.9 ± 4.6		.168
6 months after CA	27.0 ± 3.7	<.001	26.4 ± 5.0	.809	.577
CHA_2DS_2-VASc score	2.8 ± 1.3		3.0 ± 1.3		.613
HbA1c (%)	6.8 ± 0.8		6.5 ± 0.6		.143
Creatinine (mg/dL)	0.99 ± 0.35		1.00 ± 0.36		.932
eGFR (ml/min)	86.8 ± 25.7		84.3 ± 31.9		.727
Underlying diseases					
Hypertension	27 (82%)		28 (74%)		.413
Dyslipidemia	17 (52%)		25 (66%)		.222
Hyperthyroidism	5 (15%)		5 (13%)		>.999
LV systolic dysfunction	4 (12%)		3 (8%)		.697
CAD	9 (27%)		5 (13%)		.136
Stroke	0 (0%)		4 (11%)		.118
RHD	0 (0%)		0 (0%)		NA
SSS	2 (6%)		1 (3%)		.594
COPD	0 (0%)		2 (5%)		.495
Smoking	3 (9%)		3 (8%)		>.999
Anti-diabetic medications					
Metformin	25 (76%)		24 (63%)		.252
Thiazolidinediones	7 (21%)		2 (5%)		.072
GLP-1 agonists	1 (3%)		1 (3%)		>.999
Sulfonylureas	13 (39%)		5 (13%)		.011
α-glucosidase inhibitors	2 (6%)		1 (3%)		.594
Insulin	1 (3%)		1 (3%)		>.999
Anti-arrhythmic medications					
Class Ic	8 (24%)		16 (42%)		.113
Class III	8 (24%)		11 (29%)		.655
Beta-blocker	23 (70%)		24 (63%)		.561
Ablation strategy					
CPVI	33 (100%)		38 (100%)		NA
Linear ablation	14 (42%)		15 (40%)		.801
Cavotricuspid isthmus	26 (79%)		34 (90%)		.215

*Comparison between baseline and 6 months after catheter ablation.
AF, atrial fibrillation; BMI, body-mass index; CA, catheter ablation; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CPVI, circumferential pulmonary vein isolation; DPP4i, dipeptidyl peptidase-4 inhibitors; eGFR: estimated glomerular filtration rate; GLP-1: glucagon-like peptide-1; HbA1c, hemoglobin A1c; LV systolic dysfunction: left ventricular ejection fraction <50%; NA: not available; RHD: rheumatic heart disease; SGLT2i: sodium-glucose cotransporter 2 inhibitors; SSS: sick sinus syndrome.

showed improvement in the LVEF ($p = 0.042$). There were 13 patients with baseline LVEF <50%, including 6 and 7 patients in the SGLT2i and the non-SGLT2i groups, respectively. At 6-month follow-up, the SGLT2i-treated patients had significant improvement in LVEF (38.9 ± 7.1% vs. 48.7 ± 11.1%, n = 6, $p = 0.036$) with no atrial tachyarrhythmia recurrence; but the non-SGLT2i-treated patients had no significant changes in LVEF (38.2 ± 9.8% vs. 36.0 ± 11.3%, n = 7, $p = 0.595$) and 3 out of 7 patients had recurrence of atrial tachyarrhythmia. For patients with LVEF ≥50%, there were no significant changes of LVEF in the SGLT2i-treated (67.6 ± 6.2% vs. 68.7 ± 5.4%, n = 39, $p = 0.413$) and non-SGLT2i-treated (66.4 ± 6.6% vs. 65.8 ± 8.8%, n = 70, $p = 0.902$) patients.

3.3. Factors associated with absence of atrial tachyarrhythmia following CA

The Kaplan–Meier survival curves for atrial tachyarrhythmia-free survival after CA are shown in Figs. 2 and 3. The SGLT2i group had a significantly higher atrial tachyarrhythmia-free survival rate than the non-SGLT2i group (92.5% vs 72.1%, respectively; Log-rank $p = 0.015$; Fig. 2). Moreover, the atrial tachyarrhythmia-free survival rate was significantly higher in the SGLT2i subgroup than the DPP4i subgroup (96.7% vs 73.6%, respectively; Log-rank $p = 0.015$; Fig. 3).

Univariate analysis revealed that paroxysmal AF (HR, 0.34; 95% CI, 0.14–0.78; $p = 0.011$), AF duration (HR, 1.12; 95% CI, 1.01–1.25; $p = 0.035$), BMI changes (HR, 1.49; 95% CI, 1.01–1.90; $p = 0.041$), rheumatic heart disease (HR, 11.6; 95% CI, 1.49–90.7; $p = 0.019$), and SGLT2i therapy (HR, 0.26; 95% CI, 0.08–0.87; $p = 0.029$) were significant factors associated with atrial tachyarrhythmia recurrence (Table 4). Multivariate Cox regression analysis showed that paroxysmal AF (HR, 0.38; 95% CI, 0.15–0.99; $p = 0.047$) and

Table 3
Comparison of echocardiographic characteristics between the SGLT2i and non-SGLT2i groups.

	Total (n = 122)		SGLT2i group (n = 45)		Non-SGLT2i group (n = 77)		P value
1 day after CA							
LAD (mm)	43.8 ± 6.2		44.2 ± 5.7		43.5 ± 6.4		.546
LVEF (%)	63.8 ± 11.0		63.8 ± 11.7		63.8 ± 10.7		.978
E/e'							
Septal	17.3 ± 7.1		17.2 ± 7.6		17.4 ± 6.8		.882
Lateral	16.2 ± 7.1		16.4 ± 8.3		16.1 ± 6.4		.853
Average	16.7 ± 6.7		16.8 ± 7.4		16.7 ± 6.4		.937
6 months *after CA*		P value*		P value*		P value*	
LAD (mm)	42.4 ± 6.2	<.001	42.3 ± 5.0	<.001	42.5 ± 6.9	<.001	.919
LVEF (%)	63.7 ± 12.0	.272	65.7 ± 9.9	.042	62.6 ± 13.0	.915	.208
E/e'							
Septal	15.1 ± 7.3	.001	14.4 ± 7.9	.043	15.5 ± 7.0	.010	.498
Lateral	11.0 ± 5.0	<.001	10.6 ± 4.8	<.001	11.2 ± 5.1	<.001	.562
Average	12.5 ± 5.4	<.001	12.0 ± 5.3	<.001	12.8 ± 5.4	<.001	.529

*Comparison between 1-day and 6-month after catheter ablation.
CA: catheter ablation; LAD: left atrial dimension; LVEF: left ventricular ejection fraction; SGLT2i: sodium-glucose cotransporter 2 inhibitors.

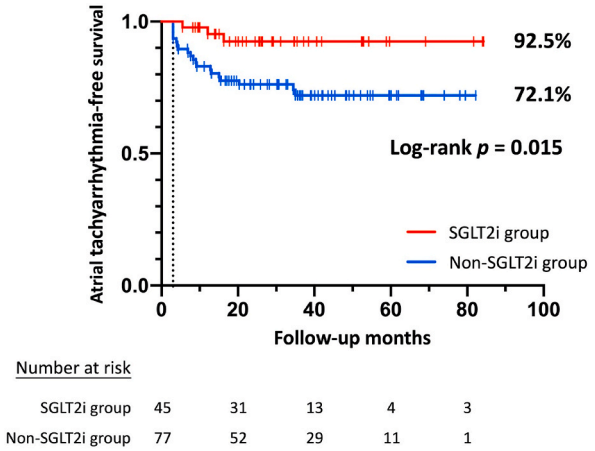

Fig. 2. Sodium-glucose cotransporter 2 inhibitors were associated with higher atrial tachyarrhythmia-free survival. Kaplan-Meier estimates of freedom from atrial tachyarrhythmia recurrence in patients treated with (red line) and without (blue line) sodium-glucose cotransporter 2 inhibitor (SGLT2i). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

SGLT2i therapy (HR, 0.18; 95% CI, 0.04–0.79; $p = 0.023$) were associated with a lower risk of atrial tachyarrhythmia recurrence after CA.

The efficacy of SGLT2i in preventing recurrence of atrial tachyarrhythmia was not statistically different in the selected subgroups, including age, gender, type of AF, BMI, and HbA1c level, except for eGFR (Supplementary Figure S1). Patients with eGFR ≥60 mL/min benefited more from SGLT2i therapy than those with eGFR <60 mL/min (p for interaction = 0.036).

4. Discussion

In this retrospective study, we found that SGLT2i therapy was associated with a lower risk of atrial tachyarrhythmia recurrence in T2DM patients undergoing CA for AF. In addition, SGLT2i therapy achieved greater suppression of AF recurrence than DPP4i therapy during long-term follow-up. Multivariate Cox regression analysis revealed that the use of SGLT2i and AF type (paroxysmal) were significantly associated with the absence of atrial tachyarrhythmia recurrence after CA. Compared to the non-SGLT2i group, the SGLT2i group had a statistically significant reduction in BMI and improvement in LVEF 6-month after ablation, which may play a role in suppressing AF recurrence post CA in T2DM patients.

4.1. SGLT2i prevent AF recurrence post ablation in patients with diabetes

T2DM is a strong and independent risk factor for the occurrence of AF. Moreover, T2DM is associated with several chronic diseases, including obesity, coronary artery disease, HF, and obstructive sleep apnea, which also increase the risk of AF [22–24]. SGLT2i may provide a specific AF-reduction benefit in the susceptible T2DM population. One post-hoc analysis from the DECLARE-TIMI 58 trial

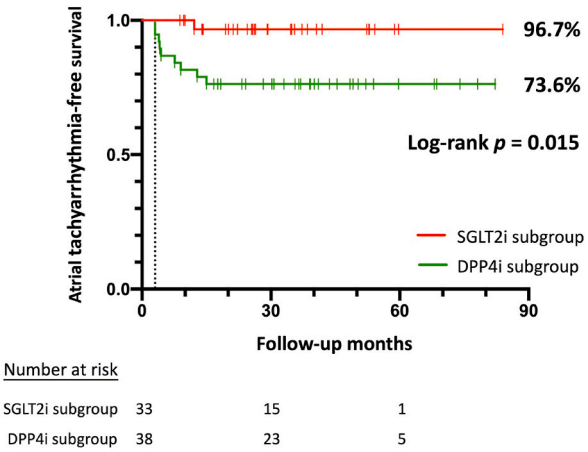

Fig. 3. Sodium-glucose cotransporter 2 inhibitors were associated with higher atrial tachyarrhythmia-free survival than dipeptidyl peptidase-4 inhibitors. Kaplan-Meier estimates of freedom from atrial tachyarrhythmia recurrence in patients treated with SGLT2i (red line) and dipeptidyl peptidase-4 inhibitors (DPP4i) (green line). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 4
Results of the univariate and multivariate Cox regression analyses of atrial tachyarrhythmia recurrence after catheter ablation.

	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Paroxysmal AF	0.34	0.14–0.78	.011	0.38	0.15–0.99	.047
AF duration	1.12	1.01–1.25	.035			
△BMI	1.49	1.01–1.90	.041			
RHD	11.6	1.49–90.7	.019			
SGLT2 inhibitors	0.26	0.08–0.87	.029	0.18	0.04–0.79	.023

AF, atrial fibrillation; BMI, body-mass index; CAD, coronary artery disease; CI: confidence interval; COPD, chronic obstructive pulmonary disease; DPP4, dipeptidyl peptidase 4; eGFR: estimated glomerular filtration rate; GLP-1: glucagon-like peptide 1; HbA1c, hemoglobin A1c; LAD: left atrial dimension; LVEF: left ventricular ejection fraction; RHD: rheumatic heart disease; SGLT2: sodium-glucose cotransporter 2; SSS: sick sinus syndrome; △BMI: the value of BMI at 6 months minus the value of BMI at 1 day after catheter ablation.

demonstrated that dapagliflozin reduced the incidence of new-onset AF and atrial flutter in patients with T2DM after a mean follow-up of 4.2 years [13]. Several meta-analyses also demonstrated that treatment of T2DM patients with SGLT2i was associated with a lower incidence of AF regardless of age, body weight, HbA1c, and systolic blood pressure (BP) at baseline [11,25].

The rate of freedom from atrial tachyarrhythmia recurrence of the study cohort was 82%, which is consistent with the literature that recurrence-free rate was around 80–90% for paroxysmal AF and 60–70% for persistent AF after CA [26,27]. Recently, low-voltage area-guided ablation strategy was suggested to reduce atrial tachyarrhythmia recurrence, especially for non-paroxysmal AF [15,28], and the rate of freedom from atrial tachyarrhythmia recurrence could be elevated to 70–80% even without anti-arrhythmic medications. Our study also showed that use of SGLT2i had significantly improved long-term outcomes in patients with T2DM undergoing CA for AF in comparison with other anti-diabetic medications (92.5% vs 72.1%). The favorable pleiotropic effects of SGLT2i have been proposed as a means of mitigating T2DM cardiometabolic disease risks [29]. Being overweight is associated with a poor prognosis for AF ablation [30], and high BMI is a significant predictor of AF recurrence after CA [31]. In addition to glycemic control, SGLT2i have the potential to improve cardiovascular risk profiles by decreasing body weight and systolic BP, thereby lowering the risk of AF [24,32]. In this study, the mean BMI reduced significantly in the SGLT2i group but the mean BMI didn't change in the non-SGLT2i group, which might play a role in a lower AF recurrence rate in the SGLT2i group. In addition, epicardial adipose tissue can release fibrotic and proarrhythmogenic factors leading to atrial myopathy and AF genesis [33]. Nagashima et al. revealed an association between epicardial adipose tissue volumes and AF recurrence after CA [34]. SGLT2i can induce epicardial adipose tissue lipolysis [35], which might also play a role in preventing AF recurrence in our patient cohort.

Reduced LVEF is strongly associated with the development of AF [36]. In this study, LVEF was significantly improved in the SGLT2i group but not in the non-SGLT2i group. Further subgroup analyses revealed that the improvement in LVEF was mainly from those patients with LVEF <50%. Successful ablation in AF patients with reduced LVEF has generally been associated with improved LVEF [37]. Because all 6 SGLT2i-treated patients with reduced LVEF had no AF recurrence (0 of 6 patients) which was better than that (3 of 7 patients) of untreated patients, it is possible that improvement in LVEF was at least partly due to a better AF ablation outcome in the SGLT2i-treated patients. Meantime, emerging evidence indicates that SGLT2i reduce the risks of worsening HF for patients with reduced LVEF regardless of the presence of T2DM [7,38]. SGLT2i therapy-derived natriuresis, improvement in BP and arterial stiffness,

and reduction in plasma volume may also contribute to the improvement in LVEF [38], and thus the prevention of AF recurrence in patients with reduced LVEF.

LV diastolic dysfunction adversely affects structural, functional, and electrical remodeling of the left atrium; therefore, patients with LV diastolic dysfunction have an increased susceptibility to AF [39,40]. Elevated LV filling pressure, estimated by E/e', is often used as a clinical surrogate for impaired diastolic function in patients with preserved LVEF [41]. Arai et al. found that E/e' $\geq$11.0 was associated with new-onset AF when adjusted for the coexistence of atherothrombotic risk factors [42]. Soga et al. observed a significant decrease in E/e' (from 9.3 to 8.5) after 6-month dapagliflozin therapy for T2DM patients with HF [43]. A recent randomized IDDIA trial also found that dapagliflozin had a beneficial effect on LV diastolic dysfunction in T2DM patients [44]. Our data showed that the average E/e' was significantly decreased both in the SGLT2i and non-SGLT2i groups 6 months after CA. The improved LV diastolic function could result from rhythm control in AF [45] because the AF recurrence rate was lower than 10% at 6-month follow-up even in the non-SGLT2i group (Fig. 1). The additional favorable pleiotropic effects of SGLT2i on LV diastolic dysfunction might play a role in preventing AF recurrence during long-term follow-up.

In streptozotocin-induced diabetic rats, atrial remodeling was characterized by an increase in spatial dispersion and frequency-dependent action potential duration (APD) shortening, enhanced conduction disturbance, and prolonged APD, which increased the susceptibility to atrial tachyarrhythmia and provided substrates for AF genesis in the diabetic atrium [46]. In animal studies, SGLT2i could ameliorate oxidative stress, interstitial fibrosis, and atrial electrical and structural remodeling, thereby reducing AF inducibility [10,47]. Similar results were observed in human cell studies. Kondo et al. [9] found that canagliflozin inhibited NADPH oxidase activity via SGLT1/AMP-activated protein kinase α2/Rac1 signaling to suppress pro-inflammatory and pro-apoptosis pathways in human cardiomyocytes. Although not directly addressed by these studies, these cardioprotective effects of SGLT2i may favorably modify the atrial substrate and prevent AF recurrence after CA.

4.2. Other antidiabetic medications associated with AF ablation outcomes

The use of DPP4i as second-line antidiabetic drugs has been reported to be associated with a lower risk of new-onset AF compared to other second-line antidiabetic drugs (TZD, meglitinide, sulfonylurea, and α-glucosidase inhibitors) among metformin-treated T2DM patients [48]. Zhang et al. [49] observed that DPP4i attenuated diabetes mellitus-induced atrial structural remodeling, mitochondrial dysfunction, and electrophysiological abnormalities, thereby reducing AF inducibility in an alloxan-induced diabetic rabbit model. Compared with DPP4i, a longitudinal cohort study revealed that SGLT2i therapy was associated with a lower risk of new-onset AF among T2DM patients [12]. Kishima et al. [18] further reported that SGLT2i use was associated with a significantly lower risk of recurrent AF after CA compared with DPP4i in univariate analysis. Consistent with previous studies, our data demonstrated that T2DM patients treated with SGLT2i were associated with a lower atrial tachyarrhythmia recurrence rate than those treated with DPP4i, and the use of SGLT2i was an independent factor associated with absence of atrial tachyarrhythmia recurrence after CA in multivariate analysis. Possibly, a stronger effect of SGLT2i than DPP4i on preventing AF could explain these findings.

Other antidiabetic medications are also associated with a decreased risk of AF and thus better AF ablation outcomes. A recent retrospective observational study showed that T2DM patients treated with metformin have better atrial tachyarrhythmia-free survival than those without metformin use [16]. Metformin might induce AMP-activated protein kinase activation, reducing susceptibility to AF. The pleiotropic effect of metformin on body weight reduction was also suggested as a potential mechanism to improve AF ablation outcomes. Pioglitazone, a TZD-type antidiabetic drug, has been reported to reduce anti-inflammatory cytokines and oxidative stress via activation of peroxisome proliferator-activated receptor-γ, which attenuated atrial fibrosis and AF promotion in HF rabbits [50]. Gu et al. reported that pioglitazone therapy was associated with better atrial tachyarrhythmia-free survival in patients with T2DM and paroxysmal AF undergoing CA [17]. In our study, although more patients in the SGLT2i group used TZD, multivariate Cox regression analysis showed neutral effects of TZD on AF ablation outcomes, suggesting that the main factor associated with improved ablation outcomes was the SGLT2i use.

5. Limitations

The cohort of this retrospective, small-scale, observational study had a few baseline differences between the groups treated with and without SGLT2i. Even if robust multivariable analyses were performed to adjust for clinical covariates known to affect the outcome of CA for AF, further large-scale prospective studies are warranted to confirm our findings. In addition, AF recurrence required ambulatory electrocardiogram documentation at specific time points or when patients exhibited with symptoms; therefore, the risk of AF recurrence might be underestimated due to unidentified asymptomatic AF episodes between visits. Our patients had good glycemic control, therefore, whether SGLT2i therapy can prevent AF recurrence after CA in T2DM patients with poor glycemic control requires further investigation.

6. Conclusions

The use of SGLT2i and AF type (paroxysmal) were independent risk factors associated with the absence of atrial tachyarrhythmia recurrence after CA in patients with T2DM and AF. The pleiotropic effects of SGLT2i on BMI reduction and left ventricular function improvement may play a role in preventing AF recurrence post CA.

Additional information

Supplementary content related to this article has been published online at [URL].

Author contribution statement

Hao-Tien Liu: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper. Hung-Ta Wo: Conceived and designed the experiments; Performed the experiments. Po-Cheng Chang; Ming-Shien Wen: Performed the experiments. Hui-Ling Lee: Analyzed and interpreted the data. Chung-Chuan Chou: Conceived and designed the experiments; Performed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Data availability statement

Data included in article/supp. material/referenced in article.

Declaration of competing interest

All authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.heliyon.2023.e16835.

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